Medicinrådet

Bilag til Medicinrådets anbefaling vedrørende ozanimod til behandling af colitis ulcerosa

Vers. 1.0

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. ozanimod
2. Forhandlingsnotat fra Amgros vedr. ozanimod
3. Ansøgers endelige ansøgning vedr. ozanimod

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Virum, 29. august 2022.

Til Medicinrådet

Bristol Myers Squibbs tilbagemelding på udkast til vurderingsrapport for ozanimod til behandling af moderat til svær aktiv colitis ulcerosa

Bristol Myers Squibb (BMS) imødeser Medicinrådets anbefaling vedr. ozanimod til behandling af moderat til svær aktiv colitis ulcerosa (UC) planlagt til 28. september 2022, knap 1 år efter MR modtog ansøgningen på datoen for CHMP positive opinion (14. oktober 2021).

BMS takker hermed for muligheden for at give en tilbagemelding på to temaer, som vi mener kan nuancere beslutningsgrundlaget; bivirkningsprofilen og sammenligningsgrundlaget i den økonomiske model.

Data supporterer, at ozanimods bivirkningsprofil er anderledes, ikke alvorligere.

Medicinrådet beskriver, at ” *For effektmålet alvorlige uønskede hændelser kunne der på baggrund af de sammenlignede analyser ikke ses forskel mellem ozanimod og de øvrige lægemidler ift. hændelsesfrekvenser.* ” - BMS appellerer til, at Rådet diskuterer om bekymringen for langtidsbivirkninger er unødigt overdrevet, evt. pga. af tidligere dårlige oplevelser med andre produkter indenfor samme sygdomsområder, eller pga. antagelse om klasseeffekt.

Medicinrådet fremhæver f.eks., at ***”ved behandling med fingolimod*** *er der rapporteret en række bivirkninger,* ***herunder forskellige kræftformer****… … Medicinrådet vurderer, at der er en risiko for, at der er en sammenlignelig klasseeffekt for ozanimod og fingolimod. Medicinrådet vurderer på den baggrund, at bivirkningsprofilen for ozanimod er mere alvorlig…*”. En konklusion som ikke genfindes i de seneste beslutninger fra Australien[1], Sverige[2] og Tyskland[3].

Ozanimod og fingolimod er ikke det samme produkt. Ozanimod er en selektiv sphingosin-1-fosfat-receptormodulator, der binder med høj affinitet til S1P subtyperne 1 og 5, modsat fingolimod, der er non-selektiv og binder til S1P subtyperne 1 samt 3-5[4]. Medicinrådet sætter et yderst problematisk lighedstegn mellem ozanimod og fingolimod ved, blandt andet, at pege på maligniteter som et problem.

Dernæst er alt, som bekendt, relativt. Medicinrådet mangler at gøre det klart for læseren at **ozanimod har vist lavere rater af maligniteter** end samtlige andre sammenlignelige studier af langtidseffekt på øvrige lægemidler til behandling af UC, se Tabel 1 i appendiks nedenfor.

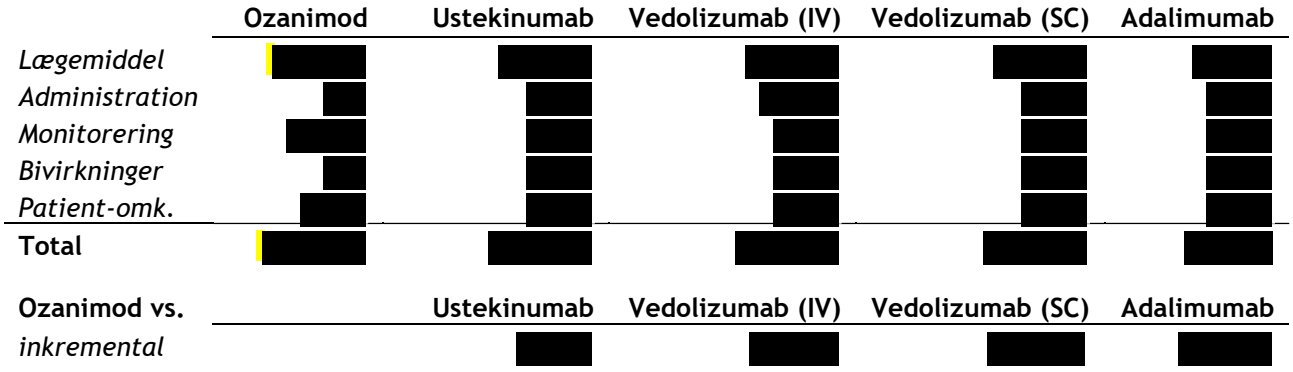
BMS minder om, at behandlingsvarigheden (og dermed eksponeringen) desuden er ganske forskellig i forhold til MS og UC. I gennemsnit vurderes UC-patienten, ifølge Medicinrådet, at være i behandling med ozanimod i 1 ½ år. Der er nu 3-års data fra open-label extension (OLE) studiet for ozanimod i UC[5], samt 5-års opfølgning fra OLE studiet indenfor MS hvor, den eksakt samme dosering anvendes[6]. Det nødvendige datagrundlag *er* således til stede.

Vigtigheden i at udvise forsigtighed med at drage direkte paralleller mellem bivirkningsprofilerne kan eksemplificeres yderligere ved at EMA stiller færre krav til den kardiologiske monitorering forud for opstart med ozanimod[7], end for fingolimod[8]. Første dosismonitorering af hjerterytmen er et krav for fingolimod[8], mens dette kun er nødvendigt for en særlig population af patienter, der opstartes i behandling med ozanimod[7]. 1,2-1,4% af patienterne som startes i ozanimod vil have behov for første dosis monitorering[9]. Faldet i det absolutte lymfocyttal og leverpåvirkningen er ligeledes mindre for ozanimod, end for fingolimod[10]. Når sikkerhedsprofilen for ozanimod er bedre end fingolimod ved 1 år og ved 2 år[10], så er det både uordentligt og ukorrekt at antage, at sikkerhedsprofilen skulle være ens på lang sigt.

Yderligere får Medicinrådet fejlagtigt kommunikeret at *" Forud for behandling med ozanimod **skal** patienter vaccineres mod herpes zoster… …. Patienter i behandling med ozanimod **skal** derudover regelmæssigt vurderes af en hudlæge*". SmPC'et beskriver blot at "*vaccination mod varicella zoster-virus (VZV) af patienter, hvor der ikke er dokumenteret immunitet mod VZV, **anbefales** før behandling med ozanimod påbegyndes*"[7] og ydermere er det ikke en SmPC anbefaling om regelmæssig vurdering hos en hudlæge.

En sundhedsøkonomisk analyse bør udføres med komparatorer og doseringer som er relevante for beslutningsgrundlaget.

Resultatet af en sundhedsøkonomisk model der udelukkende sammenligner med biosimilære lægemidler giver en ufuldstændig indsigt i ozanimods konkurrencemæssige relation til eksisterende behandlinger. Resultatet af en sådan analyse havde helt åbenlyst ikke krævet en sundhedsøkonomisk evaluering. BMS mener, at det havde været mere relevant for Rådets beslutningsgrundlag at forstå hvordan ozanimods omkostninger er sammenlignet med vedolizumab og ustekinumab; hvorfor de indgik i BMS's sundhedsøkonomiske indsendelse. Netop dette fremhæver udfordringen i, at Medicinrådets sekretariat fortsat fravælger at afrapportere resultatet af virksomhedens hovedanalyse. Resultatet af denne analyse med Amgros' netpriser ved indsendelsestidspunktet (14. oktober 2021) deles derfor her:



BMS og Medicinrådet er enige om, at for komparatorerne er den kliniske virkelighed, at omkring en 1/3 af patienterne justeres op i dosis på lægemidlerne der anvendes i dag: "*Medicinrådet vurderer videre, at en dosisøgning for komparator vil kunne forekomme, og finder også ansøgers tilgang til dosisøgning retvisende".* Dog stopper enigheden vedr. doseringen af ozanimod her fordi: *"… Medicinrådet [vurderer], at en dosisøgning ved behandling med ozanimod også vil kunne forekomme…*"

BMS vil gerne understrege at det ikke er muligt at justere på doseringen af ozanimod. Der foreligger ingen data for, hvorledes dette vil påvirke effekt-/bivirkningsforholdet på produktet. BMS ønsker, at Medicinrådet understreger, at ozanimod vedligeholdelsesbehandling udelukkende kan anbefales som én 0,92mg kapsel dagligt som beskrevet i SmPC'et. Dermed er omkostningen ved ozanimod, modsat øvrige produkter indenfor sygdomsområdet, fast og forudsigelig.

Med venlig hilsen,

Anders Thelborg
Adm. direktør
Bristol Myers Squibb, Denmark

Appendiks

Tabel 1: Incidence rate af maligniteter / 100 patient-år i colitis ulcerosa

Produkt	**Incidence rate / 100 patient-år i colitis ulcerosa**		**Patient-års observation**
	Incl. non-melanom hudkræft	**Excl. non-melanom hudkræft**	
Ozanimod vs. placebo [11]	**0,63** vs. 0,81	**0,31** vs. 0,81	**1923** vs. 249
Ustekinumab vs. placebo[12]	1,12 vs. 0,40	0,64 vs. 0,40	625 vs. 250
Vedolizumab (IV) [13]	0,98	NR	NR
Infliximab vs. placebo [14]	NR	0,6 vs. 0	832 vs. 210
Adalimumab[15]	1,0	0,79	3397
Golimumab 50mg[16]	1,26 vs. 0	NR	242 vs. 105
Golimumab 100mg[16]	0,74 vs. 0	NR	1358 vs. 105
Tofacitinib 5mg BID [17]	NR	0,44	678
Tofacitinib 10mg BID [17]	NR	0,86	1979

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01.09.2022

DBS, SNI

Forhandlingsnotat

Dato for behandling i Medicinrådet	28.09.2022
Leverandør	BMS
Lægemiddel	Zeposia (ozanimod)
Ansøgt indikation	Moderat til svær colitis ulcerosa

Forhandlingsresultat

Amgros har følgende pris på Zeposia (ozanimod):

Tabel 1: Forhandlingsresultat

Lægemiddel	Styrke	Pakningsstørrelse	AIP	Nuværende SAIP	SAIP pr 1.1.2023	Rabatprocent pr. 01.01.23 ift. AIP
Zeposia (ozanimod) *startpakke*	0,23 mg + 46 mg	4 stk. af 0,23 mg + 3 stk. af 0,46 mg	2.715,51 kr.	[redacted]	[redacted]	[redacted]
Zeposia (ozanimod)	0,92 mg	28 stk. af 0,92 mg	10.753 kr.	[redacted]	[redacted]	[redacted]

Zeposia (ozanimod) har budt ind i udbuddet for multipel sklerose med aftaleperiode 01.01.23-31.12.23. Priserne fremgår i tabel 1. Priserne vil også gælde for den ansøgte indikation, hvorfor der ikke forhandles en pris på lægemidlet.

Informationer fra forhandlingen

Zeposia (ozanimod) vil ved anbefaling til colitis ulcerosa indgå i to forskellige behandlingsvejledninger (multipel sklerose og colitis ulcerosa). Udbudsperioderne er desværre ikke ens for disse behandlingsområder.

- Behandlingsvejledningen vedr. multipel sklerose
  Zeposia blev godkendt i februar 2021 til attakvis multipel sklerose og er efterfølgende indplaceret behandlingsvejledningen.
  Periode: 01.01.2023-31.12.2023.

- Behandlingsvejledningen vedr. colitis ulcerosa
  For den ansøgte indikation colitis ulcerosa er der en behandlingsvejledning med mulighed for prisjustering af lægemidlerne hvert halve år.
  Periode: 01.10.2022 - 31.3.2023.

Da de to behandlingsvejledninger har forskellige udbudsperioder, er muligheden for prisjustering af de omfattede lægemidler med forskellig frekvens. Indgår et lægemiddel i to eller flere forskellige behandlingsvejledninger, er det som hovedregel den behandlingsvejledning, hvor lægemidlet har den mest fordelagtige position, som er afgørende for tidspunktet for prisjustering.

Aktuelt følger prisjusteringsmuligheden for Zeposia (ozanimod) behandlingsvejledningen for multipel sklerose. Næste udbudsperiode for denne er 01.01.23 – 31.12.2023. Skal Zeposia (ozanimod) i stedet følge prisjusteringsfrekvensen tilhørende behandlingsvejledningen for colitis ulcerosa, vil det være betinget af en mere fordelagtig position i denne behandlingsvejledning end i den for multipel sklerose (hvor Zeposia (ozanimod) nu er i kategorien "anvend ikke rutinemæssigt").

Konkurrencesituationen

Nedenstående lægemidler er relevante i relation til Zeposia (ozanimod), hvis lægemidlet godkendes til behandling af colitis ulcerosa.

Tabel 2: Sammenligning af lægemiddeludgifter (SAIP, DKK)

Lægemiddel	Dosis 18 måneder	Pakningsstørrelse	Pakningspris	Antal pakninger /18 måneder	Samlet lægemiddeludgift /18 måneder
Zeposia (ozanimod)	*Induktionsbehandling:* 0,23 mg dagligt i de første fire dage, 0,46 mg dagligt de efterfølgende tre dage	4 stk. af 0,23 mg + 3 stk. af 0,46 mg	[redacted]	1	X [redacted]

	Vedligeholdelsesbehandling: 0,92 mg dagligt	28 stk. af 0,92 mg	[redacted]	19,3	
Zessly (Infliximab)	*Induktionsbehandling:* I.v. 5 mg/kg uge 0, 2 og 6. *Vedligeholdelsesbehandling:* I.v. 5 mg/kg hver 8. uge.	3 stk. af 100 mg	[redacted]	13,75	[redacted]
Hymiroz (adalimumab)	*Induktionsbehandling:* 160 mg s.c. x 1 i uge 0, 80 mg s.c. x 1 i uge 2 *Vedligeholdelsesbehandling:* 40 mg s.c. x 1 hver 2. uge	2 stk. af 40 mg	[redacted]	21,5	[redacted]
Entyvio (vedolizumab)	*Induktionsbehandling:* I.v. 300 mg uge 0 og 2. *Vedligeholdelsesbehandling:* S.c. 108 mg uge 6, og herefter s.c. 108 mg hver 2. uge	2 stk. af 300 mg 36 stk. af 108 mg	[redacted]	2 36	[redacted]

**Prisen er gældende fra 01.01.2023*

Status fra andre lande

Norge: Prisnotat er på vej og lægemidlet er vurderet ved en forenklet proces.[1]
Sverige: Vurderes ikke til brug på hospitaler[2]
England: Under vurdering[3]

Konklusion

Hvis Zeposia (ozanimod) ligestilles med de øvrige lægemidler til behandling af colitis ulcerosa, som har en fordelagtig placering i behandlingsvejledningen, vil det blive nødvendigt at lave en justering så Zeposia (ozanimod) kan komme til at følge prisjusteringsfrekvensen tilhørende behandlingsvejledningen for colitis ulcerosa i fremtiden. Dette kan tidligst ske ved næste prisregulering pr. 01.04.2023.

[redacted]

[redacted]

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Medicinrådet

Application for the assessment of ozanimod (ZEPOSIA®) for the treatment of moderately to severely active ulcerative colitis

Version date: 13th of May 2022

[redacted]

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Table of contents

Medicinrådet Dampfærgevej 27-29, 3. th. | DK-2100 København Ø | +45 70 10 36 00 | medicinraadet@medicinraadet.dk | www.medicinraadet.dk

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1. Basic information

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Overview of the pharmaceutical	
Proprietary name	ZEPOSIA
Generic name	Ozanimod
Marketing authorisation holder in Denmark	Bristol Myers Squibb Hummeltoftevej 49 2830 Virum The transfer of the marketing authorisation for Zeposia (ozanimod) from Celgene Europe B.V. to Bristol Myers Squibb Pharma EEIG was approved by the European Commission on 9 October 2020. At time of submission, Celgene ApS remains the commercialising company in Denmark.
ATC code	L04AA38
Pharmacotherapeutic group	Immunosuppressants, selective immunosuppressants
Active substance(s)	Ozanimod
Pharmaceutical form(s)	Hard capsule
Mechanism of action	Ozanimod is an S1P receptor modulator that binds selectively to S1P receptor subtypes 1 and 5. Ozanimod causes lymphocyte retention in lymphoid tissues. The mechanism by which ozanimod exerts therapeutic effects in UC is unknown but may involve the reduction of lymphocyte migration into the inflamed intestinal mucosa.
Dosage regimen	The recommended dosage is 0.92 mg ozanimod once daily. The capsules can be taken with or without food. The following initial dose escalation regimen is required: ▪ Days 1-4: ozanimod 0.23 mg once daily ▪ Days 5-7: ozanimod 0.46 mg once daily ▪ Day 8 and thereafter: ozanimod 0.92 mg once daily.
Therapeutic indication relevant for assessment (as defined by the EMA)	Ozanimod is indicated for the treatment of adult patients with moderately to severely active UC who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biologic agent.
Other approved therapeutic indications	Yes. Ozanimod is indicated for the treatment of adult patients with relapsing remitting multiple sclerosis (RRMS) with active disease as defined by clinical or imaging features.

Overview of the pharmaceutical	
Will dispensing be restricted to hospitals?	Ozanimod is prescribed and dispensed in a hospital (Group BEGR), but is a hard capsule self-administered by the patient at home.
Combination therapy and/or co-medication	Not applicable
Packaging: types, sizes/number of units, and concentrations	▪ Ozanimod 0.23 mg, 0.46 mg, and 0.92 mg hard capsules. ▪ Available in polyvinyl chloride/polychlorotrifluoroethylene/aluminium foil blisters. ▪ Treatment initiation pack: pack size of 7 capsules (4 × ozanimod 0.23 mg, 3 × ozanimod 0.46 mg). ▪ Maintenance pack: pack size of 28 hard capsules (ozanimod 0.92 mg).
Orphan drug designation	Not applicable

ATC = Anatomical Therapeutic Chemical Classification System; EMA = European Medicines Agency; S1P = sphingosine 1-phosphate; UC = ulcerative colitis.

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2. Abbreviations

Abbreviation	Expansion
5-ASA	5-aminosalicylic acids
6-MP	6-mercaptopurine
ADA	adalimumab
AE	adverse event
AESI	adverse event of special interest
ALC	absolute lymphocyte count
ALT	alanine aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
BTSD	biological and targeted synthetic drug
CADTH	Canadian Agency for Drugs and Technologies in Health
CBC	complete blood count
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
CrI	credible interval
CRP	C-reactive protein
DIC	deviance information criteria
DMC	Danish Medicines Council
DSU	Decision Support Unit
ECG	electrocardiogram
EIM	extraintestinal manifestations
EMA	European Medicines Agency
ERG	Evidence Review Group
ESS	effective sample size
EU	European Union
FDA	Food and Drug Administration
GI	gastrointestinal
GOL	golimumab
HBV	hepatitis B virus
HCl	hydrochloride
HRQoL	health-related quality of life
IBD	inflammatory bowel disease
ICER	Institute for Clinical and Economic Review
IFX	infliximab
IgG	immunoglobulin G
IL	interleukin
IP	induction period
IR	Incidence rate
ITT	intention to treat
IV	intravenous
JCV	John Cunningham virus
LLN	lower limit of normal
LS	least-squares
MCID	minimal clinically important difference
MCS	Mental Component Summary
MCSE	Monte Carlo standard error

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MP	maintenance period
MS	multiple sclerosis
NA	not applicable
NCT	National Clinical Trial Number
NICE	National Institute for Health and Care Excellence
NMA	network meta-analysis
NMSC	non-melanoma skin cancer
NR	not reported
NRI	non-responder imputation
OLE	open-label extension
OLP	open-label period
OR	odds ratio
OZA	ozanimod
PBO	placebo
PCS	Physical Component Summary
PGA	physician's global assessment of disease activity
PML	progressive multifocal leukoencephalopathy
PPP	pharmacy purchase price
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PY	patient-year
Q12W	every 12 weeks
Q1W	every 1 week
Q2W	every 2 weeks
Q4W	every 4 weeks
Q8W	every 8 weeks
QD	once daily
RBS	rectal bleeding score
RCT	randomised controlled trial
ResDev	residual deviance
RMS	relapsing multiple sclerosis
RRMS	relapsing remitting multiple sclerosis
S1P	sphingosine 1-phosphate
S1P1-5	S1P receptors 1-5
S1PR	sphingosine 1-phosphate receptor
SAE	serious adverse event
SC	subcutaneous
SD	standard deviation
SDbt	standard deviation between-trial heterogeneity
SF-36	SF-36 Health Survey
SFS	stool frequency subscore
SLR	systematic literature review
SmPC	summary of product characteristics
TEAE	treatment-emergent adverse event
TNF	tumour necrosis factor
TOF	tofacitinib
TSD	Technical Support Document
TT	treat-through
UC	ulcerative colitis
ULN	upper limit of normal

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UST	ustekinumab
VAS	visual analogue scale
VEDO	vedolizumab
VZV IgG	varicella zoster virus antibody
WPAI	Work Productivity and Activity Impairment
WPAI-UC	Work Productivity and Activity Impairment–Ulcerative Colitis

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3. Tables and figures

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4. Summary

4.1. Indication

Ozanimod is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis (UC) who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biologic agent. This indication received a positive Committee for Medicinal Products for Human Use (CHMP) opinion on 14 October 2021.

4.2. Disease overview

Ulcerative colitis is a disease of unknown aetiology, characterised by diffuse inflammation of the mucosa and submucosa of the colon and rectum that may cause ulcers to develop.[1,2] Patients with UC experience significant morbidity associated with their disease with considerable impairment to health-related quality of life (HRQoL).[3,4] The most bothersome symptoms reported are rectal bleeding, rectal urgency, and tenesmus.[5]

The prevalence of UC in Denmark in 2013 was estimated to be 35,200 persons and is among the highest in the world.[6]

4.3. Current management and unmet need

The Danish Medicines Council (DMC) treatment guidance for biological and targeted synthetic drugs (BTSDs) for UC was published in 2021.[7] Here the DMC recommended that infliximab, golimumab, and vedolizumab (intravenous [IV] and subcutaneous [SC]) constitute the best treatment options for BTSD-naive patients with moderately to severely active UC. For BTSD-experienced patients with moderately to severely active UC, the DMC recommended that adalimumab, infliximab, golimumab, vedolizumab (IV and SC), and ustekinumab are the best treatment options.

Although there are multiple treatment options currently available, there remains a need for additional treatments with new mechanisms of action and a convenient route of administration.

4.4. Ozanimod

Ozanimod is a sphingosine 1-phosphate (S1P) receptor modulator that binds selectively to S1P receptor subtypes 1 and 5.[8] The recommended dose of ozanimod is 0.92 mg ozanimod once daily. Ozanimod offers a new mode of action for treatment of moderately to severely active UC and constitutes a safe, simple to initiate once daily, oral alternative to the existing therapies recommended by the DMC.

4.4.1. Clinical evidence

The efficacy and safety of ozanimod in patients with moderately to severely active UC has been demonstrated in the phase 3 placebo-controlled TRUE NORTH trial,[9] the phase 2 placebo-controlled TOUCHSTONE trial,[10] and their respective open-label extension (OLE) trials and pooled analyses.[11-14]

4.4.1.1. Efficacy

In the TRUE NORTH trial, a statistically significantly greater proportion of patients receiving ozanimod achieved clinical remission during the induction and maintenance phase versus placebo:

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- At week 10, a greater proportion of patients achieved clinical remission (3-component Mayo Score) (18.4% vs. 6.0%; *P* < 0.0001).[9]
- At week 52, a greater proportion of patients achieved clinical remission (3-component Mayo Score) (37.0% vs. 18.5%; *P* < 0.0001).[9]

Also, ozanimod was associated with improved HRQoL: During induction, the mean change from baseline in the EQ-5D Index score for ozanimod 1 mg was statistically significantly greater than the mean change from baseline for placebo (nominal *P* = 0.003).[15,16] During maintenance, patients in the ozanimod/ozanimod arm had a non-significant improvement in the EQ-5D Summary Index at week 52 (nominal *P* = 0.472), relative to patients in the ozanimod/placebo arm.[15,16]

In the TOUCHSTONE trial, the primary endpoint of clinical remission occurred at week 8 in 16%, 14%, and 6% of patients who received ozanimod 1 mg, ozanimod 0.5 mg, and placebo, respectively (*P* = 0.048 and *P* = 0.14, respectively, for the comparison of the 2 doses of ozanimod vs. placebo). Clinical remission at week 32 occurred in 21%, 26%, and 6% of patients who received ozanimod 1 mg, ozanimod 0.5 mg, and placebo, respectively (nominal *P* = 0.01 and nominal *P* = 0.002, respectively, for the comparison of the 2 doses of ozanimod vs. placebo).[10] These results were further supported by the TOUCHSTONE OLE trial, which reported that, at 4 years, partial Mayo measures indicated 93.3% of patients remained in clinical response and 82.7% remained in clinical remission based on observed cases.[12]

In the absence of head-to-head evidence of ozanimod versus existing treatments, comparative evidence was calculated using a network meta-analysis (NMA) with data from the TRUE NORTH and TOUCHSTONE trials and data for adalimumab, golimumab, infliximab, vedolizumab, and ustekinumab. The results of the NMA supported the conclusion that non-inferior efficacy of ozanimod can be considered an appropriate approach[17]:

- In the induction phase, ozanimod consistently offered comparable clinical response and remission to all other agents available to treat moderate-to-severe UC and offered statistically significant improvements over adalimumab for analyses of clinical remission and response in the biologic-experienced (bio-experienced) population.
- In the maintenance phase, ozanimod was found to be numerically superior to all other active agents in the RR studies of a bio-naive population. Vedolizumab and ozanimod offered statistically significant improvement in corticosteroid-free remission over placebo in the bio-experienced population. Ozanimod was comparable to all other active agents and in favour of vedolizumab versus ozanimod.

4.4.1.2. Safety

Ozanimod displayed an acceptable safety profile, with most adverse events (AEs) considered mild or moderate in severity. The pooled safety analysis showed that during the induction phase, the overall incidence of treatment-emergent adverse events (TEAEs) was similar for ozanimod and placebo. Exposure-adjusted incidence rates of AEs across the pooled UC study groups was lower in the ozanimod arm compared with the placebo arm. The proportion of patients in the ozanimod arm reporting a TEAE was highest during the first 3 months of treatment and decreased over time. Over the 1,922 patient-years of exposure, the incidences of malignancies and serious or opportunistic infections was low.[13]

- The opportunistic infection incidence rate was 1.48 (per 100 patient-years) in the ozanimod arm compared with 0.81 (per 100 patient-years) in the placebo arm. The serious infection incidence rate was lower in the ozanimod arm at 1.32 (per 100 patient-years) compared with 2.84 (per 100 patient-years) in the placebo arm.

- There was no increase in the overall incidence of infections, serious infections, or other opportunistic infections with longer exposure to ozanimod.[13,14] There were no reported cases of progressive multifocal leukoencephalopathy (PML) in the UC population.

The NMA reported that, during the induction phase, ozanimod consistently demonstrated comparable safety outcomes to all other agents across all analyses.. During the maintenance phase, ozanimod offered comparable safety to all other agents across all analyses.

4.4.2. Economic evidence

Cost-minimisation analyses were carried out using the pharmacy purchase price (PPP). The base-case results indicated that ozanimod therapy was associated with higher per-patient costs compared with infliximab and vedolizumab (SC) therapies in bio-naive patients, and ustekinumab, adalimumab (SC), and vedolizumab (SC) therapies in bio-experienced patients. Budget-impact analyses indicated that the introduction of ozanimod is associated with an increase in the overall budget in both populations.

4.4.3. Conclusion

Treatment with ozanimod for up to 52 weeks in subjects in a moderate-to-severe UC population was superior to placebo for clinical, endoscopic, and histologic measures of disease activity. The efficacy findings, coupled with the acceptable safety and tolerability results, reflected a favourable benefit-risk profile for ozanimod in UC. Ozanimod had at least a non-inferior efficacy and safety profile compared with currently existing treatments in Denmark. These results suggested that ozanimod offers a new mode of action for treatment of moderately to severely active UC and constitutes a safe, once daily, oral alternative to the existing therapies recommended by the DMC. When performing economic analyses with list prices of pharmaceuticals, the economic evidence suggested that ozanimod therapy was more expensive in both bio-naive and bio-experienced patients compared with the respective comparators.

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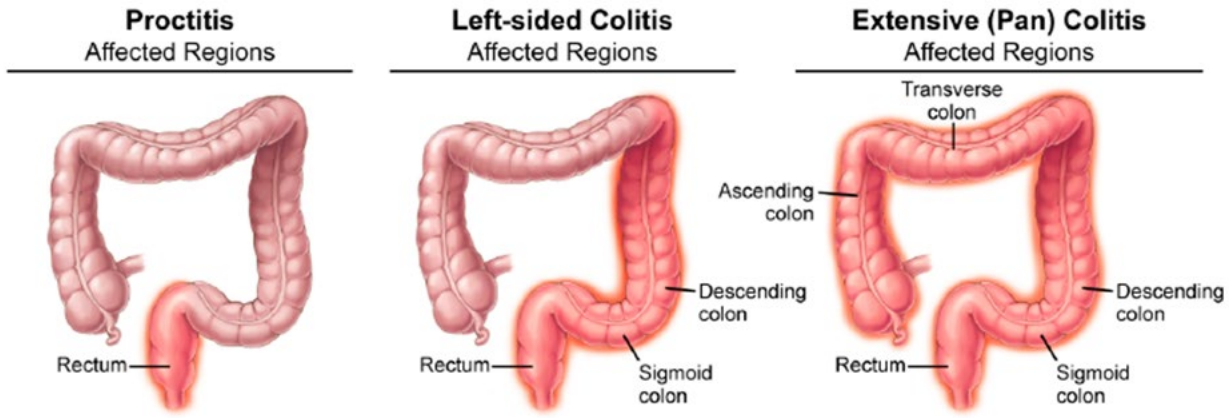
5. The patient population, the intervention, and choice of comparator(s)

5.1. The medical condition and patient population

5.1.1. Disease background

Ulcerative colitis is a disease of unknown aetiology that is characterised by diffuse inflammation of the mucosa and submucosa of the colon and rectum that may cause ulcers to develop.[1,2] In 95% of UC cases, the rectum is involved (proctitis)[1]; however, inflammation can extend continuously to nearby parts of the colon, including the sigmoid colon (proctosigmoiditis), the descending colon (left-sided colitis), or the entire colon (pancolitis) (Figure 1).[18,19]

Figure 1. Disease extent of ulcerative colitis



Source: Kayal and Shah (2019)[19]

Although UC is one of the main inflammatory diseases that affects the bowel, the pathogenesis has yet to be completely defined.[19] A combination of environmental factors, aberrant host immune responses, epithelial barrier defects, and genetic factors all likely contribute to the development of UC.[2,19]

The immune system and immune response are intimately involved in the pathogenesis of UC. As the protective mucosal barrier and epithelium are broken down, microbial products gain access through the intestinal barrier, leading dendritic cells and other antigen-presenting cells to initiate a cascade of proinflammatory and anti-inflammatory signals to activate lymphocytes.[20] However, there is not a balance between proinflammatory and anti-inflammatory signals in patients with UC.[20] The production of proinflammatory cytokines by lymphocytes, including interleukin (IL)-1β, IL-6, tumour necrosis factor α (TNF-α), and TNF-like ligand 1, is universally increased in patients with UC.[20,21] In particular, TNF-α has various proinflammatory functions in UC, including undermining the barrier function of intestinal epithelial cells and promoting angiogenesis.[22] In addition, increased secretion of IL-5 in patients with UC is associated with activation of B cells and induction of immune responses.[20] Ulcerative colitis is also associated with the presence of natural killer cells that produce IL-13, resulting in an increase of IL-13 in the lamina.[20] Taken together, there is an imbalance of increased proinflammatory signals with subsequent migration of lymphocytes to the intestinal mucosa, which results in and is perpetuated by an overstated T-cell response.[20]

Sphingosine 1-phosphate is a bioactive lipid mediator involved in the regulation of several cellular processes through the activation of a G protein–coupled receptor (S1P receptors 1-5 [S1P1-5]). S1P has been identified as a key regulator for lymphocyte migrations from lymph nodes to tissues.[23] In UC, the S1P-S1P1 interaction

allows the movement of lymphocytes from secondary lymphoid tissue to the gastrointestinal (GI) mucosa, thereby leading to inflammation.[23]

Patients with UC experience significant morbidity associated with their disease, with the most bothersome symptoms reported being rectal bleeding (reported by > 90% of patients[24]), rectal urgency, and tenesmus.[5] Extraintestinal manifestations (EIMs), which may also be present at diagnosis and arise independently from the intestinal disease, most often occur in the joints, skin, hepatobiliary tract, and eyes.[25,26] Extraintestinal complications, which differ from EIMs in that they are typically caused by UC involvement in the colon, can involve carcinoma, osteoporosis, and toxic megacolon.[25,27-30] Symptoms also can vary based on disease severity. In moderate-to-severe UC, additional symptoms that may develop include frequent, loose, bloody stools; low blood count (anaemia); and weight loss.[31,32] The symptoms of UC and its associated complications can cause considerable impairment to HRQoL.[3,4] Because of the unpredictable nature of UC symptoms, patients often suffer from anxiety and depression, as well as experiencing social isolation and decreased work productivity.[4,33] Further, increased disease severity is associated with worse HRQoL.[3,4]

Symptoms associated with UC may have multiple potential causes, including non-UC inflammatory bowel disease (IBD) and infection. This makes diagnosis at initial presentation challenging based solely on medical history and clinical evaluation, leading to a potentially delayed diagnosis. Hence, diagnosis should be confirmed by laboratory tests, radiology, endoscopy, histology, and serology.[34] In addition to confirming and accurately diagnosing UC, it is important to define the extent and severity of inflammation, which is important for prognosis and treatment selection.[35] Disease severity is typically classified as remission, mild, moderate, or severe.[36] Currently, clinical decision making is predominantly based on clinical and endoscopic measures.[37] Disease severity assessments commonly used in clinical practice and/or clinical trials are the Mayo Score, Montreal classification, and Simple Clinical Colitis Activity Index (Table 1).[35,36]

Table 1. Select ulcerative colitis disease activity assessment indices

Index name	Score range (remission threshold)	Strengths	Limitations
Clinical indices			
Truelove and Witts Severity Index	Rated based on symptom criteria (no remission threshold)	▪ Objective criteria for acute severe colitis ▪ Useful for prognosis	▪ Not validated, although widely used
Montreal classification	E1-E3 (extent of disease) S0-S3 (severity of disease) (S0)	▪ Classifies UC based on the extent and severity of disease	▪ The dynamic nature of UC as seen by the changes in the distribution and severity of the disease over time
Simple Clinical Colitis Activity Index	0-19 (≤ 2)	▪ Can be completed by patient ▪ Includes important factors such as urgency, incontinence, and nocturnal bowel movements ▪ Reliable, valid, responsive, and feasible	▪ Not validated
Mayo Score (4-Component)	0-12 (≤ 2)	▪ Most widely used ▪ Discriminates remission from active disease	▪ Not validated ▪ Relies on subjective Physician Global Assessment

Index name	Score range (remission threshold)	Strengths	Limitations
3-Component Mayo Score (partial Mayo Score)	0-9 (≤ 1)	▪ Discriminates remission from active disease	▪ Not validated
Endoscopic indices			
Ulcerative Colitis Endoscopic Index of Severity	0-8 (≤ 1)	▪ Validated ▪ Easy to use ▪ High interobserver reproducibility ▪ Accounts for 88% of variation between observers ▪ Now used in clinical trials	▪ No validated definition of mucosal healing or response ▪ Does not consider disease extent ▪ No thresholds for mild, moderate, and severe disease
Mayo Clinic score: endoscopic subscore	0-3 (0)	▪ Easy to use ▪ Commonly used in clinical trials and clinical practice	▪ Overlap of the different levels results in low interobserver agreement ▪ No validated definition of mucosal healing ▪ Subjective terms (minimal or slight friability) reduce concordance ▪ Does not consider disease extent
Histological indices			
Riley Score	0-18	▪ Widely used, simple, predictive value in outcomes in UC	▪ Partially validated; includes items with poor reproducibility
Geboes Score	0.0-5.4 (< 3.1)	▪ Widely used, predictive value in outcomes in UC	▪ Partially validated; includes items with poor reproducibility
Nancy Histological Index	0-4 (0)	▪ Validated, responsive, good intraobserver and interobserver agreement ▪ Reliable, simple, and easy to use	▪ Lacks data on predictive value in outcomes in UC
Robarts Histopathology Index	0-12 (≤ 6)	▪ Validated and responsive (compared with endoscopic and quality of life indices)	▪ Lacks data on predictive value in outcomes in UC
Biomarkers			
C-Reactive protein	0 to > 200 mg/L (≤ 5 mg/L)	▪ Predictive of outcomes in acute severe colitis (Oxford Criteria) ▪ Widely available	▪ Less useful in mild disease ▪ Poor correlation with endoscopic disease activity
Faecal calprotectin	0 to > 1,000 µg/g (< 50 to < 250 µg/g)	▪ Useful for monitoring disease activity in UC (using change in faecal calprotectin)	▪ Wide range of cutoff values for determining active vs. inactive disease

UC = ulcerative colitis.

Sources: Walsh et al. (2016)[38]; Gajendran et al. (2019)[35]

5.1.2. Epidemiology of ulcerative colitis in Denmark

5.1.2.1. Incidence and prevalence

There is considerable variability in the global incidence of UC. A systematic review of population-based studies reported that the highest prevalence of UC worldwide was within Europe (specifically in Norway, at 505 per 100,000).[39] Studies have reported the annual incidence of UC to be up to 24.3 per 100,000 person-years in Europe.[39,40] Through extrapolation of incidence using the population of the European Union (EU), 123,000 new cases of UC per year were estimated to occur annually as of 2012.[41] The presentation of UC is highly variable, owing to its variable rates of relapse and remission. The peak age for clinical presentation of UC is from 15 to 35 years, with a second smaller peak from 55 to 65 years.[42,43]

From 2003-2015, there were 22,144 incident UC cases in Denmark (mean per year, 1,703).[44] The prevalence of UC in Denmark in 2013 was estimated to be 35,200 persons and is among the highest in the world.[6]

Table 2 reports the incidence of UC in Denmark. It was not possible to obtain global or Danish prevalence data over time.

Table 2. Incidence and prevalence of ulcerative colitis in Denmark (2011-2015)

Year	2011	2012	2013	2014	2015
Incidence in Denmark	2,069	1,705	1,591	1,460	1,133
Prevalence in Denmark	NR	NR	35,200	NR	NR

NR = not reported.

Sources: Alulis et al. (2020)[44]; Lophaven et al. (2017)[6]

5.1.2.2. Mortality and survival rates

Patients with UC do not appear to have an overall increased mortality compared with the general population.[35] However, patients with UC have a higher risk of mortality resulting from GI diseases, non-alcoholic liver disease, pulmonary embolisms, and respiratory diseases.[45]

5.1.3. Patient populations relevant for this application

Ozanimod is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis (UC) who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biologic agent.[46] Infliximab, golimumab, and vedolizumab (IV and SC) constituted the best treatment options for bio-naive patients with moderately to severely active UC in the DMC treatment guidance for BTSDs for UC.[7] Adalimumab, infliximab, golimumab, vedolizumab (IV and SC), and ustekinumab were considered the best treatment options for BTSD-experienced patients with moderately to severely active UC.

Approximately 500 bio-naive patients with UC start BTSDs and 300 bio-experienced patients with UC are expected to switch biologic treatments in Denmark per year (Table 3).[7] It is anticipated that up to 800 patients annually could be considered eligible for treatment with ozanimod under the anticipated European Medicines Agency (EMA) label (Table 4).

Table 3. Eligible patient calculations

Population	No. of patients	Calculation	Source
Number of bio-naive patients with UC starting BTSD in Denmark per year	500	DMC professional committee assumption	DMC (2021)[7]
Number of bio-experienced patients with UC who are expected to switch biologic treatments in Denmark per year	300	DMC professional committee assumption	DMC (2021)[7]

BTSD = biological and targeted synthetic drug; DMC = Danish Medicines Council; UC = ulcerative colitis.

Note: Calculation assumes that only patients with moderately to severely active disease will receive treatment with biologicals.

Table 4. Estimated number of patients eligible for treatment in Denmark

Year	Year 1	Year 2	Year 3	Year 4	Year 5
Number of bio-naive patients with UC starting BTSD in Denmark	500	1,000	1,500	2000	2,500
Number of bio-experienced patients with UC who are expected to switch biologic treatments in Denmark	300	600	900	1,200	1,500

BTSD = biological and targeted synthetic drug; UC = ulcerative colitis.

Note: Calculation assumes that only patients with moderately to severely active disease will receive treatment with biologicals.

5.1.4. Age group of population affected and patient group currently eligible for treatment in Denmark

The peak age for clinical presentation of UC is from 15 to 35 years, with a second smaller peak from 55 to 65 years.[42,43] The incidence of UC in Denmark peaks at 25 to 35 years of age.[6]

In the TRUE NORTH induction period, the mean ages in cohort 1 were 41.9 years for the placebo group and 41.4 years for the ozanimod group.[9] For cohort 2 in the induction period, patients treated with ozanimod had a mean age of 42.1 years.[9] In the TRUE NORTH maintenance period, the mean patient age was 43.0 years in the ozanimod/placebo group and 42.4 years in the ozanimod/ozanimod group.[47] Patients eligible for treatment with ozanimod will have received biologics only after not responding adequately to conventional treatment. Additionally, bio-experienced patients will have previously received and subsequently not responded to other biologics. In the induction period, the mean ages at diagnosis in cohort 1 were 35.3 years for the placebo group and 34.6 years for the ozanimod group.[48] For cohort 2 in the induction period, patients treated with ozanimod had a mean age of 34.5 years at diagnosis.[48] Therefore, the TRUE NORTH trial was deemed to reflect the general moderately to severely active UC population.

5.1.5. Subgroup of patients expected to have different efficacy and safety than the entire population

No difference in efficacy or safety in any subgroup of patients is anticipated for treatment with ozanimod when compared with the indicated population of patients with moderately to severely active UC.

At week 10, the TRUE NORTH study demonstrated clinical remission, clinical response, endoscopic improvement, and mucosal healing favouring ozanimod in most subgroups. These results were based on corticosteroid use at screening, prior anti-TNF treatment, moderate UC status at baseline, extent of colitis, age at screening, baseline faecal calprotectin, baseline absolute lymphocyte count (ALC), years since initial UC diagnosis, region of the world, baseline partial Mayo Score, and baseline endoscopy score.[48]

[redacted]

5.2. Current treatment options and choice of comparator(s)

5.2.1. Current treatment options

Treatment for UC is generally divided into induction and maintenance phases. Induction therapy is used to reduce inflammation and provide relief of acute symptoms to induce remission.[49-51] Once in remission, maintenance therapy is used to keep patients in clinical remission.[50]

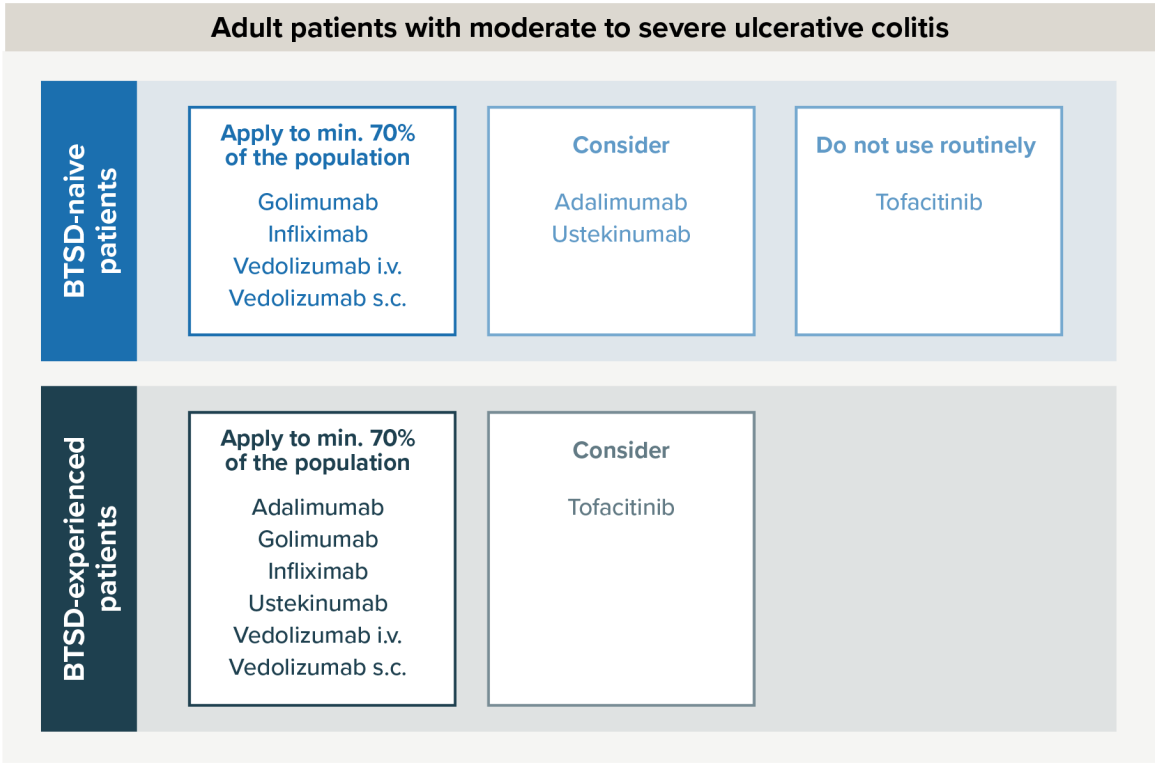
Surgery is also a treatment option for patients with acute severe UC or in those with chronic refractory UC not responding to medical therapy.[7,35,51] Despite available medical treatments, approximately 15% of patients will require surgery.[50] The most common indications for surgery include toxic megacolon, perforation, uncontrollable haemorrhage, multiorgan dysfunction, failing medical therapy (or corticosteroid dependence), cancer, or unresectable dysplasia.[50,51] Per the American College of Gastroenterology, restorative proctocolectomy with ileal pouch–anal anastomosis is currently the surgical procedure of choice for the management of refractory UC; however, complications associated with surgery have been reported in up to 65% of patients.[51]

Specifically in relation to the treatment pathway in Denmark, 5-ASAs are used as first-line treatment for both active disease and as recurrent prophylaxis. In the event of treatment failure, 5-ASAs in combination with corticosteroids are used at the induction stage; 5-ASAs in combination with immunosuppressive therapy (azathioprine or 6-mercaptopurine [6-MP]) are used as maintenance therapy. If 5-ASAs in combination with or without immunosuppressive therapy is unsuccessful and if surgery is not the preferred option, BTSDs are recommended.[7] The DMC treatment guidance for BTSDs for UC was published in 2021.[7] The DMC recommended that infliximab, golimumab, and vedolizumab (IV and SC) constitute the best treatment options for BTSD-naive patients with moderately to severely active UC. These treatments can be considered clinically equivalent and thus possible first choices. Adalimumab and ustekinumab should be considered if it is not possible to use at least 1 of the first choice options. Tofacitinib should not be used routinely in this patient population.

The DMC recommended that adalimumab, infliximab, golimumab, vedolizumab (IV and SC), and ustekinumab are the best treatment options for BTSD-experienced patients with moderately to severely active UC. These can be considered clinically equivalent and thus possible first choices. The expert committee concluded that tofacitinib can be considered in BTSD-experienced patients with moderately to severely active UC if it is not possible to use at least 1 of the first choice options. However, the expert committee emphasised that tofacitinib has a more serious adverse reaction profile than the other medicinal products, as it is associated with an increased risk of blood clots and venous thrombosis.

Figure 2 presents the treatment pathway for UC in Denmark.

Figure 2. Treatment pathway for ulcerative colitis in Denmark



BTSD = biological and targeted synthetic drug; i.v. = intravenous; s.c. = subcutaneous.
Note: The treatments in each group are presented in alphabetical order.
Source: DMC (2021)[7]

5.2.2. Choice of comparator(s)

Infliximab, golimumab, and vedolizumab (IV and SC) constituted the best treatment options for bio-naive patients with moderately to severely active UC in the DMC treatment guidance for BTSDs for UC.[7] Adalimumab, infliximab, golimumab, vedolizumab (IV and SC), and ustekinumab were considered the best treatment options for BTSD-experienced patients with moderately to severely active UC.

Therefore, BMS considers these therapies to be the appropriate comparators for ozanimod, and Appendix I includes summary tables for these comparator products.

5.2.3. Description of the comparators

Adalimumab is indicated for treatment of moderately to severely active UC in adults who have had an inadequate response to conventional therapy, including corticosteroids and 6-MP or azathioprine, or who are intolerant to or have medical contraindications for such therapies.[52]

Golimumab is indicated for the treatment of moderately to severely active UC in adults who have had an inadequate response to conventional therapy, including corticosteroids and 6-MP or azathioprine, or who are intolerant to or have medical contraindications for such therapies.[53]

Infliximab is indicated for the treatment of moderately to severely active UC in adults who have had an inadequate response to conventional therapy, including corticosteroids and 6-MP or azathioprine, or who are intolerant to or have medical contraindications for such therapies.[54]

Ustekinumab is indicated for the treatment of adults with moderately to severely active UC who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a biologic or have medical contraindications to such therapies.[55]

Vedolizumab is indicated for the treatment of adult patients with moderately to severely active UC who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a TNF-α antagonist.[56]

5.3. The intervention

Ozanimod offers a new mode of action for treatment of moderately to severely active UC and constitutes a safe, once daily, oral alternative to the existing therapies recommended by the DMC. Table 5 summarises the use of ozanimod as indicated. Full details of the prescribing information for ozanimod are available from the summary of product characteristics (SmPC) for ozanimod (see Appendix H).

Table 5. Description of ozanimod

Generic name (ATC code)	Ozanimod (L04AA38)
Mode of action	Ozanimod is a S1P receptor modulator that binds selectively to S1P receptor subtypes 1 and 5. Ozanimod causes lymphocyte retention in lymphoid tissues. The mechanism by which ozanimod exerts therapeutic effects in UC is unknown but may involve the reduction of lymphocyte migration into the inflamed intestinal mucosa.
Pharmaceutical form	Hard capsule
Posology	The recommended dose is 0.92 mg ozanimod once daily. The capsules can be taken with or without food. The following initial dose escalation regimen is required: days 1-4: ozanimod 0.23 mg once daily; days 5-7: ozanimod 0.46 mg once daily; days 8 and thereafter: ozanimod 0.92 mg once daily.
Method of administration	Oral use
Dosing	Available in 0.23 mg, 0.46 mg, and 0.92 mg hard capsules[a]
Should the pharmaceutical be administered with other medicines?	No
Treatment duration	Treatment should continue until the patient no longer derives benefit.
Necessary monitoring, both during administration and during the treatment period	▪ Detailed information on the additional tests or investigations required for administration of ozanimod is presented in the SmPC (Appendix H). The healthcare professional checklist includes monitoring requirements for before first dose, until 6 hours after first dose for patients requiring first-dose observation, and for initiating ozanimod in special populations, including those with a history of cardiac arrest, cerebrovascular disease, uncontrolled hypertension, severe untreated sleep apnoea, history of recurrent syncope, or symptomatic bradycardia.
Additional tests or investigations	▪ Detailed information on additional tests or investigations is presented in the SmPC (Appendix H).
Packaging	▪ Treatment initiation pack: pack size of 7 capsules (4 × ozanimod 0.23 mg, 3 × ozanimod 0.46 mg) ▪ Maintenance pack: pack size of 28 hard capsules (ozanimod 0.92 mg)

ATC = Anatomical Therapeutic Chemical Classification System; HCl = hydrochloride; S1P = sphingosine 1-phosphate; SmPC = summary of product characteristics; UC = ulcerative colitis.

[a] The dosing for ozanimod as listed in the SmPC is based on the milligram amount of ozanimod in the oral tablet; however, ozanimod is in salt form as ozanimod HCl. There is dose equivalency between ozanimod HCl (0.25 mg, 0.5 mg, and 1 mg) and ozanimod (0.23 mg, 0.46 mg, and 0.92 mg, respectively). Therefore, it may be referred to as either ozanimod or ozanimod HCl.

Source: Zeposia SmPC (2021)[46]

5.3.1. Ozanimod: mode of action

As described in Section 5.1.1, S1P is a bioactive lipid mediator involved in the regulation of several cellular processes through the activation of a G protein–coupled receptor (S1P receptors 1-5 [S1P1-5]). In UC, the S1P-S1P1 interaction allows the movement of lymphocytes from secondary lymphoid tissue to the GI mucosa, thereby leading to inflammation.[23]

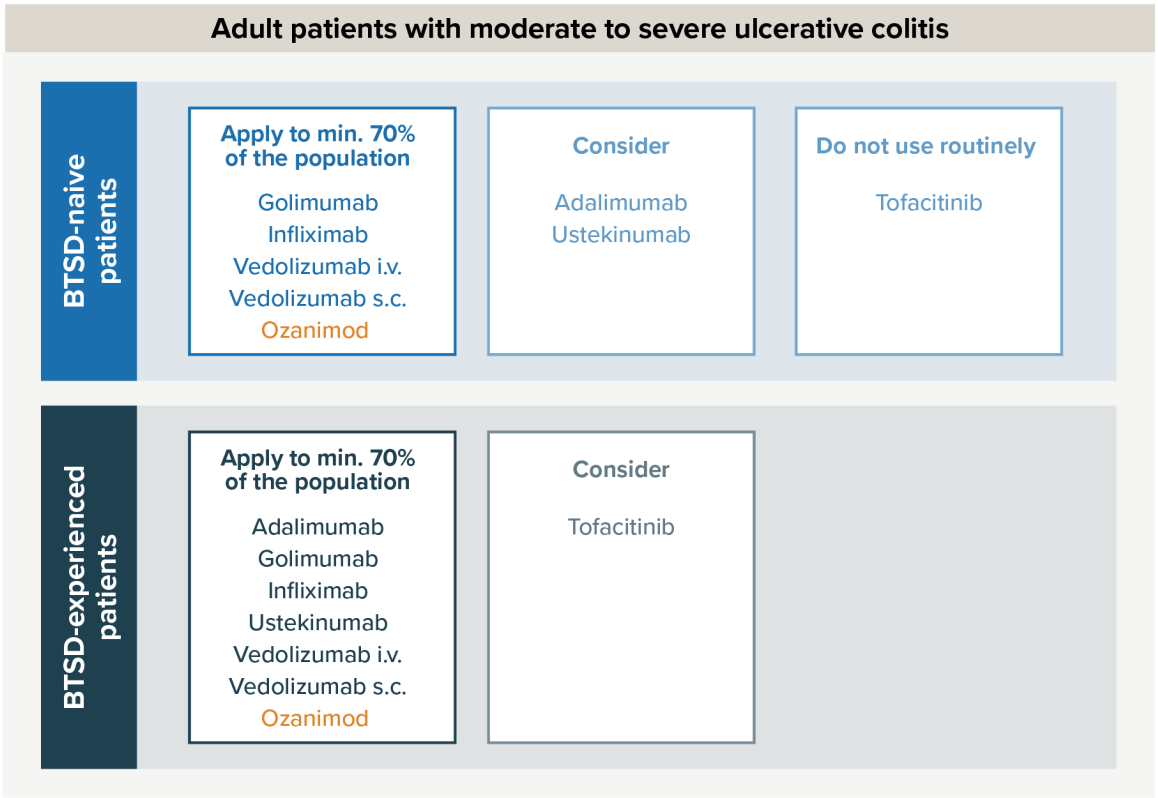
Ozanimod is an S1P receptor modulator that binds selectively to S1P receptor subtypes 1 and 5 and offers a new mode of action for treatment of moderately to severely active UC. Ozanimod causes lymphocyte retention in lymphoid tissues. The mechanism by which ozanimod exerts therapeutic effects in UC is unknown but may involve the reduction of lymphocyte migration into the inflamed intestinal mucosa.[8] Ozanimod showed significant efficacy in models of IBD, suggesting that inhibition of lymphocyte movement via S1P1 receptor engagement may be an effective strategy for treatment in this therapy area.[8]

5.3.2. Ozanimod: position in the treatment pathway

As discussed previously, infliximab, golimumab, and vedolizumab (IV and SC) constitute the best treatment options for bio-naive patients with moderately to severely active UC according to the DMC treatment guidance for BTSDs for UC.[7] Adalimumab, infliximab, golimumab, vedolizumab (IV and SC), and ustekinumab were considered the best treatment options for BTSD-experienced patients with moderately to severely active UC.

Figure 3 presents the current clinical treatment pathway for patients with moderately to severely active UC in Denmark.

Figure 3. Clinical pathway of care for patients with moderately to severely active ulcerative colitis in Denmark



BTSD = biological and targeted synthetic drug; i.v. = intravenous; s.c. = subcutaneous.
Source: DMC (2021)[7]

6. Literature search and identification of efficacy and safety studies

6.1. Identification and selection of relevant studies

A clinical systematic literature review (SLR) was conducted for primary intervention trials (randomised controlled trials [RCTs] and prospective non-RCTs) assessing the efficacy and safety of ozanimod or comparator therapies in patients with moderate-to-severe UC. The SLR was conducted on 21 October 2020. Details of the SLR can be found in Appendix A. The SLR identified 2 key studies that included the intervention in the population relevant to the scope of this submission:

- The phase 3 trial, TRUE NORTH, investigated the safety and efficacy of ozanimod in patients with moderate-to-severe UC.[48]
- The phase 2 trial, TOUCHSTONE, investigated the efficacy and safety of ozanimod in patients with moderate-to-severe UC.[10]

Since the SLR was conducted, results from the TRUE NORTH study have been published[9] along with a corresponding oral presentation.[47] The data cover the same follow-up period of the clinical study report; however, to provide as much publicly available data as possible for this submission, they have been included in this dossier.

A phase 3 trial of ozanimod in Japanese patients (NCT03915769) is ongoing and aims to evaluate the dose response, efficacy and long-term safety of ozanimod 0.46 mg or 0.92 mg in Japanese patients with moderate-to-severe UC.[57]

Hand searching also identified 4 relevant supplementary publications: the OLE of the TOUCHSTONE study,[12] a pooled safety analysis of patients with moderately to severely active UC,[13,14] a pooled safety analysis for patients with relapsing multiple sclerosis (RMS)[58] and a pooled safety analysis to assess the safety of extended ozanimod exposure in participants with RMS and UC combined, these studies were deemed not suitable for inclusion in the NMA and are reported in Table 7.[59] Although MS is not the population of interest for this submission, the study provides useful safety data in a large cohort of patients with more than 2,500 patient-years on-treatment data using the same dosage of ozanimod indicated for UC. The safety results for the pooled safety data in MS[58] are in Appendix E.

6.2. List of relevant studies

– In total, 105 publications reporting on 27 unique trials met our inclusion criteria. A list of all publications selected for inclusion is provided in Table A-5 of Appendix A, and a list of all citations excluded at the full-text stage with reasons for exclusion is provided in Table A-6 of Appendix A. The NMA feasibility assessment identified 22 RCTs for inclusion (see PRISMA[i] diagram in Appendix A). Note that the DMC requested that the submission should be aligned with the drugs that in the Danish Medicines Agency's treatment guidelines for UC have been assessed to be equivalent and are placed in the 'Apply' group for bio-naive and experienced patients (Figure 2). Three studies, Suzuki et al. (2014)[60], VARSITY and ULTRA 1 [61] were originally not included in the NMA as not relevant to the clinical setting in Denmark (because they included only biologic-naïve patients treated with adalimumab). However, DMC requested these studies be included in the analysis of SAE and for TT maintenance efficacy analyses, where they allow vedolizumab to be compared with infliximab. Therefore, an additional PRISMA item has been included to describe

[i] PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

the 25 publications and the 17 RCTs that were included in the actual analyses as a result of only including treatments relevant to Denmark and requested by the DMC; these studies are reported in Table 6. For detailed information about included the studies for ozanimod, please refer to

– Appendix B.

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Table 6. Summary of randomised clinical trials included in the NMA

Inhibitor class	Drug	Author	NCT	Trial name	Phase	Dates of study	Used in comparison with
S1P	Ozanimod	Sandborn 2021 [9]	NCT02435992	TRUE NORTH	3	June 2015 to June 2020	Placebo
		Sandborn 2016[10]	NCT01647516	TOUCHSTONE	2	December 2012 to August 2019	Placebo
TNF	Adalimumab	Reinisch 2011[61]	NCT00385736	ULTRA 1	3	August 2007 to February 2010	Placebo
		Suzuki 2014[60]	NA	NA	2/3	February 2009 to May 2011	Placebo
		Sandborn 2012[62]	NCT00408629	ULTRA 2	3	November 2006 to March 2010	Placebo
		[63]					
	Golimumab	Sandborn 2014[64]	NCT00487539	PURSUIT-SC	2/3	August 2007 to October 2010	Placebo
		Sandborn 2014[65]	NCT00488631	PURSUIT-M	3	September 2007 to February 2015	Placebo
		Hibi 2017[66]	NCT01863771	PURSUIT-J	3	March 2013 to January 2016	Placebo
	Infliximab	Rutgeerts 2005[67]	NCT00036439	ACT 1	3	February 2002 to January 2007	Placebo
		Rutgeerts 2005[67]	NCT00096655	ACT 2	3	May 2002 to August 2007	Placebo
		Jiang 2015[68]	NA	NA	NR	NR	Placebo
		Kobayashi 2016[69]	NA	NA	3	NR	Placebo
α4β7 Integrin	Vedolizumab	Feagan 2013[70]	NCT00783718	GEMINI 1	3	January 2009 to March 2012	Placebo
		Sandborn 2020[71]	NCT02611830	VISIBLE 1	3	December 2015 to August 2018	Placebo with a vedolizumab IV reference arm
		Motoya 2019[72]	NCT02039505	NA	3	February 2014 to June 2018	Placebo
		Sands 2019[63]	NCT02497469	VARSITY	3	July 2015 to January 2019	Adalimumab
IL-12/23	Ustekinumab	Sands 2019[73]	NCT02407236	UNIFI	3	July 2015 to November 2021	Placebo

IL = interleukin; IV = intravenous; NA = not applicable; NCT = National Clinical Trial Number; NR = not reported; S1P = sphingosine-1-phosphate; TNF = tumour necrosis factor.

Table 7. Summary of additional publications identified in hand searching

Inhibitor class	Drug	Author	NCT	Trial name	Phase	Dates of study	Used in comparison with
S1P	Ozanimod	Sandborn 2021[12]	NCT02531126	TOUCHSTONE OLE	3	December 2015 to February 2022	None
	Ozanimod	D'Haens 2021[13]	NA	NA	2-3	NR	Placebo
	Ozanimod	Selmaj 2021[58]	NA	NA	1-3	Data cutoff of 31 January 2019	Pooled phase 3 trial data
	Ozanimod	Danese 2021[59]	NA	NA	2-3	Data cutoff of 30 September 2020	Pooled phase 2 and 3 data

NA = not applicable; NCT = National Clinical Trial Number; NR = not reported; OLE = open-label extension; S1P = sphingosine-1-phosphate.

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7. Efficacy and safety

7.1. Efficacy and safety of ozanimod compared with placebo for moderately to severely active UC

7.1.1. Relevant studies: TRUE NORTH

– TRUE NORTH (NCT02435992) is a randomised, double-blind, placebo-controlled, phase 3 trial that compares ozanimod versus placebo for induction and maintenance therapy in adults with moderate-to-severe UC. Table 8 presents details of the TRUE NORTH methodology; further details on design, endpoints, and statistical analysis are described in Sections 7.1.1.1 and 7.1.1.2. For detailed study characteristics, please refer to

– Appendix B. For baseline characteristics of patients included in each study, refer to Appendix C. For details on statistical testing, refer to Appendix G.

Table 8. TRUE NORTH: summary of trial methodology

Study	TRUE NORTH
Key publications	Sandborn WJ, Feagan BG, D'Haens G, Wolf DC, Jovanovic I, Hanauer SB, et al. Ozanimod as induction and maintenance therapy for ulcerative colitis. N Engl J Med. 2021;385(14):1280-91.
Sample size (n)	1,012
Study design	A phase 3, multicentre, randomised, double-blind, placebo-controlled study
Location	Multicentre: includes 372 active sites in 30 countries in Europe, Asia, Africa, North America, Australasia and South America
Patient population	Patients with moderate-to-severe UC
Intervention(s)	Ozanimod 1 mg once daily during induction and maintenance periods ▪ Cohort 1 - Induction n = 429 ▪ Cohort 2 - Induction n = 367 Maintenance (re-randomised patients) ▪ Ozanimod/ozanimod n = 230
Comparator(s)	Placebo once daily during induction and maintenance periods ▪ Cohort 1 - Induction n = 216 ▪ Cohort 2 - Induction n = not applicable Maintenance (re-randomised patients) ▪ Ozanimod/placebo n = 227
Follow-up period	52 weeks

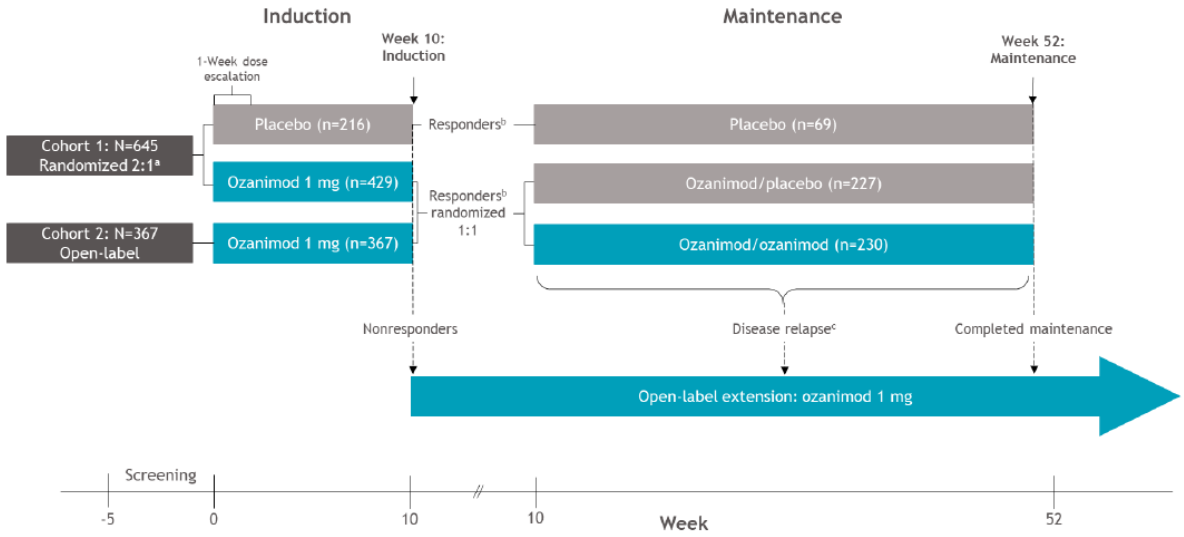
UC = ulcerative colitis.

7.1.1.1. TRUE NORTH: study design

The primary objective of TRUE NORTH was to evaluate the efficacy of daily oral doses of 1 mg of ozanimod compared with matched placebo for induction (week 10) and maintenance (week 52) therapy in adults with moderately to severely active UC.[9]

Figure 4 presents the study design for TRUE NORTH. Patients were eligible to enter a separate OLE study (RPC01-3102) if they completed the induction period but did not have a clinical response at week 10 (cohort 1 or 2), experienced disease relapse during the maintenance period, or completed the maintenance period.[9]

Figure 4. TRUE NORTH: study design



TNF = tumour necrosis factor.

[a] Patients in cohort 1 were stratified by previous anti-TNF treatment and corticosteroid use before randomisation.

Source: Sandborn et al. (2021)[9]

7.1.1.1.1. TRUE NORTH: study treatments

TRUE NORTH was composed of 2 periods: a 10-week induction period followed by a 42-week maintenance period. The 10-week induction period was composed of 2 cohorts[9]:

- Cohort 1: Patients were randomised (2:1) to receive either:
  - Ozanimod hydrochloride (HCl) 1 mg (equivalent to ozanimod 0.92 mg) once daily orally in a double-blind manner
  - Placebo once daily orally in a double-blind manner
- Cohort 2: Patients received ozanimod HCl 1 mg (equivalent to ozanimod 0.92 mg) once daily orally in an open-label manner

Patients in cohort 1 were stratified by corticosteroid use and previous anti-TNF treatment before randomisation.[9] In cohort 1, 30.2% of patients (195 of 645) had prior anti-TNF treatment and 43.3% (159 of 367) in cohort 2 had prior anti-TNF treatment.[9]

All patients initiated study drug with a 7-day dose escalation regimen starting with ozanimod HCl 0.25 mg (equivalent to ozanimod 0.23 mg) or matching placebo (matching placebo for cohort 1 only) on days 1 to 4 and ozanimod HCl 0.5 mg (equivalent to ozanimod 0.46 mg) once daily or matching placebo on days 5 to 7. Starting on day 8, patients received the final dose level of 1 mg once daily ozanimod HCl (equivalent to ozanimod 0.92 mg) or matching placebo for 9 weeks.[9]

Patients from cohort 1 or cohort 2 with a clinical response (by either 3-component or 4-component Mayo Score) at week 10 of the induction period continued on to the maintenance period. Patients who received ozanimod (cohort 1 or cohort 2) and had a clinical response at week 10 of the induction period were re-randomised to receive either ozanimod or matching placebo in a 1:1 ratio in a double-blind manner during the maintenance period.[9] Patients who received placebo (cohort 1) and had a clinical response at week 10 of the induction period continued to receive placebo in the maintenance period in a double-blind manner. Patients who were re-randomised during the maintenance period were stratified by clinical remission status at week 10 and corticosteroid use at week 10.[9]

7.1.1.2. TRUE NORTH: endpoints

Appendix D presents the definitions used for efficacy endpoints for the induction and maintenance periods. Note that for many decades, mucosal healing equated endoscopic healing; the definition of today also includes histological healing and the term used is endoscopic improvement.

7.1.1.2.1. TRUE NORTH: efficacy endpoints during the induction period

The primary efficacy endpoint of the induction period was the proportion of patients in clinical remission assessed by Mayo Score (3-component Mayo Score; all subsequent mentions of clinical remission are based on the 3-component Mayo Score unless otherwise specified) at week 10.[9]

Hierarchically ranked key secondary efficacy endpoints of the induction period were as follows[9]:

- Proportion of patients with a clinical response at week 10
- Proportion of patients with endoscopic improvement at week 10
- Proportion of patients with mucosal healing at week 10

Other secondary efficacy endpoints of the induction period for cohort 1 were as follows[9]:

- Changes from baseline to week 10 in 3-component Mayo Score, 4-component Mayo Score, and partial Mayo Score (the sum of the Rectal Bleeding sub score, Stool Frequency sub score, and the Physician Global Assessment sub score)
- Proportion of patients with histologic remission at week 10
- Proportion of patients in clinical remission (4-component Mayo Score) at week 10
- Proportion of patients with a clinical response (4-component Mayo Score) at week 10
- Proportion of patients with clinical response, clinical remission, or endoscopic improvement at week 10 in patients who previously received anti-TNF therapy
- Changes from baseline to week 10 in the SF-36 Health Survey (SF-36) and the EQ-5D-5L
- Work productivity at week 10

7.1.1.2.2. TRUE NORTH: efficacy endpoints during the maintenance period

The primary efficacy endpoint of the maintenance period was the proportion of patients in clinical remission assessed by Mayo Score (3-component Mayo Score; all subsequent mentions of clinical remission are based on the 3-component Mayo Score unless otherwise specified) at week 52.[9]

Hierarchically ranked key secondary efficacy endpoints of the maintenance period were as follows[9]:

- Proportion of patients with a clinical response at week 52
- Proportion of patients with endoscopic improvement at week 52
- Proportion of patients with maintenance of remission (clinical remission at week 52 among patients in remission at week 10)
- Proportion of patients with corticosteroid-free remission (clinical remission at week 52 after ≥ 12 weeks without corticosteroids)
- Proportion of patients with mucosal healing at week 52
- Proportion of patients with durable clinical remission (remission at weeks 10 and 52 among patients entering maintenance period)

Other secondary efficacy endpoints of the maintenance period were as follows[9]:

- Changes from baseline to week 52 in 3-component Mayo Score, 4-component Mayo Score, and partial Mayo Score
- Proportion of patients with histologic remission at week 52
- Proportion of patients in clinical remission (4-component Mayo Score) at week 52
- Proportion of patients with a clinical response (4-component Mayo Score) at week 52
- Proportion of patients with clinical response, clinical remission, or endoscopic improvement at 52 weeks in patients who previously received anti-TNF therapy
- Proportion of patients in clinical remission at 52 weeks while off corticosteroids for any length of time
- Changes from baseline to week 52 in the SF-36 and the EQ-5D-5L
- Health resource utilisation at weeks 28, 40, and 52
- Work productivity at weeks 28, 40, and 52

7.1.1.2.3. TRUE NORTH: safety endpoints

Safety and tolerability of ozanimod during the induction and maintenance periods (weeks 10 and 52, respectively) were assessed in terms of incidence, severity, and relationship to study drug of TEAEs, serious AEs (SAEs), TEAEs leading to discontinuation of study drug, and TEAEs of special interest.[9]

7.1.2. TRUE NORTH: efficacy and safety

In the maintenance period of TRUE NORTH, data from patients who were re-randomised (double-blind ozanimod or placebo) after treatment with ozanimod in the induction period are presented in this submission for efficacy and safety endpoints. Patients who received placebo during both study periods received a different treatment in

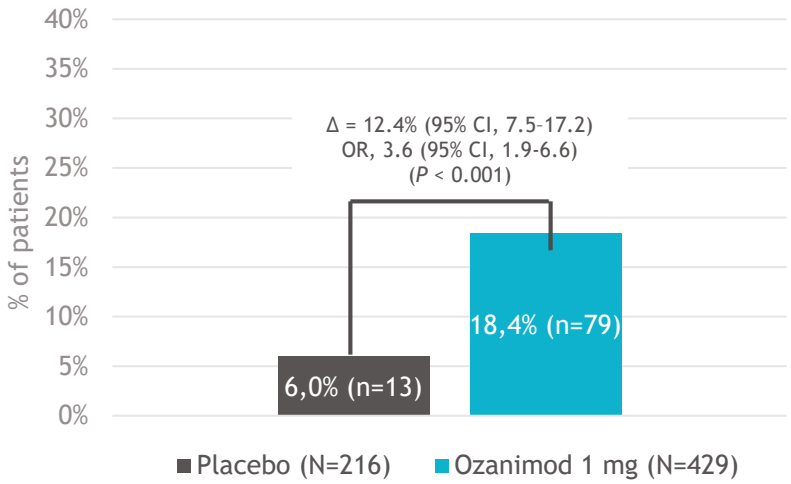
the induction period than patients who were re-randomised; therefore, maintenance period data from patients who received placebo during both study periods are not presented in this submission. The 2-sided $P < 0.05$ values calculated in the efficacy analyses were deemed nominally significant because no multiplicity adjustment was applied.

7.1.2.1. TRUE NORTH: efficacy endpoints during the induction period

7.1.2.1.1. TRUE NORTH: primary efficacy endpoint during the induction period

At week 10, a statistically significantly greater proportion of patients achieved clinical remission (3-component Mayo Score) in the ozanimod arm compared with the placebo arm (18.4% vs. 6.0%; 95% confidence interval [CI], 7.5%-17.2%; $P < 0.001$) (Figure 5).[9]

Figure 5. TRUE NORTH: clinical remission at week 10 - induction period (ITT Population, Non-Responder Imputation)

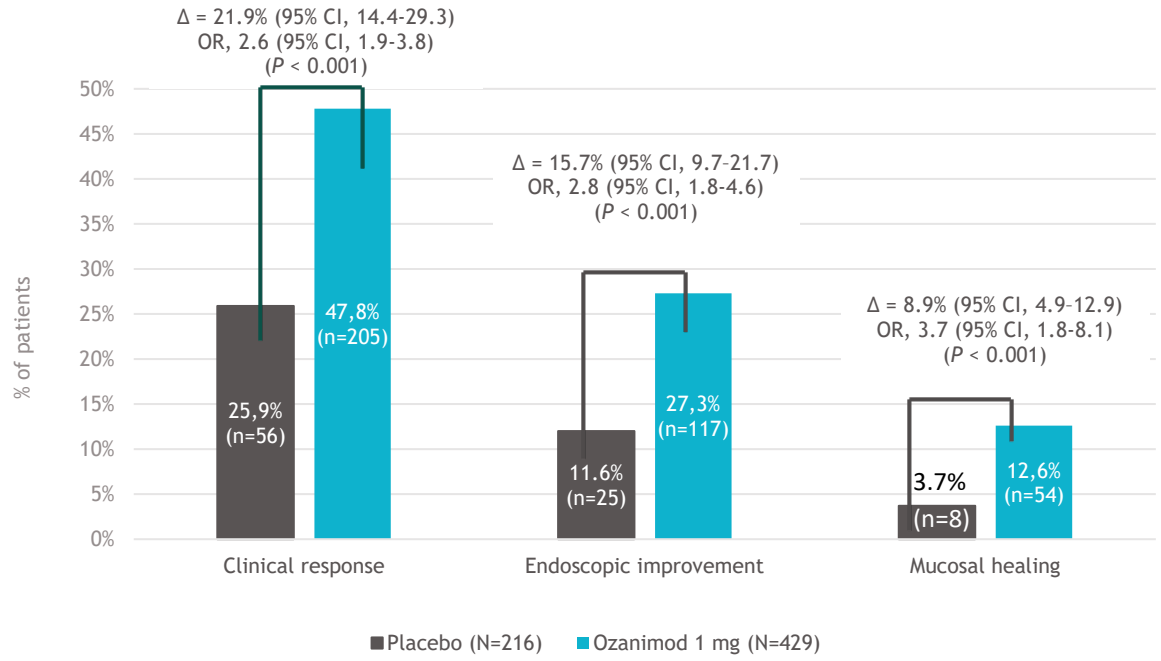


CI = confidence interval; ITT = intent-to-treat; OR = odds ratio.
Source: Sandborn et al. (2021)[9]

7.1.2.1.2. TRUE NORTH: secondary efficacy endpoints during the induction period

At week 10, each of the key secondary efficacy endpoints (clinical response, endoscopic improvement, and mucosal healing) were achieved by statistically significantly greater proportions of patients in the ozanimod arm versus the placebo arm (each $P < 0.001$) (Figure 6).[9]

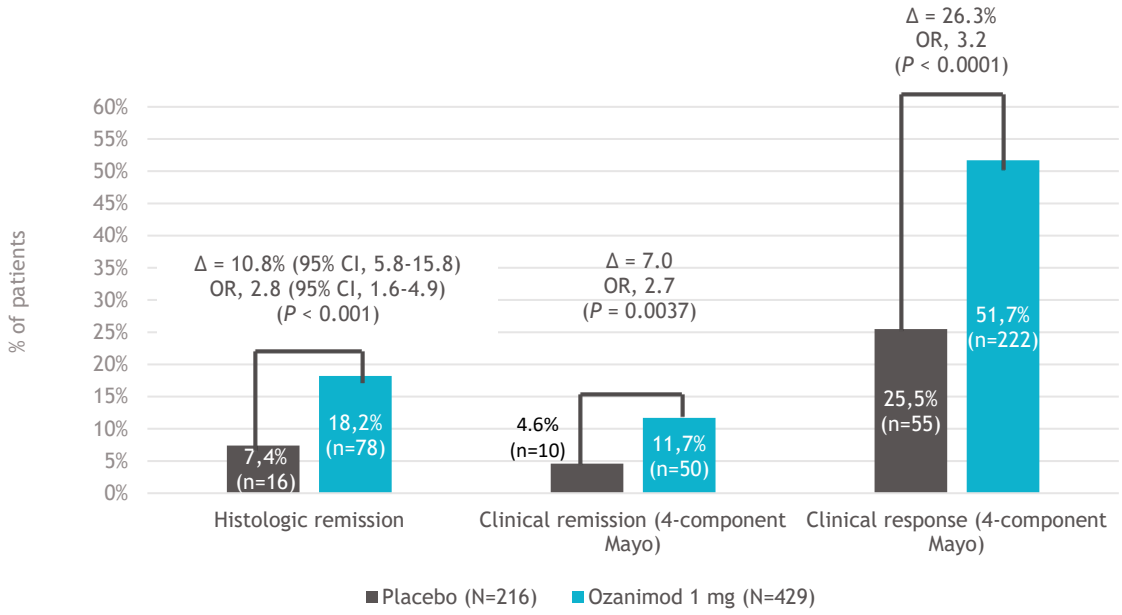
Figure 6. **TRUE NORTH: key secondary endpoints at week 10 —induction period (ITT Population, Non-Responder Imputation)**



CI = confidence interval; OR = odds ratio.
Sources: Sandborn et al. (2021)[9]

Other secondary efficacy endpoints included histologic remission, clinical remission (4-component Mayo), and clinical response (4-component Mayo) (Figure 7). Histologic remission (Geboes index score < 2.0) was achieved in 18.2% (n = 78) of patients in the ozanimod arm and 7.4% (n = 16) in the placebo arm, resulting in a 10.8% (95% CI, 5.8%-15.8%; *P* < 0.001) difference.[9] Clinical remission (4-component Mayo) and clinical response (4-component Mayo) were achieved by greater proportions of patients in the ozanimod arm versus the placebo arm (Figure 7) (see Appendix D, for further analysis).[48]

Figure 7. **TRUE NORTH: other efficacy endpoints at week 10 —induction period (ITT Population, Non-Responder Imputation)**

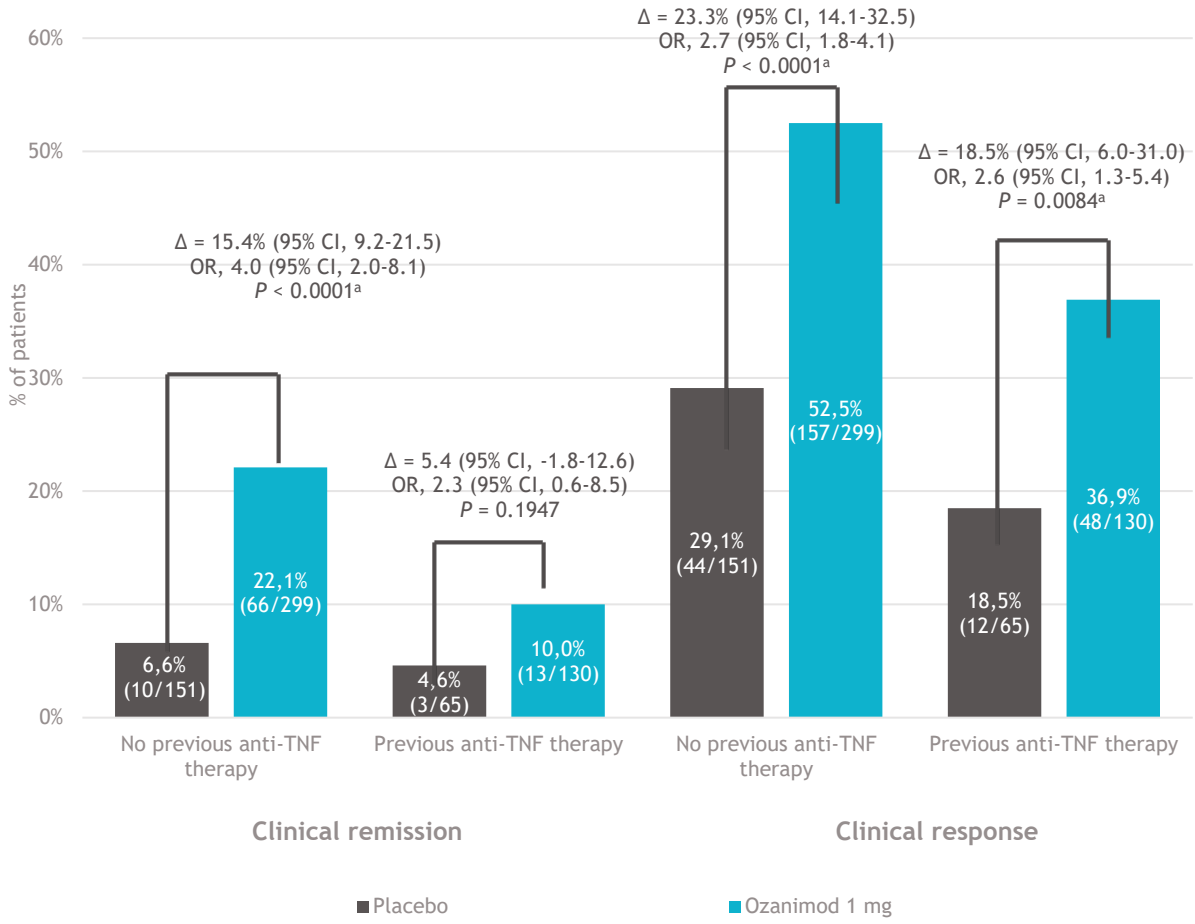


CI = confidence interval; OR = odds ratio.
Sources: Sandborn et al. (2021)[9]; BMS data on file (2020)[48]

7.1.2.1.3. TRUE NORTH: subgroup analyses—prior anti-TNF exposure during the induction period

More patients with no previous anti-TNF therapy achieved clinical remission with ozanimod than placebo at week 10 (nominally significant results: 22.1% vs. 6.6%; nominal $P < 0.001$). In patients with previous anti-TNF therapy, clinical remission favoured ozanimod but did not achieve nominal significance. Clinical response at week 10 was achieved by more patients on ozanimod regardless of previous anti-TNF therapy status (nominally significant results) (Figure 8).[47] Patients with no previous anti-TNF therapy demonstrated nominally significantly greater mucosal healing and endoscopic improvement (nominal $P < 0.001$). In patients with previous anti-TNF therapy, although more patients treated with ozanimod achieved these endpoints over placebo, the difference did not achieve nominal significance.[47] Please see Appendix D, for additional clinical endpoints and the forest plots of the subgroup analyses for other secondary endpoints at week 10.

Figure 8. **TRUE NORTH: previous anti-TNF exposure subgroup analyses for efficacy endpoints at 10 weeks — induction period (ITT Population, Non-Responder Imputation)**



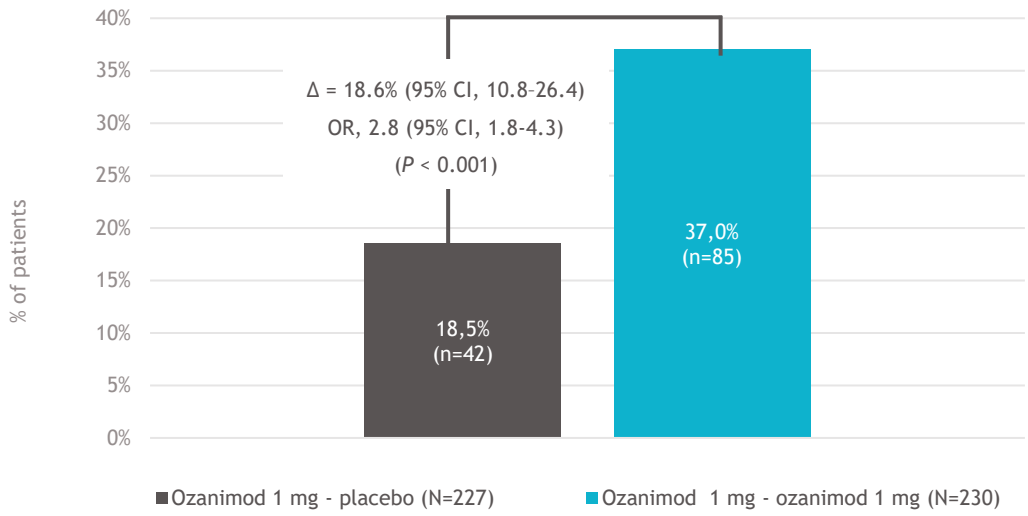
CI = confidence interval; HCl = hydrochloride; OR = odds ratio; TNF = tumour necrosis factor.
[a] $P < 0.05$ is considered nominally significant because no multiplicity adjustment was applied.
Source: Sandborn et al. (2020)[47], BMS data on file (2020)[48]

7.1.2.2. TRUE NORTH: efficacy during the maintenance period

7.1.2.2.1. TRUE NORTH: primary efficacy endpoint during the maintenance period

At week 52, a statistically significantly greater proportion of patients achieved clinical remission (3-component Mayo Score) in the ozanimod 1 mg/ozanimod 1 mg arm (hereafter referred to as the *ozanimod/ozanimod arm*) compared with the ozanimod 1 mg/placebo arm (hereafter referred to as the *ozanimod/placebo arm*) (37.0% vs. 18.5%; $P < 0.001$) (Figure 9).[9]

Figure 9. **TRUE NORTH: clinical remission at week 52 - maintenance period (ITT Population, Non-Responder Imputation)**

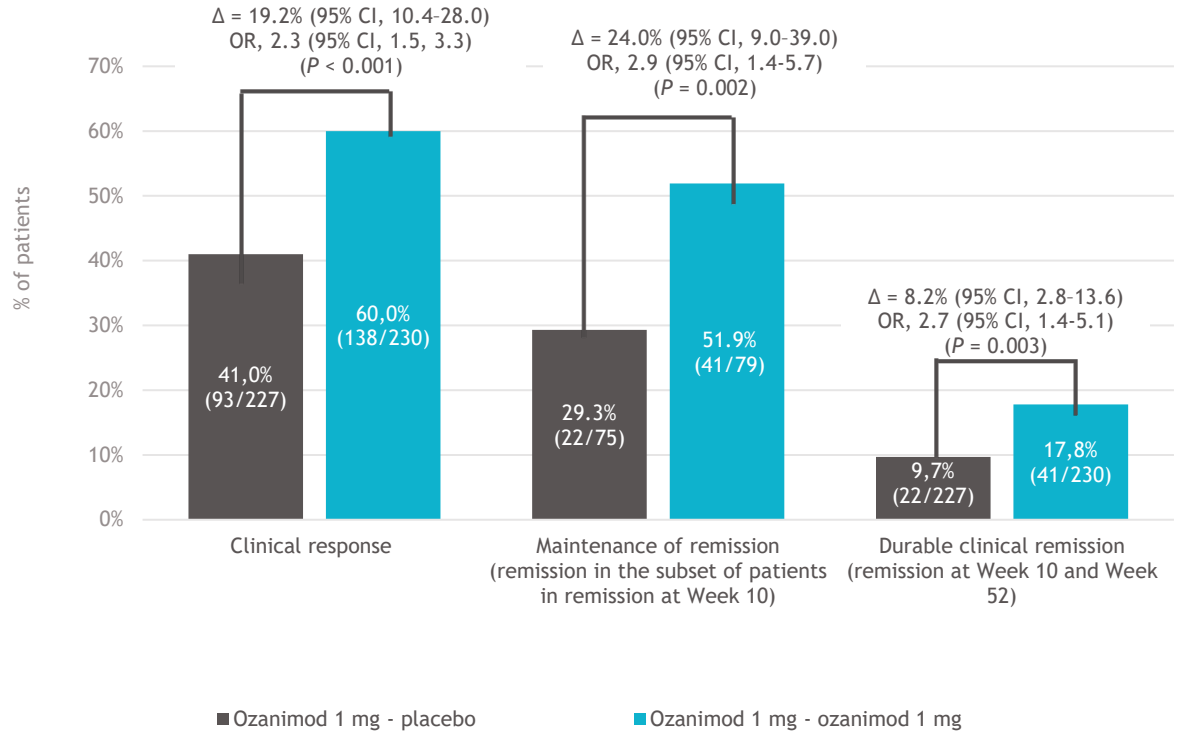


CI = confidence interval; OR = odds ratio.
Source: Sandborn et al. (2021)[9]

7.1.2.2.2. TRUE NORTH: secondary efficacy endpoints during the maintenance period

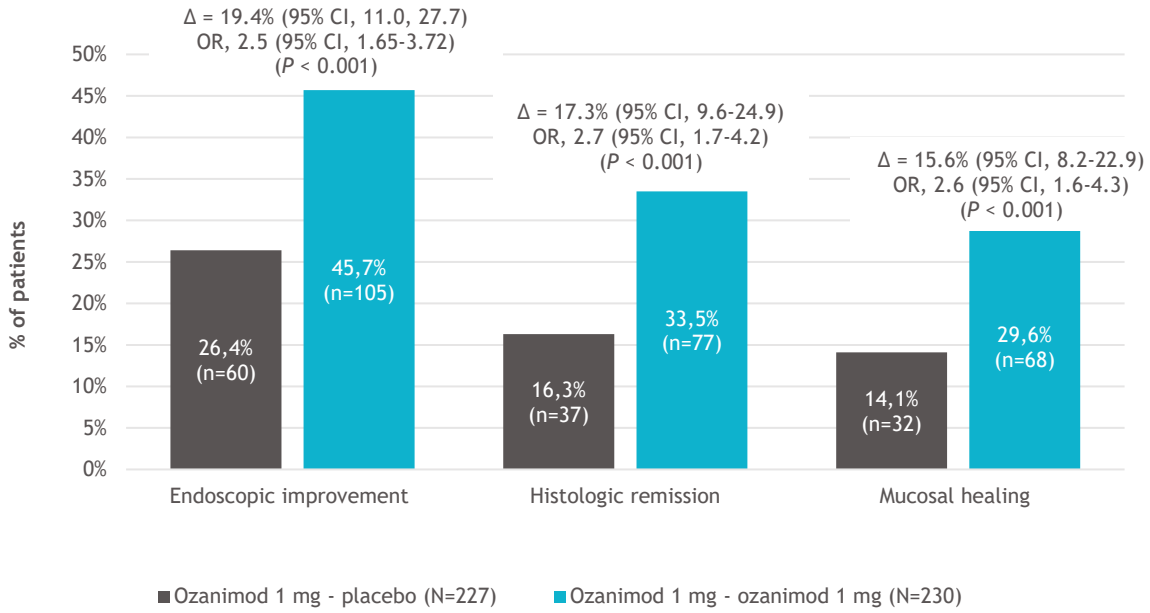
At week 52, each of the key secondary efficacy endpoints (clinical response, endoscopic improvement, maintenance of remission, corticosteroid-free remission, mucosal healing, and durable clinical remission) were achieved by a statistically significantly greater proportions of patients in the ozanimod/ozanimod arm versus the ozanimod/placebo arm (each $P < 0.01$). Of particular importance, ozanimod-treated patients in clinical response at week 10 who were re-randomised to placebo had a lower response rate at week 52; patients re-randomised to continue ozanimod were 2 times more likely to still be in response at week 52 (60.0% vs. 41.0% for ozanimod/ozanimod vs. ozanimod/placebo; odds ratio, 2.3; $P < 0.001$) (Figure 10).[9]

Figure 10. **TRUE NORTH: clinical response, maintenance of remission, and durable clinical remission at week 52 (ITT Population, Non-Responder Imputation)**



CI = confidence interval; OR = odds ratio.
Source: Sandborn et al. (2021)[9]

Figure 11. **TRUE NORTH: endoscopic improvement, histologic remission, and mucosal healing at week 52 (ITT Population, Non-Responder Imputation)**



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CI = confidence interval; OR = odds ratio.
Source: Sandborn et al. (2021)[9]

Corticosteroid-free remission was defined as clinical remission at 52 weeks while off corticosteroids for ≥ 12 weeks, which is considered a clinically meaningful period given that relapse within 12 weeks after discontinuation of corticosteroids is a defining characteristic of patients with steroid-dependent UC.[9] Table 9 reports the proportion of patients with corticosteroid-free remission (3-component Mayo definition using 7-day scoring algorithm) at week 52 of total treatment for the intention to treat (ITT) population using the non-responder imputation. Non-responder imputation was used to handle missing values for the primary analyses as well as for the analyses of all secondary efficacy endpoints that were proportions. Patients with missing week 10 efficacy data for the induction period and/or patients with missing week 52 efficacy data for the maintenance period were classified as non-responders. In addition, patients meeting criteria for treatment failure were considered non-responders using non-responder imputation for efficacy analyses (please see Appendix G, section G.1.3 for further details).[48] Non-response was imputed for [redacted] patients who received placebo, [redacted] patients in the ozanimod 1 mg/placebo arm, and [redacted] patients in the ozanimod 1 mg/ozanimod 1 mg arm.[74] A statistically significantly higher proportion of patients re-randomised to ozanimod (31.7%) had corticosteroid-free remission compared with patients re-randomised to placebo (16.7%) at week 52 of the maintenance period (Table 9).[9] Among patients continuously treated with placebo, 24.6% had corticosteroid-free remission at week 52.[48]

Table 9. **TRUE NORTH: proportion of patients with corticosteroid-free remission (3-component Mayo definition using 7-day scoring algorithm) at week 52 of total treatment—maintenance period (ITT population, non-responder imputation)**

		Re-randomised patients	
	Placebo (n = 69)	Ozanimod 1 mg/ placebo (n = 227)	Ozanimod 1 mg/ ozanimod 1 mg (n = 230)
Patients in corticosteroid-free remission, n (%)[a]	17 (24.6)	38 (16.7)	73 (31.7)
Odds ratio (95% CI)[b]	—	2.557 (1.598-4.093)	
Difference in proportions (95% CI)[b]	—	15.2% (7.8-22.6)	
P value[b]	—	< 0.001	

CI = confidence interval; CMH = Cochran-Mantel-Haenszel; ITT = intention to treat; RBS = rectal bleeding score; SFS = stool frequency subscore.

Note: Patients with any of RBS, SFS, and endoscopy subscores missing at week 52 are classified as non-remitters.

[a] Corticosteroid-free remission is defined as clinical remission (defined as RBS = 0 point and SFS ≤ 1 point[and a decrease of ≥ 1 point from the Baseline SFS] and Endoscopy subscore ≤ 1 point) at 52 weeks while off corticosteroids for ≥ 12 weeks.

[b] Odds ratio (active/placebo), treatment difference, 2-sided 95% Wald CI, and *P* value for comparison between the ozanimod 1 mg/ozanimod 1 mg and ozanimod 1 mg/placebo groups are based on the CMH test, stratified by remission status at week 10 (yes or no) and corticosteroid use at week 10 (yes or no).

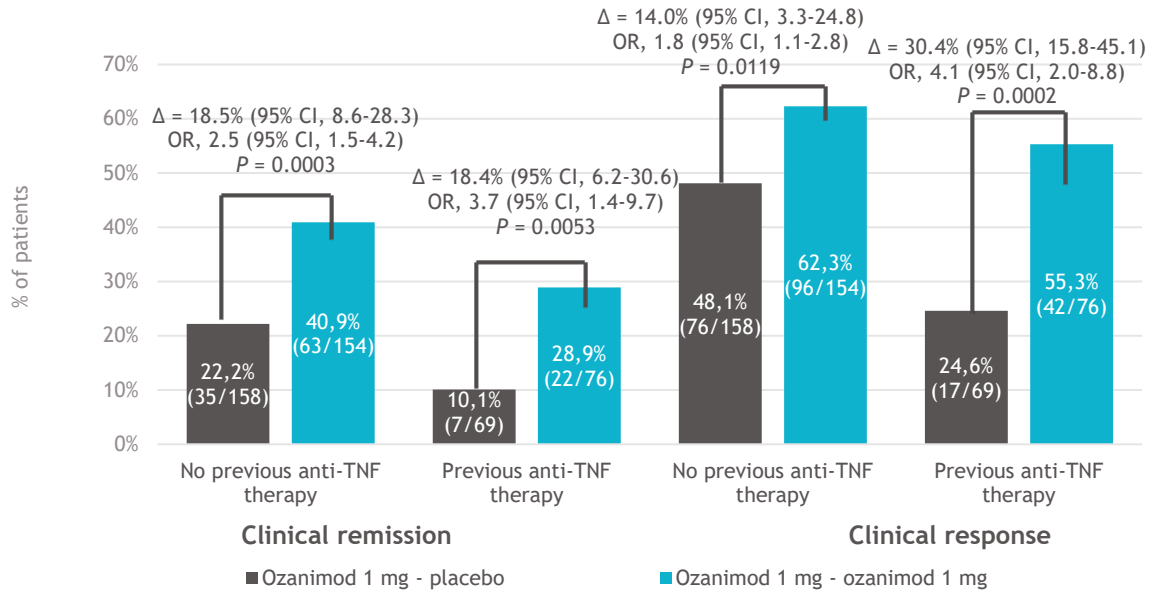
Sources: BMS data on file (2020)[48]; Sandborn et al. (2021)[9]

At week 52, other secondary efficacy endpoints (clinical remission [4-component Mayo Score], clinical response [4-component Mayo Score], and clinical remission at 52 weeks while off corticosteroids for any length of time) were achieved by greater proportions of patients in the ozanimod/ozanimod arm versus the ozanimod/placebo arm (each nominal $P < 0.001$) (see Appendix D for further analysis).[48]

7.1.2.2.3. TRUE NORTH: subgroup analyses—prior anti-TNF exposure during the maintenance period

Higher percentages of patients achieved clinical remission and clinical response at week 52 in the ozanimod/ozanimod arm versus the ozanimod/placebo arm regardless of previous anti-TNF therapy status (nominally significant $P < 0.05$ for each comparison) (Figure 12). Furthermore, more patients in the ozanimod/ozanimod arm versus the ozanimod/placebo arm achieved endoscopic improvement, corticosteroid-free remission, and mucosal healing (nominally significant results; see Appendix D, for additional clinical endpoints).[47]

Figure 12. **TRUE NORTH: previous anti-TNF exposure subgroup analyses efficacy endpoints at 52 weeks — maintenance period (ITT Population, Nonresponder Imputation)**



CI = confidence interval; OR = odds ratio; TNF = tumour necrosis factor.
Source: Sandborn et al. (2020)[47]

7.1.2.3. TRUE NORTH: health-related quality of life

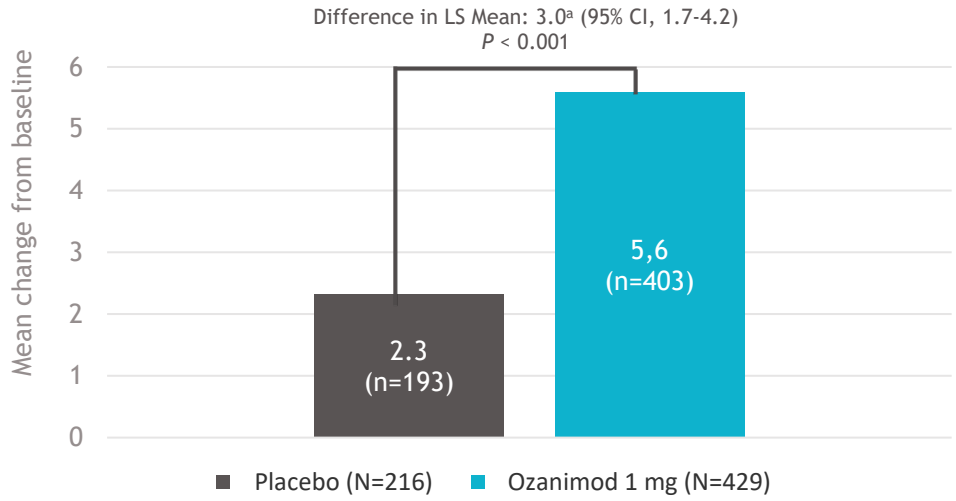
The HRQoL endpoints for the TRUE NORTH trial consisted of change in the SF-36 and EQ-5D-5L from baseline to week 10 (induction) and week 52 (maintenance) for the ITT population. For both the induction and maintenance periods, the minimal clinically important difference (MCID) for the SF-36 Physical Component Summary (PCS) and Mental Component Summary (MCS) scores was defined as a ≥ 5-point improvement in each summary score.

7.1.2.3.1. TRUE NORTH: health-related quality of life during induction

7.1.2.3.1.1. SF-36

SF-36 scores generally improved for patients in the ozanimod and placebo arms during the induction period. The SF-36 PCS is composed of 4 scales assessing physical function, role limitations caused by physical problems, bodily pain, and general health. The mean change from baseline for the SF-36 PCS score represented a significantly greater benefit for those treated with ozanimod 1 mg versus placebo at week 10 ($P < 0.001$) (Figure 13).

Figure 13. **TRUE NORTH: mean change from baseline in SF-36 Physical Component Summary score at week 10 (ITT Population, Observed Cases)**



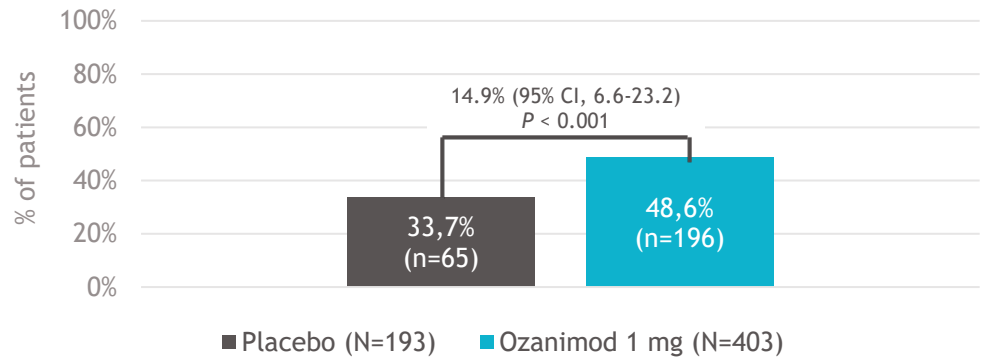
CI = confidence interval; LS = least-squares; SF-36 = SF-36 Health Survey; TNF = tumour necrosis factor.

[a] Based on analysis of covariance for change from baseline adjusted for corticosteroid use at Screening (yes or no), prior anti-TNF use (yes or no), and the Baseline SF-36 summary score.

Source: BMS data on file (2020)[15]; BMS data on file (2020)[74]

At week 10, a higher proportion of patients in the ozanimod 1 mg arm had nominally significant improvements in SF-36 PCS scores (defined as percentage of patients with ≥ 5-point improvement) relative to the proportion of patients with improvements in the placebo arm (48.6% vs. 33.7%, respectively; nominal $P < 0.001$) (Figure 14).

Figure 14. **TRUE NORTH: minimal clinically important difference for SF-36 Physical Component Summary score at week 10 (ITT Population, Observed Cases)**



CI = confidence interval; MCID = minimal clinically important difference; PCS = physical component summary; SF-36 = SF-36 Health Survey.

Note: MCID for SF-36 PCS scores was defined as a ≥ 5-point improvement. Post hoc analysis.

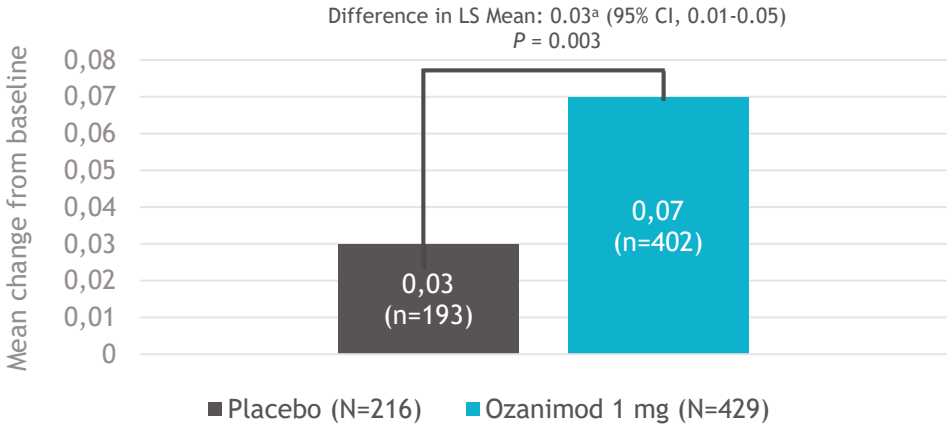
Source: BMS data on file (2020)[48]

7.1.2.3.1.2. EQ-5D-5L

The EQ-5D-5L is composed of 5 dimensions (Mobility, Self-care, Usual Activities, Pain/Discomfort, Anxiety/Depression), each of which has 5 severity levels. The mean change from baseline to week 10 in the EQ-5D

Index score for ozanimod 1 mg was statistically significantly greater than the mean change from baseline for placebo (nominal *P* = 0.003) (Figure 15).

Figure 15. TRUE NORTH: mean change from baseline in EQ-5D at week 10 (ITT Population, Observed Cases)



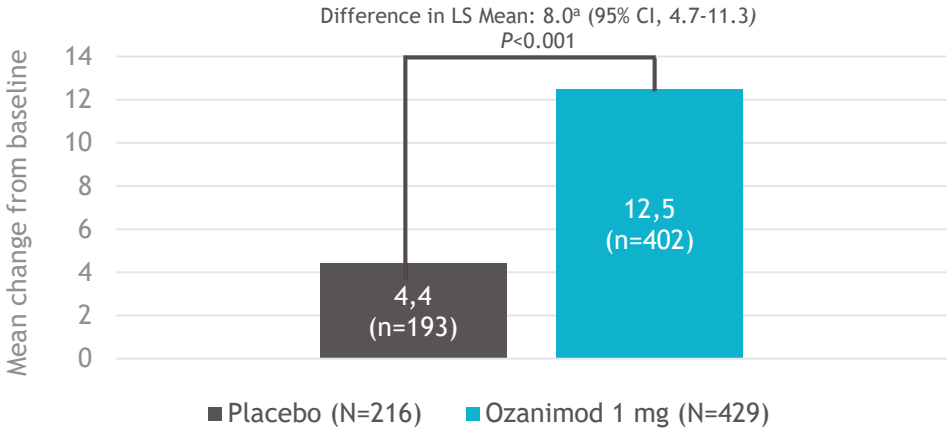
CI = confidence interval; LS = least-squares; TNF = tumour necrosis factor.

[a] Based on analysis of covariance for change from baseline adjusted for corticosteroid use at Screening (yes or no), prior anti-TNF use (yes or no), and the Baseline EQ-5D summary index.

Source: BMS data on file (2020)[15]; BMS data on file (2020)[74]

The EQ-5D self-reported questionnaire includes a visual analogue scale (VAS), which records the respondent's self-rated health status on a graduated (0-100) scale. The mean change from baseline in the EQ-5D VAS score for ozanimod 1 mg was statistically significantly greater (better) than the mean change from baseline for placebo (nominal *P* < 0.001) (Figure 16).

Figure 16. TRUE NORTH: mean change from baseline in EQ-5D visual analogue scale score at week 10 (ITT Population, Observed Cases)



CI = confidence interval; LS = least-squares; TNF = tumour necrosis factor.

[a] Based on analysis of covariance for change from baseline adjusted for corticosteroid use at Screening (yes or no), prior anti-TNF use (yes or no), and the Baseline EQ-5D visual analogue scale.

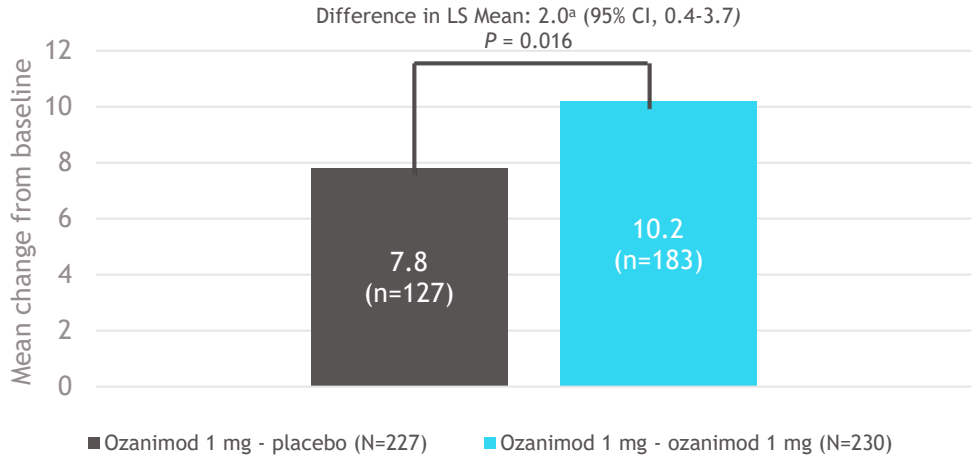
Source: BMS data on file (2020)[15]; BMS data on file (2020)[74]

7.1.2.3.2. TRUE NORTH: health-related quality of life during the maintenance period

7.1.2.3.2.1. SF-36

SF-36 scores generally improved for patients in the ozanimod/ozanimod and ozanimod/placebo arms during the maintenance period. At week 52, patients in the ozanimod/ozanimod arm had nominally significant improvements in SF-36 PCS scores (nominal *P* = 0.016) relative to patients in the ozanimod/placebo arm (Figure 17).

Figure 17. TRUE NORTH: mean change from baseline in SF-36 Physical Component Summary score at week 52 (ITT Population, Observed Cases)



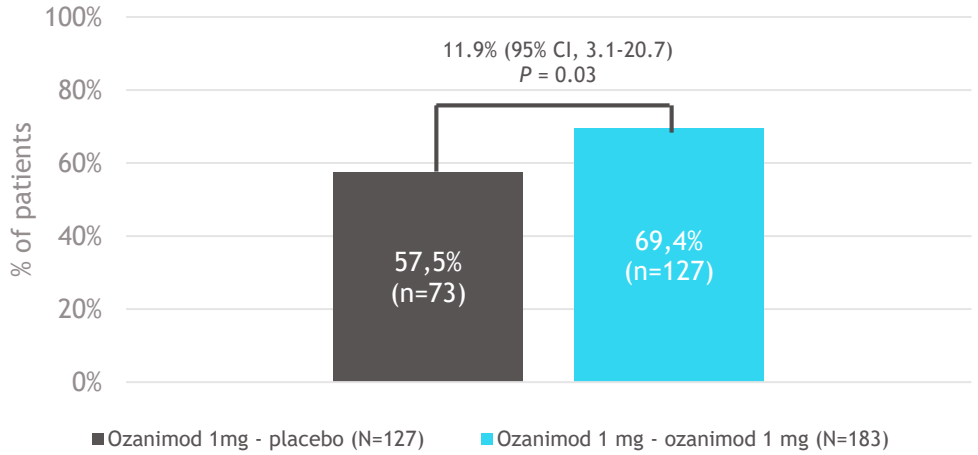
CI = confidence interval; LS = least-squares; SF-36 = SF-36 Health Survey.

[a] Based on analysis of covariance for change from baseline adjusted for remission status at Week 10 (yes or no), corticosteroid use at Week 10 (yes or no), and the Baseline SF-36 summary score.

Source: BMS data on file (2020)[16]; BMS data on file (2020)[74]

At week 52 from baseline, a greater proportion of patients achieved an MCID (defined as a ≥ 5-point improvement) in the SF-36 PCS in the ozanimod/ozanimod arm versus the ozanimod/placebo arm (nominally significant results: 69.4% vs. 57.5%, respectively; nominal *P* = 0.03) (Figure 18).

Figure 18. TRUE NORTH: minimal clinically important difference for SF-36 Physical Component Summary score at week 52 (ITT Population, Observed Cases)



CI = confidence interval; MCID = minimal clinically important difference; PCS = physical component summary; SF-36 = SF-36 Health Survey.

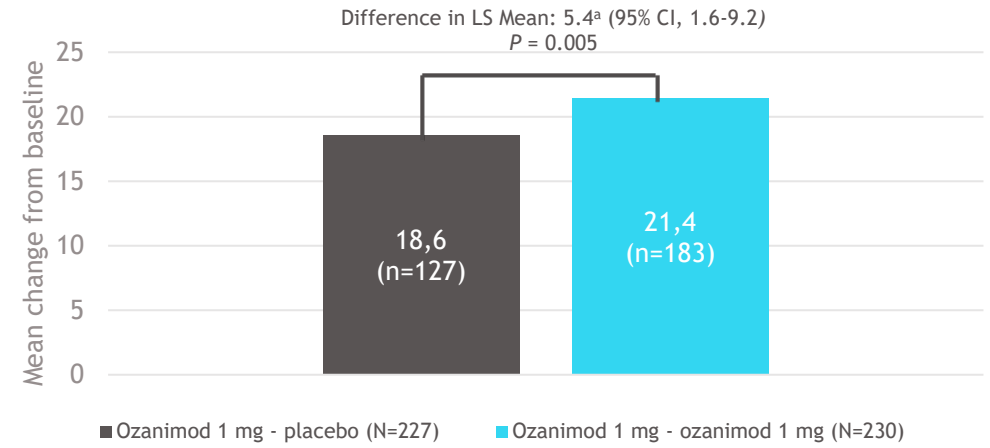
Note: MCID for SF-36 PCS scores was defined as a ≥ 5-point improvement. Post hoc analysis.

Source: BMS data on file (2020)[48]

7.1.2.3.2.2. EQ-5D-5L

Patients in the ozanimod/ozanimod arm had nominally significant improvements in the EQ-5D VAS at week 52 from baseline (nominal *P* = 0.005) (Figure 19) but not in the EQ-5D Summary Index (nominal *P* = 0.472) (Figure 20), relative to patients in the ozanimod/placebo arm.[48]

Figure 19. TRUE NORTH: mean change from baseline in EQ-5D visual analogue scale at week 52 (ITT Population, Observed Cases)

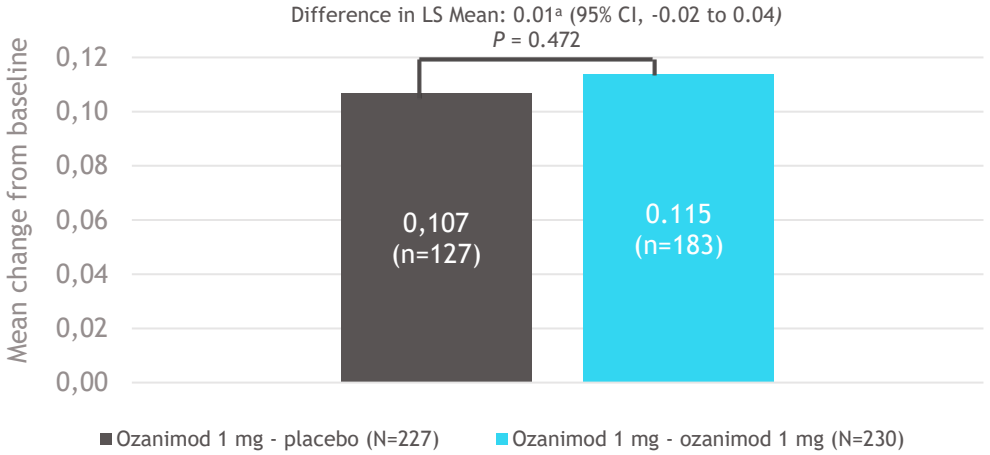


CI = confidence interval; LS = least-squares.

[a] Based on analysis of covariance for change from baseline adjusted for remission status at Week 10 (yes or no), corticosteroid use at Week 10 (yes or no), and the Baseline EQ-5D visual analogue scale.

Source: BMS data on file (2020)[16]

Figure 20. TRUE NORTH: mean change from baseline in EQ-5D Summary Index at week 52 (ITT Population, Observed Cases)



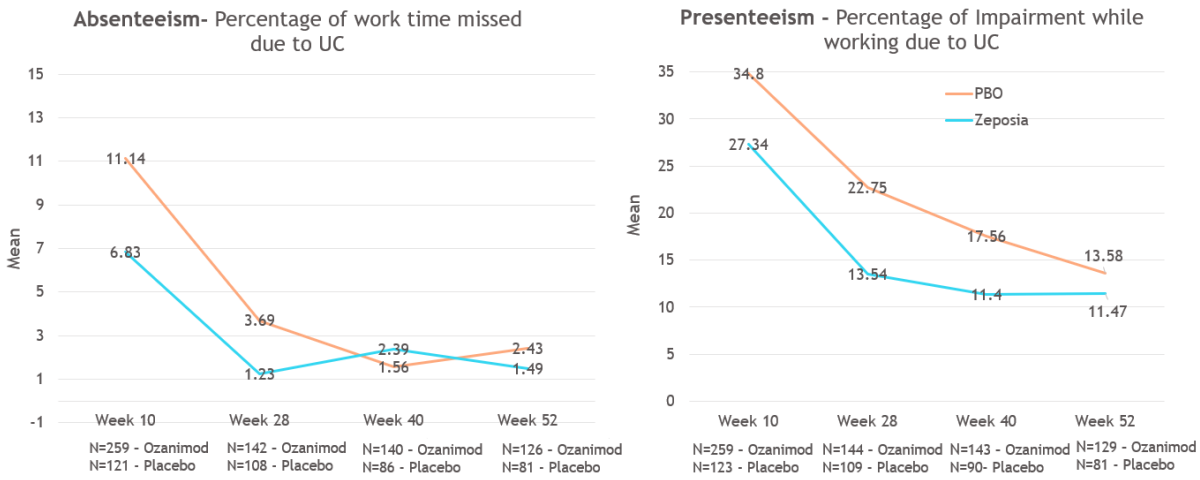
CI = confidence interval; LS = least-squares.

[a] Based on analysis of covariance for change from baseline adjusted for remission status at Week 10 (yes or no), corticosteroid use at Week 10 (yes or no), and the Baseline EQ-5D visual analogue scale.

Source: BMS data on file (2020)[16]; BMS data on file (2020)[74]

Work Productivity and Activity Impairment (WPAI): Patients who had received the ozanimod arm for 52 weeks generally had less impairment in work productivity and regular activities, as assessed by the Work Productivity and Activity Impairment–Ulcerative Colitis (WPAI-UC), during the induction period than patients in the placebo arm. Patients in the ozanimod arm had fewer hours of work missed (nominal *P* = 0.006), a lower degree of UC-affected work productivity and regular activities (nominal *P* = 0.01), lower presenteeism (nominal *P* = 0.01), and a lower percentage of overall work (nominal *P* = 0.001) and daily activity impairment (nominal *P* = 0.003), all owing to UC. There were no nominally significant differences between patients in the ozanimod/ozanimod arm compared with patients in the ozanimod/placebo arm in work productivity and regular activities, as assessed by the WPAI-UC, during the maintenance period; however, the ozanimod/ozanimod arm, relative to the ozanimod/placebo arm, trended toward fewer work hours missed, a lower degree of UC-affected work productivity and regular activities, less absenteeism, and a lower percentage of overall work and daily activity impairment, all owing to UC.[48]
Figure 21 presents the percentage of work time missed and percentage of impairment while working owing to UC from week 10 to week 52. Figure 22 presents the non-work and work productivity loss as assessed by the WPAI-UC from week 10 through week 52.[15,48]

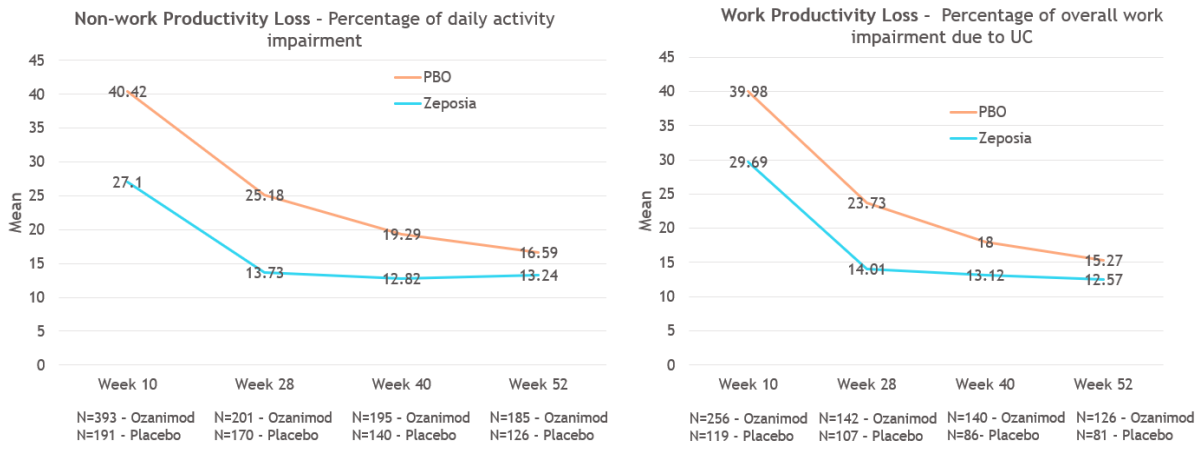
Figure 21. TRUE NORTH: absenteeism and presenteeism



PBO = placebo; UC = ulcerative colitis.

Source: BMS data on file (2020)[15]

Figure 22. TRUE NORTH: WPAI non-work and work productivity loss



PBO = placebo; UC = ulcerative colitis; WPAI = Work Productivity and Activity Impairment.
Source: BMS data on file (2020)[15]

7.1.2.4. TRUE NORTH: safety during the induction period

Overall, there was a similar incidence of TEAEs, serious TEAEs, suspected serious related TEAEs, and TEAEs leading to discontinuation for ozanimod compared with placebo (Table 11).[9] The most common TEAEs (≥ 3%) in either group were anaemia, nasopharyngitis, and headache. More TEAEs of special interest occurred in the ozanimod arm than in the placebo arm; however, TEAEs of special interest were generally rare.[9]

Appendix E contains more detailed summaries from the induction period of TEAEs by system organ class (Table E-1), TEAEs by preferred term (Table E-2), adverse events of special interest (AESIs) (Table E-3), and extended cardiac monitoring results (Table E-4).

Table 11. TRUE NORTH: safety summary—induction period (Safety Population)

Event, n (%)	Placebo (n = 216)	Ozanimod 1 mg (n = 429)
Any TEAE	82 (38.0)	172 (40.1)
Serious TEAE	7 (3.2)	17 (4.0)
TEAE leading to treatment discontinuation	7 (3.2)	14 (3.3)
Suspected related serious TEAE	2 (0.9)	1 (0.2)
Most common TEAEs (≥ 3% in any group)		
Anaemia	12 (5.6)	18 (4.2)
Nasopharyngitis	3 (1.4)	15 (3.5)
Headache	4 (1.9)	14 (3.3)
ALT increased[a]	0	11 (2.6)
Arthralgia	3 (1.4)	10 (2.3)
γ-Glutamyltransferase increased[a]	0	5 (1.2)
Infection	25 (11.6)	46 (10.7)
Serious infection	1 (0.5)	4 (0.9)

Event, n (%)	Placebo (n = 216)	Ozanimod 1 mg (n = 429)
Nasopharyngitis	3 (1.4)	15 (3.5)
Upper respiratory tract infection	1 (0.5)	5 (1.2)
Herpes zoster infection[b]	0	2 (0.5)
Cancer		
Basal cell carcinoma	0	0
Rectal adenocarcinoma	0	0
Adenocarcinoma of the colon	0	0
Breast cancer	0	0
TEAEs of special interest		
Bradycardia	0	2 (0.5)
Hypertension	0	6 (1.4)
Hypertensive crisis	0	1 (0.2)
Macular oedema	0	1 (0.2)
Laboratory assessments, no./total no. (%)		
ALT		
≥ 2 × ULN	2/216 (0.9)	25/423 (5.9)
≥ 3 × ULN	1/216 (0.5)	11/423 (2.6)
≥ 5 × ULN	1/216 (0.5)	4/423 (0.9)
ALC		
< 200 cells per mm^3	0/209	9/421 (2.1)
< 500 cells per mm^3	0/209	113/421 (26.8)

ALC = absolute lymphocyte count; ALT = alanine aminotransferase; TEAE = treatment-emergent adverse event; ULN = upper limit of normal.

Note: Data are from the safety population.

[a] Laboratory values were flagged by the central laboratory if they fell outside the standard reference range. The investigator decided whether the laboratory value qualified as an adverse event.

[b] All the patients had documented presence of varicella zoster virus immunoglobulin G antibody or complete varicella zoster vaccination at screening.

Source: Sandborn et al. (2021)[9]

7.1.2.5. TRUE NORTH: safety during the maintenance period

Overall, the incidence of TEAEs was higher in the ozanimod/ozanimod arm than in the ozanimod/placebo arm (Table 12). The incidence of serious TEAEs and TEAEs leading to discontinuation was lower in the ozanimod/ozanimod arm versus the ozanimod/placebo arm.[9] The most common TEAEs (> 3%) in either group were anaemia, alanine aminotransferase (ALT) increased, headache, arthralgia, nasopharyngitis, and gamma-glutamyl transferase increased. Treatment-emergent AEs of special interest were generally rare. Infections occurred more frequently in the ozanimod/ozanimod arm than in the ozanimod/placebo arm; however, serious infections were lower in the ozanimod/ozanimod arm.[9]

Appendix E contains more detailed summaries from the maintenance period of TEAEs by system organ class (Table E-5), TEAEs by preferred term (Table E-6), and AESIs (Table E-7).

Table 12. TRUE NORTH: safety summary—maintenance period (Safety Population)

Event, n (%)	Ozanimod 1 mg/placebo (n = 227)	Ozanimod 1 mg/ozanimod 1 mg (n = 230)
Any TEAE	83 (36.6)	113 (49.1)
Serious TEAE	18 (7.9)	12 (5.2)
TEAE leading to treatment discontinuation	6 (2.6)	3 (1.3)
Suspected related serious TEAE	1 (0.4)	0
Most common TEAEs (≥ 3% in any group)		
Anaemia	4 (1.8)	3 (1.3)
Nasopharyngitis	4 (1.8)	7 (3.0)
Headache	1 (0.4)	8 (3.5)
ALT increased[a]	1 (0.4)	11 (4.8)
Arthralgia	6 (2.6)	7 (3.0)
γ-Glutamyltransferase increased[a]	1 (0.4)	7 (3.0)
Infection	27 (11.9)	53 (23.0)
Serious infection	4 (1.8)	2 (0.9)
Nasopharyngitis	4 (1.8)	7 (3.0)
Upper respiratory tract infection	4 (1.8)	2 (0.9)
Herpes zoster infection[b]	1 (0.4)	5 (2.2)
Cancer		
Basal cell carcinoma	0	1 (0.4)
Rectal adenocarcinoma	0	1 (0.4)
Adenocarcinoma of the colon	1 (0.4)	0
Breast cancer	1 (0.4)	0
TEAEs of special interest		
Bradycardia	0	0
Hypertension	3 (1.3)	4 (1.7)
Hypertensive crisis	1 (0.4)	1 (0.4)
Macular oedema	0	1 (0.4)
Laboratory assessments, no./total no. (%)		
ALT		
≥ 2 × ULN	12/227 (5.3)	32/230 (13.9)
≥ 3 × ULN	4/227 (1.8)	7/230 (3.0)
≥ 5 × ULN	1/227 (0.4)	2/230 (0.9)
ALC		
< 200 cells per mm^3	0/227	5/230 (2.2)
< 500 cells per mm^3	4/227 (1.8)	100/230 (43.5)

ALC = absolute lymphocyte count; ALT = alanine aminotransferase; TEAE = treatment-emergent adverse event; ULN = upper limit of normal.

Note: Data are from the safety population.

[a] Laboratory values were flagged by the central laboratory if they fell outside the standard reference range. The investigator decided whether the laboratory value qualified as an adverse event.

[b] All the patients had documented presence of varicella zoster virus immunoglobulin G antibody or complete varicella zoster vaccination at screening.

Source: Sandborn et al. (2021)[9]

7.1.3. Relevant studies: TOUCHSTONE

- The TOUCHSTONE trial (NCT01647516) was a randomised, double-blind, placebo-controlled, phase 2 trial that compares ozanimod versus placebo in patients with moderate-to-severe UC. Table 13 presents details of the TOUCHSTONE methodology; further details on design, endpoints, and statistical analysis are described in Sections 7.1.3.1 to 7.1.3.3. For detailed study characteristics, please refer to
- Appendix B. For baseline characteristics of patients, refer to Appendix C. For details on statistical testing, refer to Appendix G.

Table 13. TOUCHSTONE: summary of trial methodology

Study	TOUCHSTONE
Key publications	Sandborn WJ, Feagan BG, Wolf DC, D'Haens G, Vermeire S, Hanauer SB, et al. Ozanimod induction and maintenance treatment for ulcerative colitis. N Engl J Med. 2016 May 5;374(18):1754-62. doi:http://dx.doi.org/10.1056/NEJMoa1513248. Sandborn WJ, Feagan B, Hanauer SB. Long-term safety and efficacy of ozanimod in patients with moderate-to-severe ulcerative colitis: results from the TOUCHSTONE open-label extension [oral presentation: OP087]. Presented at: United European Gastroenterology (UEG) Week; 11-13 October 2020. Virtual.
Sample size	197
Study design	Phase 2, multicentre, randomised, double-blind, placebo-controlled, 3-arm study
Location	Multicentre: 88 sites in 15 countries in Europe, Asia, North America, and Australasia
Patient population	Patients with moderately to severely active UC
Interventions	▪ Ozanimod 0.5 mg (n = 65) ▪ Ozanimod 1 mg (n = 67)
Comparator	Placebo (n = 65)
Follow-up period	32 weeks

UC = ulcerative colitis.

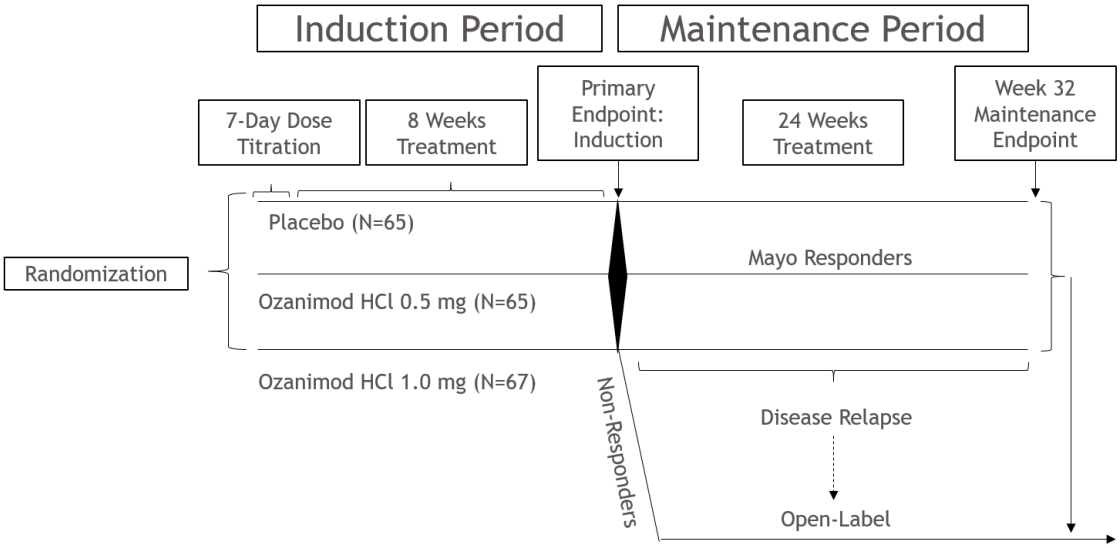
7.1.3.1. TOUCHSTONE: study design

The primary objective of TRUE NORTH was to evaluate the efficacy of daily oral doses of 0.5 mg of ozanimod HCl (equivalent to ozanimod 0.46 mg) or 1 mg of ozanimod HCl (equivalent to ozanimod 0.92 mg) compared with placebo for induction (week 8) and maintenance (week 32) therapy in adults with moderately to severely active UC.[10] The trial was conducted from December 2012 through April 2015.[10]

Figure 23 presents the study design for TOUCHSTONE. Patients were eligible to enter the TOUCHSTONE OLE period if they completed the induction period but did not have a clinical response at week 8, experienced disease relapse during the maintenance period, or completed the maintenance period. The TOUCHSTONE OLE ended in 2019 after

all active patients had completed at least 4 years of follow-up. All active patients at the point of study closure were invited to enrol into the RPC01-3102 phase 3 OLE study (see Section 7.1.1.1).[11]

Figure 23. TOUCHSTONE: study design



HCl = hydrochloride.
Source: Sandborn et al. (2016)[10]

7.1.3.2. TOUCHSTONE: study treatments

Patients were randomised (1:1:1) to one of the following treatments for 32 weeks[10]:

- Ozanimod HCl 0.5 mg (equivalent to ozanimod 0.46 mg) once daily orally
- Ozanimod 1 HCl mg (equivalent to ozanimod 0.92 mg) once daily orally
- Placebo once daily orally

Randomisation was performed centrally using a computerised system. Patients were stratified before randomisation by previous exposure to an anti-TNF.[10] Patients with a clinical response at week 8 (defined as a reduction in 4-component Mayo Score of ≥ 3 points and ≥ 30% from baseline, with a decrease in the rectal bleeding score [RBS] of ≥ 1 point or a subscore of ≤ 1) continued their blinded treatment regimen during the maintenance period. Patients who did not have a clinical response at week 8 could cross over to optional open-label treatment.[10]

7.1.3.2.1. TOUCHSTONE open-label extension period

Patients received ozanimod 1 mg once daily orally.[11]

7.1.3.3. TOUCHSTONE: endpoints

Appendix D includes the definitions used for efficacy endpoints for the induction and maintenance periods.

The primary efficacy endpoint was the proportion of patients in clinical remission at week 8.[10]

Hierarchically ranked secondary efficacy endpoints were as follows[10]:

- Proportion of patients with a clinical response (defined as a reduction in 4-component Mayo Score of ≥ 3 points and ≥ 30% from baseline, with a decrease in the RBS of ≥ 1 point or a subscore of ≤ 1) at week 8
- Change from baseline to week 8 in the 4-component Mayo Score
- Proportion of patients with mucosal healing (endoscopic subscore of ≤ 1) at week 8

Exploratory efficacy endpoints included the proportion of patients with clinical response, clinical remission, mucosal healing, and change in the 4-component Mayo Score at week 32, and the proportion of patients with histologic remission (Geboes Score < 2 on a scale from 0-5) at weeks 8 and 32.[10]

Pharmacodynamic endpoints included changes from baseline in the following biomarkers: ALC and the concentrations of C-reactive protein (CRP), faecal calprotectin, and faecal lactoferrin.[10]

Safety was assessed in terms of incidence and types of AEs, SAEs, and AEs leading to discontinuation of study drug.[10]

7.1.3.3.1. TOUCHSTONE open-label extension period

Efficacy endpoints included clinical response (defined as a reduction from baseline in partial Mayo Score [≥ 2 points and ≥ 30%] or 4-component Mayo Score [≥ 3 points and ≥ 30%], with a reduction in RBS of ≥ 1 point or absolute RBS of ≤ 1), clinical remission (defined as partial Mayo Score or 4-component Mayo Score of ≤ 2, with no subscore > 1), endoscopic improvement (defined as endoscopic subscore of ≤ 1), histologic remission at weeks 56 and 104, and change in partial Mayo Score.[11]

Pharmacodynamic endpoints included changes from baseline in the following biomarker concentrations: CRP and faecal calprotectin.[11]

Safety and tolerability were assessed in terms of incidence of TEAEs and serious TEAEs.[11]

7.1.3.4. TOUCHSTONE: efficacy and safety

A total of 197 patients were randomised to ozanimod 1.0 mg (n = 67), ozanimod 0.5 mg (n = 65), and placebo (n = 65). Clinical remission (primary endpoint) at week 8 occurred in 16%, 14%, and 6% of patients who received ozanimod 1 mg, ozanimod 0.5 mg, and placebo, respectively ($P = 0.048$ and $P = 0.14$, respectively, for the comparison of the 2 doses of ozanimod vs. placebo). Clinical response at week 8 occurred in 57%, 54%, and 37% of patients who received ozanimod 1 mg, ozanimod 0.5 mg, and placebo, respectively (nominal $P = 0.02$ and nominal $P = 0.06$, respectively, for the comparison of the 2 doses of ozanimod vs. placebo). Clinical remission at week 32 occurred in 21%, 26%, and 6% of patients who received ozanimod 1 mg, ozanimod 0.5 mg, and placebo, respectively (nominal $P = 0.01$ and nominal $P = 0.002$, respectively, for the comparison of the 2 doses of ozanimod vs. placebo). Clinical response at week 32 occurred in 51%, 35%, and 20% of patients who received ozanimod 1 mg, ozanimod 0.5 mg, and placebo, respectively (nominal $P < 0.001$ and nominal $P = 0.06$, respectively, for the comparison of the 2 doses of ozanimod vs. placebo).[10]

During the induction and maintenance periods, no important differences were observed between the treatment arms in terms of the percentages of AEs reported during the trial (39% in ozanimod 1 mg and 40% in placebo).

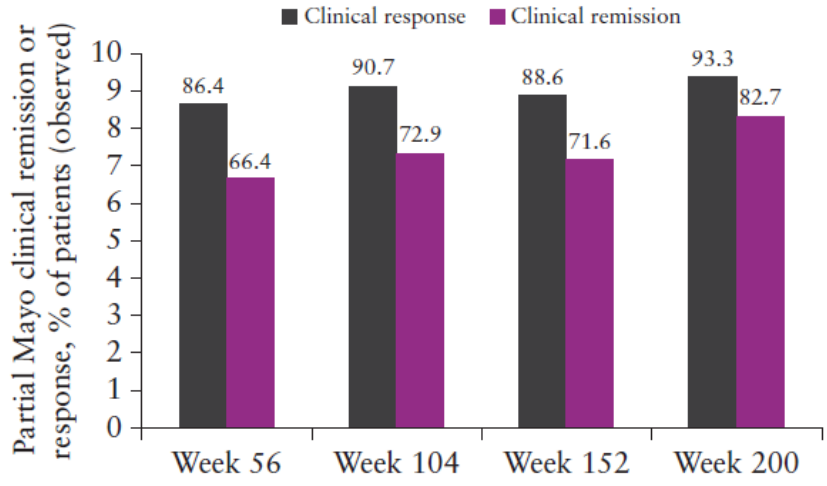
There were fewer SAEs (4% and 9%, respectively) and AEs leading to discontinuation (1% and 6%) with ozanimod 1 mg than placebo.[10] An elective termination was reported during the study period.[75]

Please refer to Appendix E for additional reporting of the safety endpoints from TOUCHSTONE.

7.1.3.5. TOUCHSTONE open-label extension period

Of the 197 patients who enrolled into the main TOUCHSTONE trial, 170 entered the OLE study. At 4 years, partial Mayo measures indicated 93.3% of patients remained in clinical response and 82.7% remained in clinical remission based on observed cases (Figure 240).

Figure 24. Patients with partial Mayo clinical response or remission based on observed cases

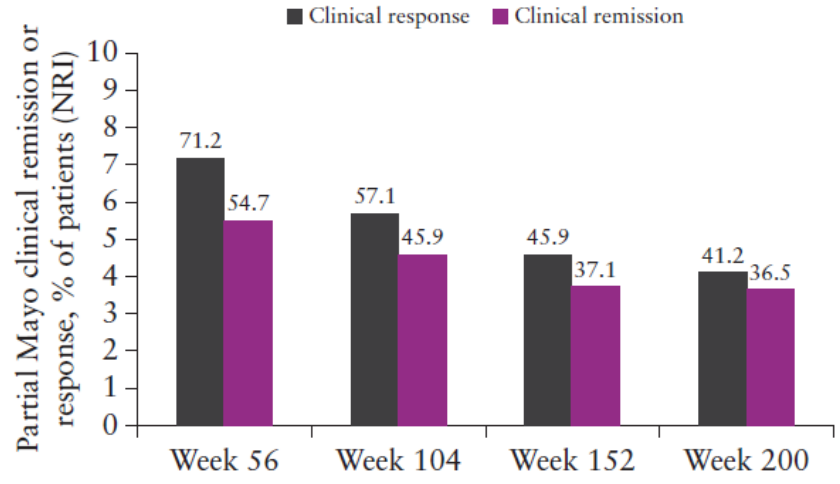


Clinical response, n/N	121/140	97/107	78/88	70/75
Clinical remission, n/N	93/140	78/107	63/88	62/75

Source: Sandborn et al. (2021)[12]

Using the more conservative non-responder imputation analysis (non-response was imputed for 30 of 170 patients at week 56, 63 of 170 patients at week 104, 82 of 170 patients at week 152, and 95 of 170 patients at week 200.), 41.2% of patients remained in clinical response and 36.5% remained in clinical remission (Figure 25).[12]

Figure 25. **Patients with partial Mayo clinical response or remission based on non-responder imputation analysis**



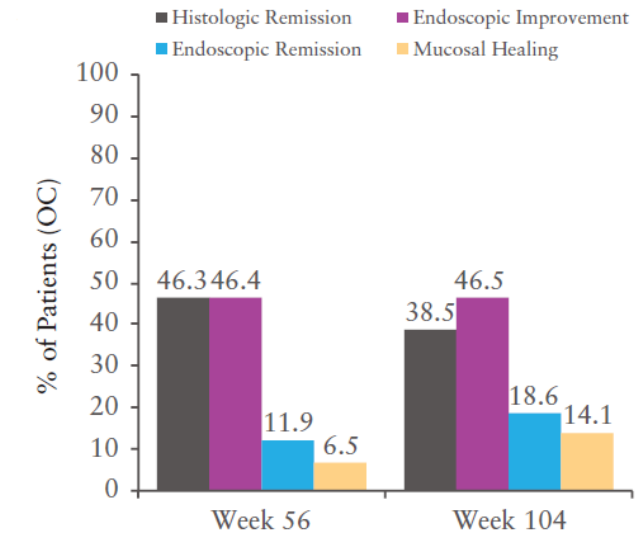
Clinical response, n/N	121/170	97/170	78/170	70/170
Clinical remission, n/N	93/170	78/170	63/170	62/170

NRI = non-responder imputation.

Source: Sandborn et al. (2021)[12]

Based on observed cases, at weeks 56 and 104, respectively, histological remission rates were 46.3% and 38.5%, endoscopic improvement rates were 46.4% and 46.5%, endoscopic remission was 11.9% and 18.6%, and mucosal healing was 6.5% and 14.1% (Figure 26).

Figure 26. **Patients achieving histological remission, endoscopic improvement, endoscopic remission, and mucosal healing based on observed cases at weeks 56 and 104**



Total observed cases, n	67	84	10	4		78	86	16	11

OC = observed cases.

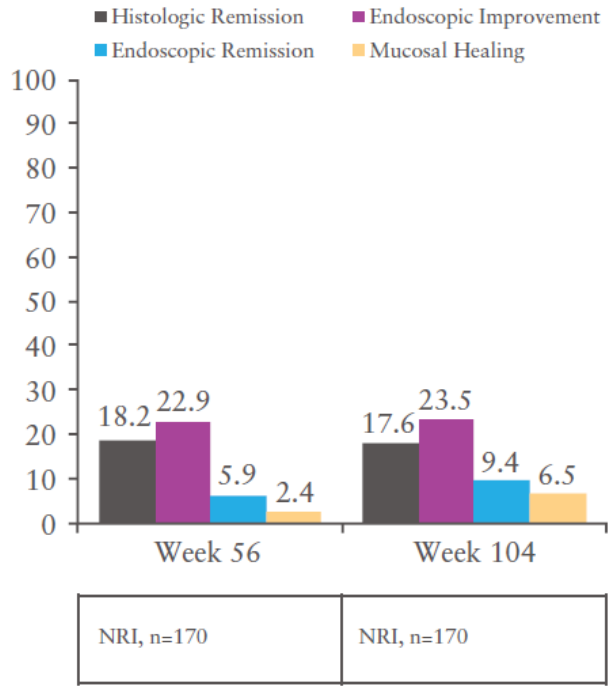
Source: Sandborn et al. (2021)[12]

Figure 27 presents the more conservative non-responder imputation analysis.[12] Non-response was imputed as follows:

- Histologic remission:
  - 103 of 170 patients at week 56
  - 92 of 170 patients at week 104
- Endoscopic improvement:
  - 86 of 170 patients at week 56
  - 84 of 170 patients at week 104
- Endoscopic remission:
  - 160 of 170 patients at week 56
  - 154 of 170 patients at week 104
- Mucosal healing:
  - 166 of 170 patients at week 56
  - 159 of 170 patients at week 104

At week 104, 17.6%, 23.5%, 9.4%, and 6.5% of patients had histologic remission, endoscopic improvement, endoscopic remission and mucosal healing, respectively.[12]

Figure 27. Patients achieving histological remission, endoscopic improvement, endoscopic remission, and mucosal healing based on non-responder imputation analysis at weeks 56 and 104



NRI = non-responder imputation.
Source: Sandborn et al. (2021)[12]

Long-term treatment with ozanimod was well tolerated, and the mean duration of exposure to ozanimod was 2.8 patient-years. There were no new safety signals, and the most common TEAEs were UC-related symptoms (6.5%), hypertension (5.9%), upper respiratory tract infection (5.9%), and gamma-glutamyl transferase increased (5.3%) (Table 14). There was no indication that long-term use of ozanimod is associated with an increased risk of clinically significant infections, bradyarrhythmia, hepatic or pulmonary dysfunction, malignancy, or macular oedema.

Based on the mode of action for ozanimod, a reduction in ALC is an expected pharmacodynamic effect.[12] A reduction in lymphocyte count was reported as a treatment-related AE in 9 patients; however, none of these events were associated with serious or opportunistic infections.[12]

Table 14. Overview of adverse events during open-label extension period

	Total (N = 170)
Mean person-years of exposure (SD)	2.8 (1.85)
Total person-years of exposure	478.7
TEAEs in ≥ 5% of patients in any group, n (%)	
UC	11 (6.5)
Hypertension	10 (5.9)
Upper respiratory tract infection	10 (5.9)
Gamma-glutamyltransferase increased	9 (5.3)
Anaemia	8 (4.7)
Back pain	7 (4.1)
Nasopharyngitis	7 (4.1)
Headache	7 (4.1)
ALT increased	6 (3.5)
Lymphocyte count decreased	6 (3.5)
Bronchitis	4 (2.4)
Viral respiratory tract infection	4 (2.4)
SAEs in > 1 patient, n (%)[a]	
UC	6 (3.5)
Anaemia	2 (1.2)
Ischaemic stroke	2 (1.2)

ALT = alanine aminotransferase; SAE = serious adverse event; SD = standard deviation; TEAE = treatment-emergent adverse event; UC = ulcerative colitis.

[a] The following SAEs occurred in 1 patient each: acute coronary syndrome, adenocarcinoma, ascites, autoimmune haemolytic anaemia, basal cell carcinoma, colitis, colon adenoma, dehydration, erysipelas, haemolytic anaemia, hypochromic anaemia, hyperbilirubinaemia, idiopathic pulmonary fibrosis, inguinal hernia, interstitial lung disease, intestinal obstruction, jaundice, joint dislocation, nephrolithiasis, pleurisy, pneumonia, pneumococcal pneumonia, prostate cancer, pulmonary bulla, pulmonary microemboli, rheumatoid arthritis, schizophrenia, spinal column stenosis, spontaneous abortion, umbilical hernia, viral gastroenteritis, and wrist fracture.

Source: Sandborn et al. (2021)[12]

In patients originally randomised to ozanimod 0.5 mg, SAEs deemed potentially related to study treatment by the investigator were adenocarcinoma (of unknown origin) and ascites, which occurred in the same patient who discontinued treatment. Other SAEs were pneumococcal pneumonia, pneumonia, and hyperbilirubinaemia (n = 1 each). In patients originally randomised to ozanimod 1 mg, SAEs included haemolytic anaemia and jaundice, which occurred in the same patient, and a spontaneous abortion in a 29-year-old woman. The positive pregnancy test occurred 43 days after the patient's last menstrual period, and ozanimod was discontinued immediately. The patient experienced a miscarriage 18 days after the positive pregnancy test, which was 61 days after her last menstrual period and was deemed "possibly" related to the study medication by investigators.[12]

A pooled safety analysis to assess the safety of extended ozanimod exposure in participants with RMS specifically addressed pregnancy outcomes and reported that spontaneous abortions and preterm births were within the expected rates in the general population.[58] Participants enrolled in any of the studies were required to use effective contraception. At the time of the cutoff, 36 of 1,868 female participants became pregnant while on either dose of ozanimod, which included 1 set of twins. There was a total of 24 live births (65%), 18 of which were deemed normal and 3 were premature but normal infants (12.5% of live births). There were reports of neonatal icterus (n = 1), late intrauterine growth retardation with subsequent normal progress over the first year (n = 1), and duplex kidney (n = 1). Of the pregnancies that did not result in a live birth, 7 (18.9%) were elective terminations and 5 (13.5%) were early spontaneous abortions (of which one was loss of a twin). One participant refused consent to follow-up.[58]

7.2. Efficacy and safety of ozanimod compared with currently existing medications for moderately to severely active UC

7.2.1. Indirect treatment comparison analyses of efficacy and safety

No head-to-head evidence comparing ozanimod with currently existing medications was identified in the SLR. As there is no head-to-head evidence comparing ozanimod with currently existing treatments, a comparison of efficacy and safety among treatments cannot be directly inferred from a trial. Therefore, comparative evidence has been calculated using an NMA. An NMA is a widely used evidence synthesis technique to derive comparisons of treatment effects between interventions that may not have been compared head-to-head in RCTs or for which both direct and indirect evidence is available for synthesis.[76] Therefore, NMAs are suitable to assess the relative effectiveness of the several treatments available for patients with moderate-to-severe UC. The following sections outline the methodology and results.[17]

7.2.1.1. Scope of the NMA

Studies considered for inclusion in the NMA were informed by the SLR with details presented in Appendix A. The SLR adopted a broad approach to capture data for all potentially relevant studies and outcomes from a global perspective, regardless of whether these data would be relevant for analysis. For example, the SLR extracted information pertaining to a variety of outcomes, such as HRQoL, whereas the NMA focused on the outcomes of clinical remission, clinical response, and endoscopy improvement as defined by the Mayo Score (for more details on outcome definitions, see Appendix D) as well as safety outcomes. Likewise, the NMA did not include treatments that have not been approved by the Food and Drug Administration (FDA) or EMA for moderate-to-severe UC at the time of this report, including filgotinib and etrasimod. Therefore, the scope of this feasibility assessment pertains to inclusion of data from the 22 unique trials with respect to the NMA eligibility criteria outlined in Table 15. This

predefined scope of analysis aligns with previous NMAs that have evaluated studies in moderate-to-severe UC.[17] Subsequently, 3 studies, Suzuki et al. (2014)[60], VARSITY (Sands et al. 2019)[63] and ULTRA 1 [61] that were originally not included in the NMA as not relevant to the clinical setting in Denmark (because they included only biologic-naïve patients treated with adalimumab). However, DMC requested these studies be included in the analysis of SAE and for TT maintenance efficacy analyses, where they allow vedolizumab to be compared with infliximab. Therefore, data have been included from 25 publications and 17 RCTs.

Note that the DMC requested that the submission should provide an analysis relevant to Denmark, therefore the NMA methodology reported here is based on the broader NMA which aimed to address how do agents approved for moderate-to-severe UC compare in terms of key clinical efficacy (clinical response, clinical remission, and endoscopic improvement) and safety (AEs, SAEs, withdrawals due to AEs, and serious infections) outcomes evaluated at induction and maintenance of phase 2 and 3 RCTs. The NMA results reported in Sections 7.2.14 to 7.2.16 are aligned with the drugs that in the Danish Medicines Agency's treatment guidelines for UC have been assessed to be equivalent and are placed in the 'Apply' group for bio-naive and experienced patients (see Figure 2).[17]

Table 15. Eligibility criteria for inclusion of data in analyses

Criteria	Inclusion criteria
Outcomes	Clinical response, clinical remission, and endoscopic improvement defined by the Mayo scale as well as occurrence of adverse events, serious adverse events, serious infections, and discontinuations due to adverse events
Comparators	Adalimumab (160/80/40 mg), infliximab (5 mg/kg), golimumab (200/100 mg for induction therapy, 100/50 mg for maintenance therapy), vedolizumab (300 mg for induction therapy, 108 mg for maintenance therapy), ustekinumab (6 mg/kg for induction therapy, 90 mg every 12 weeks for maintenance therapy), and ozanimod (1 mg) according to licensed EMA doses
Population	Patients with moderate-to-severe UC
Subgroups	Bio-naive: patients who have not previously been exposed to or who have not responded to a prior biologic therapy Bio-experienced: patients who have been exposed to or who have not responded to a prior biologic therapy

EMA = European Medicines Agency; FDA = Food and Drug Administration; UC = ulcerative colitis.

Follow-up for maintenance period could be defined by either timepoint from start of study or duration of maintenance period. The same number studies fall between 44-60 weeks regardless of choice.

7.2.2. Trial eligibility criteria

Trial eligibility criteria is an important source of potential heterogeneity as it defines the patient population of interest within each trial, which may vary between trials and introduce heterogeneity in analyses. Eligibility criteria for each trial is summarised in Appendix N (Table N-1). In general, inclusion and exclusion criteria were similar across trials, often requiring a combination of:

- Adults aged ≥ 18 years
- Active UC based on Mayo score of 6 to 12, with endoscopic subscore of ≥ 2
- Inadequate response to, or had failed to tolerate, at least 1 of the conventional therapies: oral aminosalicylates, oral corticosteroids, azathioprine, and/or mercaptopurine

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However, differences in eligibility criteria were noted regarding whether the eligible patient population was either naive to biologic therapies or could have inadequate response to or have failed to tolerate biologic therapies. As a result of this, separate subgroup analyses were performed that stratified patients by biologic exposure status with the NMAs, an approach that has been widely adopted in previous NMAs in UC. For details regarding heterogeneity attributable to these subgroups, please see Section 7.2.5. The minimum duration of the diagnosis of UC required for eligibility differed between trials and ranged from at least 2 weeks to 6 months. Trials also differed in terms of the concomitant medications allowed and the duration for which patients were required to have not taken non-biologic therapies to be eligible for enrolment.[17]

Of note, the Probert et al. (2003)[77] trial required UC patients to be glucocorticoid resistant, which represents a smaller sub-population of the prior therapies described above wherein studies required inadequate response or failure to conventional therapies in general. Of note, this trial also defined outcomes using Ulcerative Colitis Symptom Score instead of the Mayo Score used by other trials, a source of heterogeneity discussed in detail in Section 7.2.6. Similarly, Sands et al. (2001)[78] required patients to have active UC based on modified Truelove and Witts classification instead of the Mayo score–based definition used by other trials. For these reasons, the Probert et al. (2003)[77] and Sands et al. (2001)[78] trials were excluded from analyses to prevent introducing heterogeneity attributable to a variety of sources related to differences in the study population and outcomes.

7.2.3. Study design

The primary induction period assessment varied from 2 to 14 weeks across trials, while the maintenance period varied from 22 to 50 weeks after the induction period (See Appendix N.2). Total trial duration varied from 8 to 60 weeks, excluding any open-label safety extension periods. The timepoint of assessment deemed eligible for the NMA was restricted to 6-12 weeks for induction, and 44-60 weeks for maintenance to limit heterogeneity attributable due to timepoint of assessment. Therefore, VARSITY was deemed ineligible for inclusion in the induction phase because the induction phase was defined as 14 weeks. For the maintenance phase, several trials were deemed ineligible for inclusion in the maintenance phase analyses despite including a maintenance phase, as the maintenance assessment occurred at < 44 weeks. In addition, the previously mentioned Sands et al. (2001)[78] trial evaluating only a handful of patients included a 2-week induction assessment timepoint and was excluded from NMAs altogether to limit the influence of this heterogeneity and biases in estimates attributable to very small sample sizes in the fixed effect NMAs explored. This approach to exclude trials that have significantly different timepoints of assessments aligns with previous UC NMAs.[79-81] Despite restricting the induction and maintenance phase timepoint eligible for the NMA, some heterogeneity may remain within the allowable timeframes.

7.2.3.1. Maintenance trial designs

In addition to the timepoint of assessment, trials that included a maintenance phase were a combination of “treat-through” and “re-randomised” trial designs, the latter of which involves an additional randomisation phase at the end of induction on top of the initial randomisation that usually occurs at baseline in both treat-through (TT) and re-randomised trials (Figure 28).

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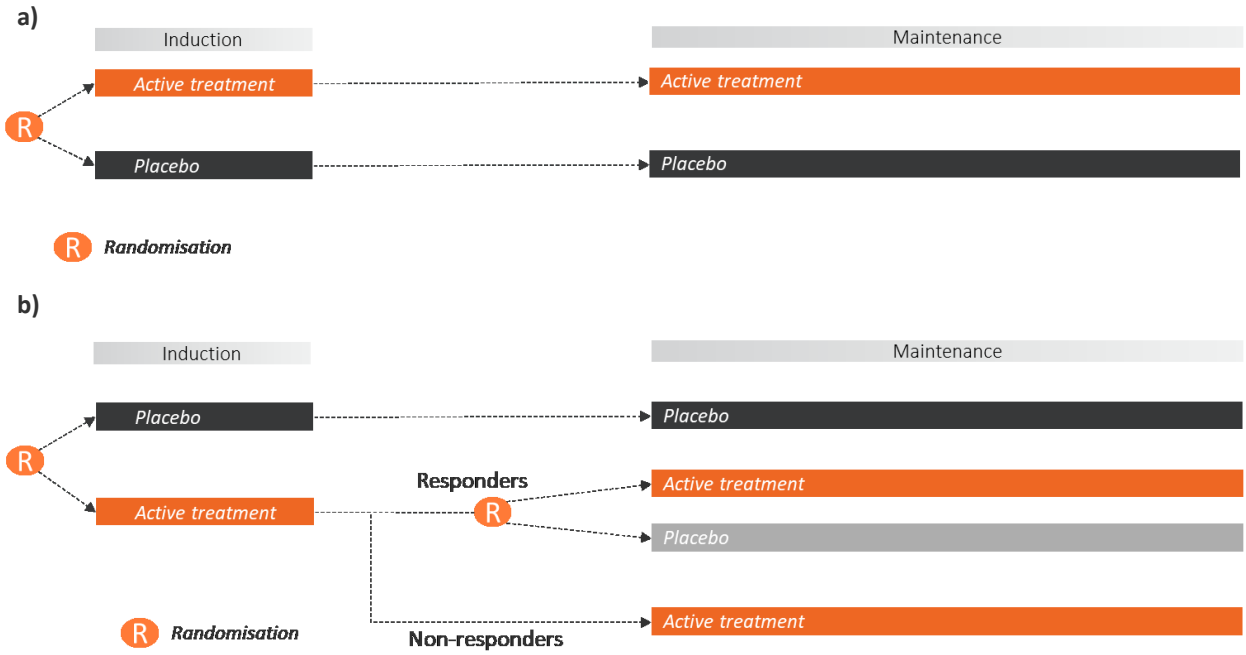
Figure 28. Treat-through and re-randomised trial design schematics



Trial schematics for **a)** conventional treat-through design that involves a single baseline randomisation step and **b)** response-based re-randomised design that involves an additional re-randomisation step for patients who are responders at induction.

Source: Adapted from NICE (2020)[79]

In such re-randomised trials, a certain subset of patients are re-randomised into the maintenance phase, while other patients receive open-label active treatment. In almost all re-randomised trials, the re-randomised patients are responders among those who received active treatment during induction (see Appendix N.3 for more details). Of note, the UNIFI trial allowed patients who were delayed responders, defined as patients who did not respond to placebo during the 8-week induction phase who then received ustekinumab at week 8 and were responders at week 16, to undergo re-randomisation into the maintenance phase. Across all trials, patients who were non-responders during the induction phase (excluding delayed responders from UNIFI) received open-label active treatment during the maintenance phase.[17]

In addition to this heterogeneity regarding which patients are re-randomised, instead of including an initial randomisation phase, the PURSUIT-J and VISIBLE 1 re-randomised trials only included an open-label active treatment phase, where all patients received golimumab and vedolizumab during induction, respectively. In such cases, responders to the open-label, active treatment were re-randomised to maintenance, as described above. Of note, this single-arm induction design prevents inclusion in the induction NMA due to the lack of a comparator.

As a result of their design, re-randomised trials report fundamentally different outcomes than TT trials, despite using the same term to describe each outcome. For example, clinical remission in the maintenance phase for a re-randomised trial is clinical remission at the end of maintenance among induction phase responders, whereas a TT trial would not have this induction phase responder requirement. Likewise, clinical response at maintenance in a re-randomised trial would represent maintenance of clinical response from a TT trial.[17]

Further, there may be differences in the "carry over" effect of the therapy received during induction, since patients in a re-randomised trial may have residual benefits in the maintenance phase from the active therapy received during the induction phase. Therefore, patients who are re-randomised to placebo may display a heightened level of response at the maintenance assessment timepoint.

In summary, there is considerable heterogeneity associated with the various trial designs in UC that may influence the maintenance NMA findings by comparing maintenance results for patients who were induction responders versus those who are not induction responders, a covariate that is likely to modulate treatment effect. Therefore, the data from TT trials cannot be directly compared in analyses with data from re-randomised trials; therefore, the 2 different types of maintenance trials have been analysed separately.

7.2.4. Treatment effect modifier assessment

Some differences in patient characteristics between trials were noted in Appendix C. Of note, baseline mean CRP levels, years since UC diagnosis (range: 3.8-14.6 years), extent of disease (i.e., left-sided [range: 15%-69.2%] vs. extensive [range: 6.6%-80.8%] vs. other [range: 0%-63.4%]), and use of concomitant steroids (range: 25%-100%) were found to vary across trials more often relative to other characteristics. Likewise, the percentage of patients who were naive to anti-TNF or other biologics was also variable, partially due to the eligibility criteria of early UC trials restricting the patient population to those who are biologic-naive (bio-naive), as outlined in see Section 7.2.2.

Previous NMAs in UC have highlighted similar differences in patient characteristics as a potential source of heterogeneity, such as prior exposure to biologics, extent of disease, and baseline or concomitant corticosteroid use (Section 7.2.8).[79-81] To observe the influence of such variables on results of the NMA, we conducted univariate treatment effect modifier assessments by categorising these variables and observing the influence on the treatment effect for ozanimod versus placebo within the True North trial at induction and maintenance for the key outcomes of clinical remission and clinical response (see Appendix C for further details).

Results of the assessment indicated that concomitant steroid use at baseline, CRP level at baseline, duration of disease, extent of colitis, and previous treatment with anti-TNF were potential effect modifiers. Unfortunately, the dosage and duration of corticosteroid use at baseline was not defined consistently across trials. In addition, CRP levels at baseline were not reported by all trials. When reported, the trials summarised CRP level at baseline inconsistently using either median or mean CRP levels. Likewise, duration of disease was inconsistently defined as the clinical criteria for the initial diagnosis of UC has evolved over time, and older trials were conducted when fewer treatment options for UC were available. Due to the inconsistencies in how these variables are reported and defined, adjustment for their potential treatment effect modification was not feasible.

Despite these limitations, previous treatment with anti-TNF/biologics emerged as the most important potential effect modifier and was well-reported across trials, although definitions of prior exposure and biologic status varied across trials (Section 7.2.5). Hence, we explored subgroup analyses that stratified patients by previous treatment with biologics or anti-TNFs in alignment with previous UC NMAs.[17]

7.2.5. Biologic subgroup definitions

As described in the previous sections, prior treatment with biologics varies across trials and may influence treatment effect as observed for certain outcomes in the True North trial. In accordance with this, several studies

have shown lower efficacy with second-line biologics than with first-line biologics in UC (i.e., lower response rates, more patients requiring dose escalation).[82-85] Therefore, as with all major previous NMAs in UC, separate analyses were conducted for bio-naive and bio-experienced patient populations.

Twelve trials included some patients who previously received biologic therapy, while the other trials recruited an entirely bio-naive population. However, the definition for what exactly constitutes "bio-naive" and "bio-experienced" patients varied across the trials. For example, for the bio-experienced group, certain trials reported data on a subset of patients who had failed (i.e., were intolerant or inadequate responders) previous biologic therapies while others reported on data for patients who were exposed to previous biologic therapies (i.e., failed or exposed without failure) (see Appendix N.3 Table N-4 for further details). Likewise, the naive populations could have been defined as a lack of failure or a lack of exposure to a previous biologic. Thus, there were 2 possible definitions for the bio-experienced and bio-naive subgroups:

- Biologic experienced:
  - Prior exposure to a biologic therapy
  - Prior failure (intolerant or inadequate response) of a biologic therapy
- Biologic naive:
  - No prior exposure to a biologic therapy
  - No prior failure of a biologic therapy

Of the trials that were entirely bio-naive, all defined naive as a lack of exposure to a previous biologic. Therefore, the heterogeneity attributable to these population definitions is a result of the subgroups defined in the mixed population trials available. The availability of subgroup data in the 12 mixed population trials is summarised in Table N-4 in Appendix N. All trials except for TOUCHSTONE reported some form of bio-experienced and bio-naive subgroup data.

In addition, for several trials, the term "biologic" was heterogeneous since it often only considers previous biologic agents available for treatment of UC at the time of study. For example, earlier trials are often TNF-experienced in the bio-experienced population. Recent studies have had to consider previous exposure to newer biologic UC agents, namely vedolizumab and ustekinumab, which may introduce some heterogeneity in populations. In either case, the term "biologic" is used to describe both "TNF" and more recent biologic agents available for UC, such as vedolizumab and ustekinumab. This can be especially problematic for the ULTRA 2 bio-experienced population, wherein all experienced patients would previously failed TNFs, which is the same class of therapy as adalimumab.

For the trials that reported both exposure-based and failure-based data (UNIFI), the data were primarily sought from populations of patients who had failed previous biologic therapy, consistent with prior health technology assessments (e.g., National Institute for Health and Care Excellence [NICE] TA547 and TA633) as well as the approach adopted by the Institute for Clinical and Economic Review (ICER) in their recent UC evidence report.[81]

Data reported directly in the articles was selected to inform the NMA over calculated subgroup data, to avoid any potential double-counting of patients if the subgroup populations were not entirely mutually exclusive. As a result, the GEMINI 1 data used to inform the biologic-exposed and bio-naive NMAs came from failed and non-exposed patients, respectively, and excludes 13 patients with prior exposure but no failure during the induction phase and

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10 of these patients in the maintenance phase. This approach aligns with the data used by ICER in their UC evidence report as well as the ustekinumab NICE evidence review group re-analyses according to the data reported in each report.[81]

Despite the heterogeneity described above, there are often only minor differences in the number of patients in the "exposed" and "failure" subgroups, as patients who are previously treated with a biologic agent often stop therapy due to reasons associated with failure. This is especially apparent for the True North trial, where only a few patients were exposed to previous biologic therapy but not failures. Therefore, the impact of such heterogeneity on the NMAs is likely minimal.

In addition, although TOUCHSTONE did not report any subgroup data, 82% of patients were naive to any biologic treatment, so a sensitivity analysis was conducted to explore the effect of including the trial on ozanimod results in the bio-naive induction analyses.

7.2.6. Outcome definitions

Outcome definitions across trials are summarised in Appendix D for the key outcomes of clinical remission, clinical response, and endoscopic improvement explored in NMAs. The use of local versus central endoscopy readings is also discussed. Outcome definitions for safety outcomes are only briefly discussed as they were often implicitly or poorly defined in comparator trials.[17] It is important to note that the outcome of "endoscopic improvement" in True North, defined as a Mayo endoscopy subscore of ≤ 1 point, was previously known as "mucosal healing." Therefore, where studies reported mucosal healing with this definition, the data were included in the NMA of endoscopic improvement.

7.2.7. Placebo response

Placebo response, otherwise known as baseline risk, is a proxy for heterogeneity caused by differences in patient and trial characteristics, since identical trials conducted in an identical population should have similar placebo responses.[86] Because of this, placebo response can reflect differences in unmeasured patient characteristics that may not be captured in clinical trial setting, such as the general standard of care received by patients, making it an effective tool to observe potential differences in prognostic variables across trials.[17]

Figure 29 summarizes the placebo response observed for clinical remission across trials during the induction phase in the overall population. Figures for other outcomes and populations are presented in Appendix N.4. Note that for TT trials in the maintenance phase, these placebo responses represent re-calculated rates conditioned on induction clinical responders, to mimic a trial of re-randomised design (see Section 7.2.11 for additional details).

In general, the True North trial had lower-than-average placebo responses during the induction phase for clinical response and remission in the overall and bio-naive populations. For the bio-experienced population, True North had a higher-than-average placebo rate for clinical remission but lower-than-average placebo rate for clinical response. During the maintenance phase, the True North placebo arm had a higher-than-average placebo rate in the overall, bio-naive, and bio-experienced populations for clinical remission and response. Of note was the analyses of clinical response for the overall and bio-naive populations, wherein the True North placebo response was considerably higher than average, alongside results observed in the UNIFI trial. This effect may be attributable to residual carry-over effects of active treatment from the induction phase of these re-randomised trials, a source

of heterogeneity previously highlighted in earlier NMAs evaluating treatments in UC[79-81], alongside differences in patient characteristics across trials described in Appendix C and Section 7.2.4.

As placebo response alone is not necessarily effect modifying, we observed the influence of placebo response on treatment effects on a treatment-level basis to potentially motivate exploration of network meta-regression accounting for placebo response. Figure 30 presents a scatterplot of the treatment effect observed for each treatment versus the placebo response in the trial the treatment is being evaluated in. Each line represents a given treatment and each data point represents a trial evaluating said treatment. Lines are drawn to visualise treatment effect vs. placebo response across trials for each given treatment. For example, Figure 30 shows that there a strong negative relationship between treatment effect and placebo response for adalimumab based on the relationship observed in 2 adalimumab trials. Other treatments show a more moderate negative relationship. Plots for other outcomes are shown in Appendix N.4. Across almost all analyses, an overall negative relationship was observed, wherein trials with a higher placebo response often had a worse treatment effect (Table 16). This could potentially bias results against studies with considerably high observed placebo response such as True North, which may reflect underlying differences in underlying patient characteristics or trial designs, as described above.[17]

In response to this heterogeneity across placebo arms and a potential relationship observed with treatment effects, we explored placebo-adjusted, network meta-regression NMA models as sensitivity analyses for the primary outcomes of clinical response, remission, and endoscopic improvement, when feasible based on network structure. This placebo-adjusted approach has been adapted by ICER in their recent UC evidence report[81], and has precedence in terms of reducing bias in estimates attributable from measured and unmeasured characteristics.

Table 16. Summary of ozanimod trial placebo rates and potential influence on network meta-analyses

Timepoint	Outcome	Population	Ozanimod placebo rates	Relationship of placebo response with treatment effect[a]
Induction	Clinical response	Overall	Approximately average	Slightly negative
		Bio-Naive	Lower than average	Negative
		Bio-Experienced	Lower than average	Slightly negative
	Clinical remission	Overall	Lower than average	Slightly negative
		Bio-Naive	Lower than average	Slightly negative
		Bio-Experienced	Approximately average	No strong relationship
Maintenance	Clinical Response	Overall	Higher than average	Slightly negative
		Bio-Naive	Higher than average	Negative
		Bio-Experienced	Approximately average	No strong relationship
	Clinical Remission	Overall	Approximately average	No strong relationship
		Bio-Naive	Approximately average	Negative
		Bio-Experienced	Approximately average	No strong relationship

[a] A negative relationship indicates that higher placebo response is correlated with smaller treatment effects, and vice versa. No strong relationship signifies that the treatment-level relationship of placebo response with the treatment effects is either minimal or mixed across treatments.

Source: BMS Celgene data on file (2021)[17]

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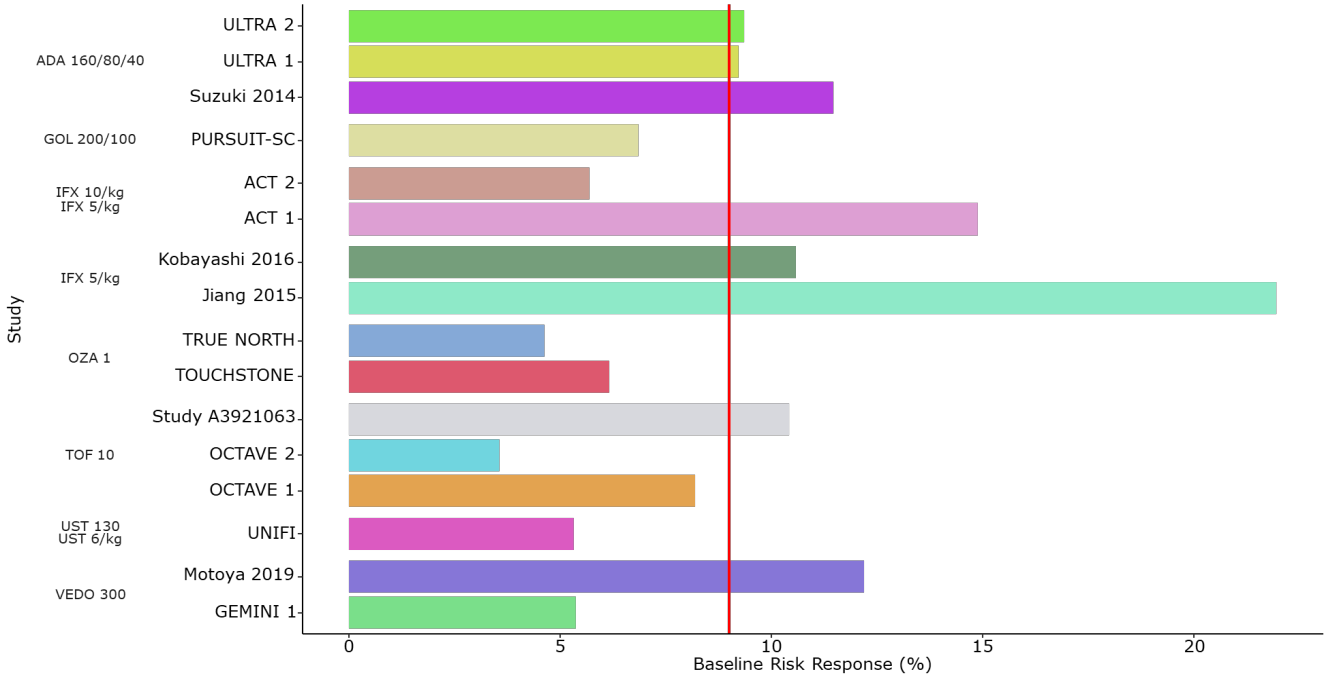
Figure 29. Placebo rates for clinical remission at induction across trials (overall population)



ADA = adalimumab; GOL = golimumab; IFX = infliximab; OZA = ozanimod; TOF = tofacitinib; UST = ustekinumab; VEDO = vedolizumab.
Note: red line represents the average placebo response across all trials. Baseline risk is equivalent to placebo response.

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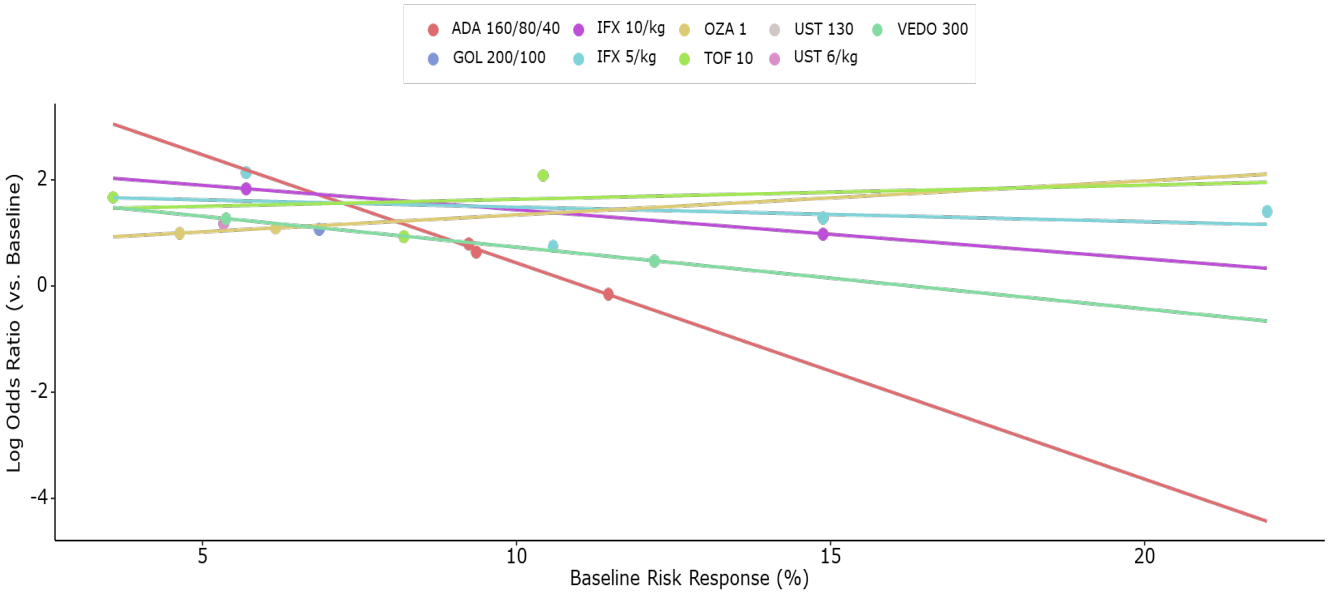
Figure 30. Placebo rates versus treatment effect for clinical remission at induction by treatment (overall population)



ADA = adalimumab; GOL = golimumab; IFX = infliximab; OZA = ozanimod; TOF = tofacitinib; UST = ustekinumab; VEDO = vedolizumab

Plot of treatment effects organised by treatment on the log odds scale versus placebo response. Baseline risk is equivalent to placebo response.

7.2.8. Alignment with previous NMAs in UC

7.2.8.1. Summary of trials included

Several previous NMAs in UC have evaluated the comparative safety and efficacy of targeted therapies in moderate-to-severe UC. The trials included in these previous NMAs has been summarised in Appendix N.5. In general, the trials included in analyses align with those previously included in recent NMAs. Of note is the variable inclusion of Probert 2003, which was included in the most recent ustekinumab submission to NICE but was excluded in all previous submissions due to the heterogeneity attributable to outcome definitions and the patient population within the trial, described within this report. Of course, none of these previous NMAs have included data from the ozanimod True North or TOUCHSTONE trials. In addition, the Mshimesh 2017 trial[87] has been included in some previous NMAs, but the full-text publication has since been redacted and therefore was deemed ineligible for inclusion at the SLR stage due to lack of data reported. In addition, the UC-SUCCESS trial was omitted from almost all previous NMAs in UC as the trial compared infliximab to azathioprine, an immunomodulator that is used concomitantly in several of the trials evaluated. Despite this, previous evidence review groups for NICE have highlighted that the trial may be relevant to the research question of evaluating treatments with moderate-to-severe UC and therefore it has been included in sensitivity analyses. Overall, a conservative approach to trial inclusion was taken to limit the influence of the heterogeneity described throughout this section on analysis findings.[17]

7.2.8.2. Heterogeneity highlighted in previous NMAs

The heterogeneity described throughout this section is not unique to these analyses but has been characterised in evaluations in preceding NMAs. Table N-6 in Appendix N outlines a high-level summary of recent NMAs in UC that have been leveraged in previous health technology assessment submissions as well as the recent UC clinical evidence report published by the ICER and the ustekinumab submission to the Canadian Agency for Drugs and Technologies in Health (CADTH). Similar concerns regarding eligibility criteria, trial designs, patient characteristics, biologic population definitions, outcome definitions, and placebo response were often highlighted in these reviews and addressed where feasible through use of sensitivity analyses.

Across these reviews, trial eligibility criteria were often not a major concern as the SLRs informing the NMAs were restricted to trials evaluating patients with moderate-to-severe UC, which was often similarly defined across trials. Of note, several trials conducted sensitivity analyses to exclude trials that recruited an entirely Asian population. Trial design was universally identified as a major source of heterogeneity that must be addressed in order for NMAs to be feasible in the maintenance period. Patient characteristics were often also highlighted as a potential source of heterogeneity but were rarely accounted for in NMAs. In the ICER report, these characteristics and their influence on the treatment effect were indirectly accounted for using placebo-response adjustment when feasible, an approach described in Section 7.2.7. Therefore, the amount of heterogeneity that may influence NMA findings in the analyses conducted is similar to that presented in previous NMAs performed by or provided to evidence review groups such as NICE, ICER, or CADTH. As with these previous analyses, appropriate sensitivity analyses and adjustments were conducted to control for this heterogeneity, where feasible.[17]

7.2.9. Summary of feasibility assessment

In summary, 4 trials were excluded from all NMA assessments due to heterogeneity or the assessment of unapproved therapies (Table 17), 21 trials were included in the base-case analyses, and 1 trial (UC-SUCCESS) was included in a sensitivity analysis.

Table 17. Summary of trials excluded from the network meta-analyses

Primary agent	Trials	Reason for exclusion
Etrasimod	OASIS	▪ Pipeline therapy
Adalimumab	Sands 2001	▪ Trial design ▪ Outcome definition heterogeneity
	SERENE-UC	▪ Compared an approved dose of adalimumab against an unapproved dose
Infliximab	Probert 2003	▪ Eligibility criteria heterogeneity ▪ Outcome definition heterogeneity

There are several sources of heterogeneity identified that may introduce bias in the NMAs but do not necessarily preclude the feasibility of conducting NMAs altogether, as similar levels of heterogeneity have been described by previous evidence review groups that have conducted NMAs in UC. Some of these sources of heterogeneity are unavoidable due to the nature of the clinical trials evaluating patients with moderate-to-severe UC, such as the timepoint of assessment, while others can be mitigated through exploration of sensitivity or subgroup analyses evaluating the influence of these sources of heterogeneity on the NMA, such as trials recruiting an entirely Asian population.[17]

Table 18 below summarises each source of potential heterogeneity and how the influence of each component on the NMA was mitigated or addressed, when feasible. Several sensitivity analyses and statistical adjustments mitigating or removing the source of heterogeneity in the NMAs were explored to evaluate the impact on results, an approach that aligns with previous NMAs conducted in UC. Despite attempts to address heterogeneity where feasible, some heterogeneity may remain present in NMAs which may influence findings. For this reason, random effects models that allow for additional uncertainty in the NMAs were generally favoured a priori when these models were feasible and did not compromise the face validity of findings by introducing excessive uncertainty in particularly sparse networks or networks with very low event rates. Additional details regarding the model selection approach are outlined in Section 7.2.12. This rationale aligns with previous NMAs in UC that have justified a similar model selection approach.[79-81]

Table 18. Summary of heterogeneity identified and addressed

Source of potential heterogeneity	Summary of heterogeneity	Potential impact on NMA	Addressed
Trial timepoint of assessment	▪ Varies from 2 to 14 weeks for induction ▪ Varies from 22 to 60 weeks for maintenance	▪ Certain treatments may have more or less time to respond to therapy	▪ Limited induction period to 6-12 weeks ▪ Limited maintenance period to 44-60 weeks ▪ Above approach has been adapted in previous NMAs in UC
Trial eligibility criteria	▪ Certain trials included Asian patients only	▪ If race is effect modifying, could bias NMA results	▪ Conducted a sensitivity excluding trials recruiting entirely Asian patients
Trial designs	▪ Certain trials use a treat-through design while others use a re-randomised design ▪ The patients who are re-randomised to maintenance in re-randomised trials varies	▪ Treat-through trials have much lower placebo response and will be biased in favour of within the NMA	▪ Conduct separate analyses for studies that rerandomize and those that treat-through
Patient characteristics	▪ Variation identified in certain disease and patient characteristics (e.g., disease history, extent of disease)	▪ If the characteristics are effect modifying, could bias NMA results	▪ Explored treatment effect modifier assessments in True North trial
Biologic subgroup definitions	▪ Certain trials use biologic exposure status to stratify patients, while others use biologic failure status ▪ Difference between exposed and failed groups is often a small subset of patients	▪ Patients who have previously failed therapy are likely more severe than those who are simply exposed which may bias against trials including biologic failure patients in the bio-experienced subgroup	▪ Leveraged data that aligned with the True North populations of exposed and non-exposed where possible ▪ Same data has been used by previous NMAs in UC, plus addition of ozanimod data ▪ Almost all patients who were exposed in True North were failures, likely little impact

Source of potential heterogeneity	Summary of heterogeneity	Potential impact on NMA	Addressed
Outcome definitions	▪ Some trials define outcomes based on scales other than the Mayo score ▪ Some variation due to threshold of response and remission ▪ Adalimumab trials used worst rank method to measure Mayo scores	▪ Stricter outcome definitions will bias against trials using such definitions ▪ Influence of trials using entirely different scales to assess response and remission is unclear	▪ Leveraged 4-component data from True North ▪ Excluded outcomes that did not define response and remission based on Mayo score
Endoscopy read	▪ Earlier studies in UC leverage local endoscopy read, ozanimod and tofacitinib trials used central	▪ Unclear; may bias results in unknown direction if endoscopy read is effect modifying	▪ No alternative data available, highlighted as source of heterogeneity
Placebo response	▪ Varied across trials with certain outcomes being more variable (e.g., response and remission during the maintenance phase)	▪ Placebo response shown to have treatment effect for certain outcomes in certain populations	▪ Explored placebo-response adjustment as sensitivity using meta-regression methods

NMA = network meta-analysis.

Source: BMS Celgene data on file (2021)[17]

Table 17 shows a summary of randomised clinical trials included and their contribution in the different NMAs presented in this dossier.

Table 19. Summary of randomised clinical trials included in the various NMAs.

				Setting			Prior bio experience			
Intervention	Author	Trial name	Comparator	Induction	Maint RR	Maint TT	Naive	Experienced	Overall (Any-for SAEs)	Notes
Ozanimod	Sandborn 2021 [9]	TRUE NORTH	Placebo	✓	✓	x	✓	✓	✓	
	Sandborn 2016[10]	TOUCHSTONE	Placebo	✓	x	x	x	x	✓	Induction - included in SAE analysis but not in efficacy analysis includes a mixed bio-naive and experienced population Maintenance - follow-up was to week 32, so also excluded from SAE analysis but included in "overall SAE" analysis
	Sandborn 2021[12]	TOUCHSTONE OLE	None	x	x	x	x	x	x	OLE not included in NMA as no comparator
	D'Haens 2021[13]	Pooled analysis	Placebo	x	x	x	x	x	x	Primary studies used in NMA, not pooled analysis
Adalimumab	Sandborn 2012[62]	ULTRA 2	Placebo	✓	x	✓	x	✓	x	Induction – bio-experienced data used in efficacy and safety NMAs, bio-naive data available but not relevant to Denmark efficacy analysis. Maintenance – used in TT bio-naive analysis to link VARSITY to ACT-1, but not relevant to Denmark efficacy analysis Maintenance - not included in SAE analysis data only available for entire trial (induction and maintenance)
	Reinisch 2011[61]	ULTRA 1		✓	x	x	x	x	✓	In safety only as bio-naive not relevant to Denmark for efficacy outcomes
	Suzuki 2014 [60]	Suzuki		✓	x	✓	✓	x	✓	Induction - in safety only; bio-naive not relevant to Denmark for efficacy outcomes Maintenance - not included in SAE analysis as data only available for entire trial (induction and maintenance)

Intervention	Author	Trial name	Comparator	Setting			Prior bio experience			Notes
				Induction	Maint RR	Maint TT	Naive	Experienced	Overall (Any-for SAEs)	
Golimumab	Sandborn 2014[64]	PURSUIT-SC	Placebo	✓	x	x	✓	x	✓	
	Sandborn 2014[65]	PURSUIT-M	Placebo	x	✓	x	✓	x	✓	
	Hibi 2017[66]	PURSUIT-J	Placebo	x	✓	x	✓	x	✓	
Infliximab	Rutgeerts 2005[67]	ACT 1	Placebo	✓	x	✓	✓	x	x	Not in safety analysis as only reports results for entire trial (induction + maintenance)
	Rutgeerts 2005[67]	ACT 2	Placebo	✓	x	x	✓	x	x	Maintenance - not included in efficacy analysis as follow-up is 30 weeks Maintenance - not included in SAE analysis as data only available for entire trial (induction and maintenance)
	Jiang 2015[68]	NA	Placebo	✓	x	x	✓	x	x	Maintenance - not included in efficacy analysis as follow-up is 30 weeks Not included in induction SAE analysis as data only available for entire trial (induction and maintenance)
	Kobayashi 2016[69]	NA	Placebo	✓	x	x	✓	x	✓	Maintenance - not included in efficacy analysis as follow-up is 38 weeks
Vedolizumab	Feagan 2013[70]	GEMINI 1	Placebo	✓	✓	x	✓	✓	✓	
	Sandborn 2020[71]	VISIBLE 1	Placebo with a vedo reference arm	x	✓	x	x	x	✓	Only used in the SAE analysis as results not presented separately for bio-naive and experienced
	Motoya 2019[72]	NA	Placebo	✓	✓	x	✓	✓	✓	

Intervention	Author	Trial name	Comparator	Setting			Prior bio experience			Notes
				Induction	Maint RR	Maint TT	Naive	Experienced	Overall (Any-for SAEs)	
	Sands 2019[63]	VARSITY	Vedolizumab	x	x	✓	✓	✓	x	Induction - measured at 14 weeks therefore excluded from induction Maintenance - TT ,experienced data available for remission, corticosteroid-free remission and endoscopic improvement. Connects to ACT-1 via Suzuki and ULTRA 2 Maintenance - not in safety analysis as only reports results for entire trial (induction + maintenance)
Ustekinumab	Sands 2019[73]	UNIFI	Placebo	✓	✓	x	✓	✓	✓	Note: ~50% of patients were bio-naive and bio-experienced, with results presented separately for some outcomes Induction – data available for SAE analysis only

NA = not applicable; NMA = network meta-analysis; RR = re-randomised trial design ; SAE = serious adverse event; TT = treat-through trial design.

7.2.10. NMA methodology

All NMAs were performed using a Bayesian framework. The chosen reference treatment for all analyses was placebo, given its presence as the anchor treatment across almost all studies and outcomes assessed. Network diagrams were drawn to visualise the evidence base for each analysis in Sections 7.2.14 through 7.2.16. In these figures, lines that connect nodes signify the presence of 1 or more RCTs that directly compare treatments, with the thickness of each line reflecting the number of RCTs informing the comparison; thicker lines signify more RCTs comparing treatments. Unadjusted, fixed effect and random effects models were explored in addition to sensitivity analyses conducted for placebo-adjusted, fixed effect and random effects models, when feasible. Details of the model selection approach are provided in Section 7.2.12.

7.2.10.1. Subgroups & timepoints

As introduced previously, separate analyses were performed for the overall, bio-naive, and bio-experienced populations, given expected differences in clinical efficacy associated with prior treatment and precedence from previous NMA publications in UC.[79-81] Likewise, separate analyses were performed for studies reporting data at the induction (6-12 weeks) and maintenance (44-60 weeks) periods. For the maintenance studies, separate analyses were conducted for those trials that rerandomized patients and those with a treat-through design.

7.2.11. Statistical methods for NMA

An ordinal model with a probit link was used to assess clinical response and clinical remission, given these outcomes approximately represent ordered categories of the underlying Mayo score. Leveraging an ordinal model allows for efficient use of data from both outcomes and maintains any existing correlation between categories, which is expected. A probit link was preferred over a logit link to allow for easier clinical interpretation regarding clinical response and remission outcomes, as this permits a separate odds ratio to be provided for each outcome. Precedence for ordinal probit modelling approach has also been established in previous UC NMAs, being leveraged by the recent ICER UC evidence report as well as the tofacitinib UC NICE submission.[81] A sensitivity using an ordinal model with a logit link was also explored. For endoscopic improvement, a standard binomial model with a logit link was used as this outcome is described by a single dichotomous variable. In all cases, outcomes were transformed to odds ratios to facilitate clinical interpretation of findings consistent with the standard outcome reporting method used by clinical trials in UC as well as previous NMAs conducted by evidence review groups.

Individual doses of treatments were not pooled in the base case to allow for the maximum flexibility regarding assessment of relative effectiveness for individual treatments. Of note, the downstream cost-effectiveness model that leverages the NMA used data from the pooled dose sensitivity. Treatments populated entirely with zero events were dropped from networks of evidence, although this was not required for any of the primary analyses. Various sensitivities were performed to explore alternative analytic approaches, such as pooling doses of similar treatments.

Results throughout Sections 7.2.14 and 7.2.15 focuses on pairwise results in form of odds ratios and associated 95% credible intervals from best-fitting models according to the criteria outlined in Section 7.2.12 for the key outcomes of interest of clinical response, clinical remission, and endoscopic improvement in the overall, bio-naive, and bio-experienced patient populations for both the induction and maintenance phase. Results for safety analyses are also presented.

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All NMAs were performed using R (R Core Team, Vienna, Austria) and JAGS, based on the code outlined in the NICE Evidence Synthesis Decision Support Unit (DSU) Technical Support Document (TSD) Series.[17]

7.2.11.1. Meta-regression on placebo response

As introduced in Section 7.2.7, qualitative assessment of placebo response and its potential influence on treatment effects motivated exploration of placebo-adjusted sensitivity analyses of the primary outcomes of clinical response and clinical remission, which accounts for this relationship of placebo response with treatment effects. In these models, placebo response (i.e., baseline risk) was calculated using the unweighted average of placebo rates of all placebo-controlled trials for a given treatment as determined by the baselines in the NMA. The standard meta-regression approach described in Technical Support Document (TSD) 2 was used to adjust for placebo response, using a single interaction effect for all treatments compared with placebo.[88] Briefly, the treatment effect relationship versus placebo response was measured for each treatment, combined into a single interaction term (β), and accounted for throughout the network via linear network meta-regression. A negative regression term signifies there is a negative relationship between placebo response and treatment effects, and therefore trials with larger placebo responses may be biased against in the network, and vice versa.[17]

7.2.11.2. Outcome measures

Pairwise comparisons of interventions estimated from NMAs are presented through league tables that report odds ratios[ii] with 95% credible intervals, the Bayesian analogue to CIs that represent the interval wherein there is a 95% probability that the estimated parameter will fall within. Statements regarding treatment differences are primarily informed by pairwise differences in effect estimates, with "statistically significant" conclusions derived from overlap of pairwise credible intervals with unity (i.e., no difference).[17]

7.2.11.3. Model effects

Given differences in patient characteristics and study designs, heterogeneity is to be expected within networks. Both random effects and fixed effect models were explored, when feasible, with random effects models favoured by default due to the heterogeneity described above. Additional details on the model selection approach are outlined in Section 7.2.12.

7.2.11.4. Model convergence

All analyses were performed using 4 unique sets of starting values and were based on burn-in and sampling durations of 20,000 iterations or more, with additional samples taken to achieve convergence when necessary. Convergence was monitored quantitatively using the latest implementation Gelman-Rubin diagnostic (*Rhat*) based on 4 chains.[89] This new implementation captures non-convergence from stationary but non-overlapping chains, overlapping non-stationary chains, chains with heavy tails, and chains with different variance. Samples were considered to have converged if *Rhat* was equal to or less than 1.05. After convergence has been reached, concerns turn to whether there are sufficient independent samples for stable estimates. The newest version of effective sample size (ESS) and Monte Carlo standard error (MCSE) estimation were used to ensure sufficient post-convergence samples were taken to support inference.[89] If the rank-normalised effective sample size was greater than 400 (i.e., 100 per chain) then samples were taken to ensure that MCSE was small

[ii] Note that throughout this report, ORs displayed in figures may be reversed relative to what is quoted in-text in order to highlight a particular treatment. In these cases, the RR and associated CrIs are simply the inverse (1/#) of what is displayed within the figure (e.g., OZA vs. PBO: OR = 2.00; then PBO vs. OZA: OR = 0.50).

enough to allow for stable estimates to at least 1 decimal place.[89] All assessments of ESS and MCSE were made for each parameter that is reported.

7.2.11.5. Model priors

Default vague prior distributions that take the conservative approach of assuming no pre-existing information were assigned for the treatment effects, trial baselines, common regression terms (β), and between-study variance in all primary analyses for both unadjusted and baseline risk-adjusted models (Table 20). A sensitivity that explores a half-normal prior on the between-trial heterogeneity parameter in the random effects leveraged by the previous ustekinumab and TNF inhibitor submissions to NICE in UC was also explored.

Table 20. Default model prior used across analyses

Parameter	Prior Distribution
Baselines, unadjusted models (mu)	dnorm(0,0.0001)
Baselines, baseline risk-adjusted models (mu)	dnorm(0,0.01)
Basic parameters (d)	dnorm(0,0.0001)
Between-trial variation (sd)	dunif(0,2)
Meta-regression coefficient (B)	dnorm(0,0.0001)
Ordinal category cut-points (z)	dunif(0,5)

Source: BMS Celgene data on file (2021)[17]

7.2.11.6. Model thinning

Across outcomes, models incorporated thinning such that 10,000 iterations of each parameter would be saved. For example, a model using 20,000 iterations given 4 independent chains would keep every eighth iteration. Thinned samples are still required to pass the same convergence diagnostics outlined in Section 7.2.11.4. This was done to accommodate the incorporation of NMA data into probabilistic sensitivity analyses in the downstream cost-effectiveness analysis economic model, which requires a consistent amount of convergence diagnosis and output analysis across outcomes.[17]

7.2.12. Approach to model selection

The preferred model was chosen based on a combination of statistical and clinical considerations. From a statistical standpoint, lower deviance information criteria (DIC) and residual deviance (ResDev) were favoured as outlined in NICE TSD 3.[86] DIC is the sum of the posterior mean of the ResDev (how the data observed compares to what the model is predicting) and the number of effective parameters in the NMA, and is a measure of model fit that penalises complexity. Lower DIC values represent a more parsimonious model, with differences greater than 5 often considered meaningful. Residual deviance is a similar measure of model fit that that is equal to the deviance for a given model, minus the deviance for a "saturated" model, wherein all of the predictions from the model are identical to those observed.[17]

From a clinical perspective, as introduced in Section 7.2.11.3, random effects models likely have better clinical validity relative to fixed effect models due to the potential clinical heterogeneity, and were therefore favoured by default, where a fixed effect model was only implemented when estimates lacked face validity to ensure that models were not generating conclusions contrary to the direct evidence observed in the clinical trials informing the network (e.g., wherein all patients are considered comparable to placebo in the random effects model). This was also accompanied by an inspection of the networks of evidence available for each outcome, wherein outcomes informed primarily by single-study connections can generate underpowered between-trial

heterogeneity in the random effects models, potentially making fixed effect more suitable.[86] For the key outcomes of clinical remission, clinical response, and endoscopic improvement, the model selection rationale is detailed throughout Sections 7.2.14 and 7.2.15.

7.2.13. Assessment of consistency

Another important assumption underlying NMA is that the analysed network is *consistent*, meaning that there is no evidence of disagreement between the direct and indirect evidence being combined caused by imbalances in the distribution of effect modifiers from direct and indirect evidence.[90,91] An unrelated mean effects model (i.e., an inconsistency model) was used to test for inconsistency. This model solely relies on direct evidence and ignores indirect evidence and assumes no consistency throughout the network, allowing isolation of inconsistency estimates which can be compared with estimates in the traditional consistency model. This is similar to performing completely separate pairwise meta-analyses of all contrasts, but the unrelated mean effects approach allows for accommodation of multi-arm trials. Of note, inconsistency analyses requires closed loops of evidence to compare direct and indirect estimates, however, most closed loops in the evidence networks evaluated were informed entirely or partially by multi-arm trials or by a single head-to-head trial, which makes separating inconsistency and heterogeneity difficult and can lead to underpowered inconsistency models.[90,91] Regardless, inconsistency assessments for key primary outcomes (clinical remission, clinical response, endoscopic improvement) were performed, showing similar posterior mean deviances between consistency and inconsistency models across all outcomes through deviance plots**.** Briefly, these plots help identify loops in which inconsistency is present, wherein contributions to the deviance (i.e., how well the model predicts the data) should be similar between the inconsistency and consistency models (i.e., on the dotted line presented). In addition, across all outcomes, there was significant overlap of the pairwise conclusions as well as the model fit statistics derived by the consistency and inconsistency models. Therefore, no evidence of significant inconsistency was observed.[17]

7.2.14. Efficacy results from the comparative analysis at induction

As outlined in Section 6, the DMC requested that the submission should be aligned with the drugs that in the Danish Medicines Agency's treatment guidelines for UC have been assessed to be equivalent and are placed in the 'Apply' group for bio-naive and bio-experienced patients (Figure 2). Therefore, only studies investigating the use of adalimumab, infliximab, golimumab, ustekinumab, and vedolizumab in patients with UC have informed the indirect treatment analysis (ITC) of ozanimod versus relevant biologic therapies.

For the key outcomes of clinical remission, clinical response, the model selection is detailed in each NMA. Models for each analysis were selected by inspecting model fit statistics (see Table 21 to Table 22). Preferred models are highlighted in bold. For each analysis, the default preference was for random effects models over fixed effect when possible, to acknowledge the heterogeneity identified in the networks. When model fit statistics disagree substantially, preference should be given to the model with lower DIC and lower ResDev, provided posterior standard deviation (SD) was reasonably estimated. In this case, fits were generally similar for all models. However, despite similar fits between fixed and random effects models, in several analyses the random effects models produced improbably wide credible intervals for pairwise treatment comparisons. This was due to the limited size of these networks, which were reduced by removing entire trials, or removing treatment arms from some included trials, to accommodate specific comparator, dosage, and follow-up time requirements for Denmark. This resulted in the majority of links in the treatment networks consisting of single trials, necessitating fixed effects models, which are more appropriate under those constraints. Only the bio-naive induction analyses for clinical response-remission, ultimately used random effects models. All others required fixed effect models.

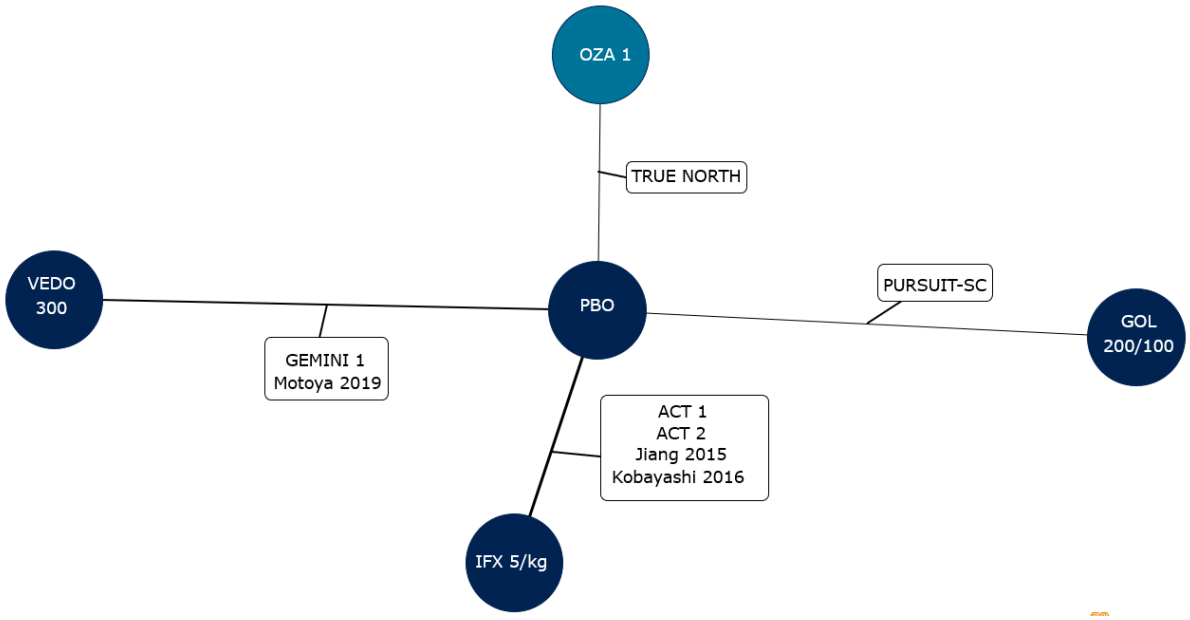
7.2.14.1. Bio-naive: clinical response and clinical remission at induction

7.2.14.1.1. Network of evidence

A network diagram of the evidence included in the NMA for clinical remission and response during the induction phase for the overall population is shown in Figure 31, which summarises the available evidence such that each treatment is represented by a node and randomised comparisons between treatments are shown by lines between the nodes. The same figures are presented for all subsequent outcomes.

All interventions were assessed in 1 or more placebo-controlled studies, with some studies evaluating multiple doses of the same biologic. The bio-naive network is composed of several multiple-study connections which allows the use of random effects analysis.

Figure 31. Evidence network for clinical remission and response at induction in the bio-naive population (Ordinal)



GOL = golimumab; IFX = infliximab; OZA = ozanimod; PBO = placebo; VEDO = vedolizumab.
Source: BMS data on file (2022)[92]

7.2.14.1.2. Model fit statistics

Table 21. Model fit statistics for clinical response and remission at induction (bio-naive population)

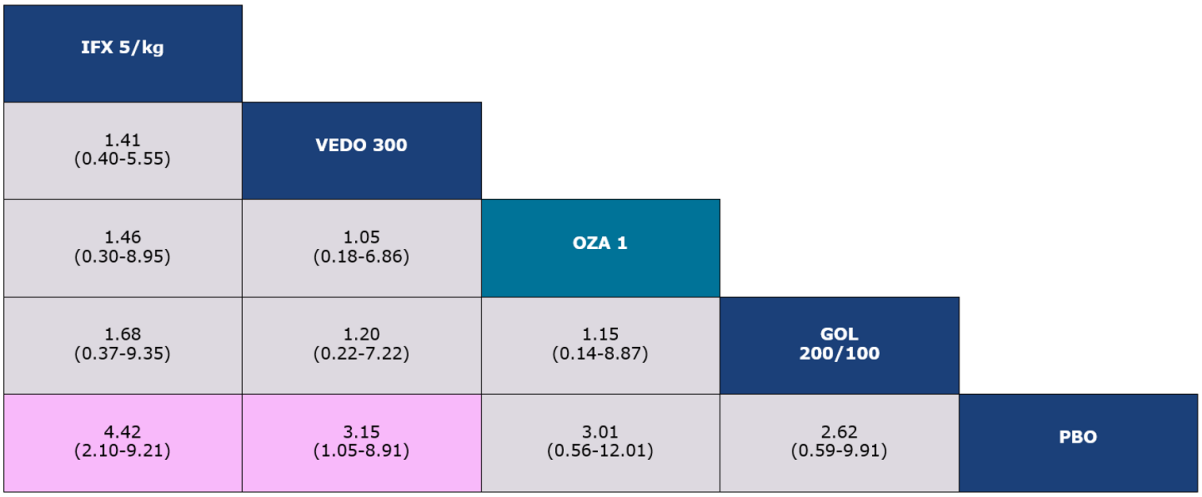
Diagnostic	Fixed effects model	Random effects model
DIC	65.00	**64.29**
ResDev (vs. 32 data points)	51.75	47.84
SDbt (95% CrI)	NA	0.25 (0.02-0.97)

CrI = credible interval; DIC = deviance information criterion; NA = not applicable; ResDev = residual deviance; SDbt = standard deviation between-trial heterogeneity.
Note: bold text denotes the preferred model
Source: BMS data on file (2022)[92]

7.2.14.1.3. Results

The results for clinical remission are presented in Figure 32 and clinical response in Figure 33. No statistically significant differences were found between ozanimod and other active therapies.

Figure 32. League table for clinical remission induction in the bio-naive population (Ordinal, Unadjusted, Random effects)

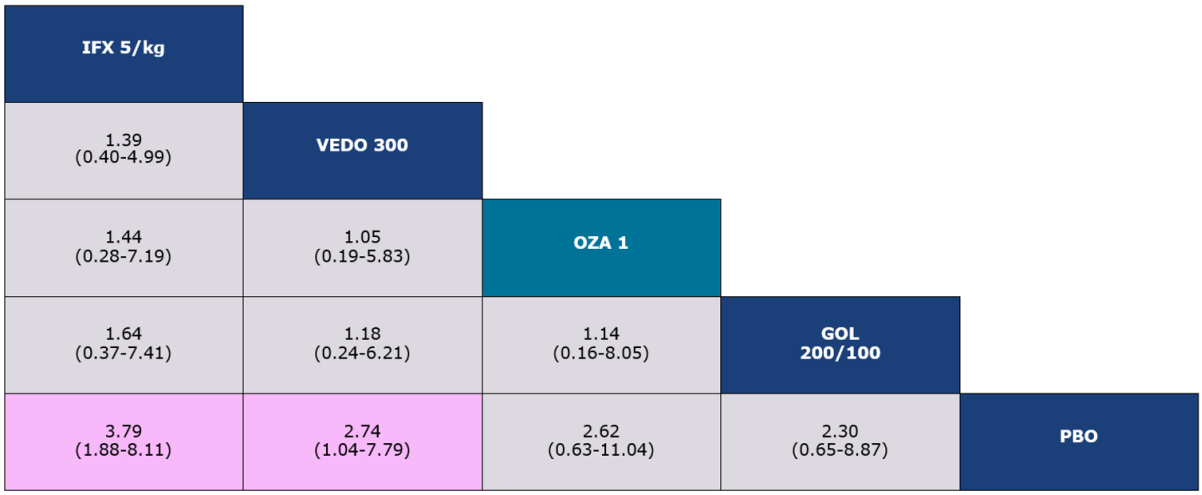


GOL = golimumab; IFX = infliximab; OZA = ozanimod; PBO = placebo; VEDO = vedolizumab.

Treatments are ordered from top-left to bottom-right by decreasing rank. For each pairwise comparison, the row treatment serves as the reference group. Pairwise comparisons from the best-fitting network meta-analysis model are shown in terms of odds ratios and 95% credible interval. An odds ratio > 1 favours the treatment in each column. Odds ratios with credible intervals that do not span unity are shown with a purple background to indicate significance.

Source: BMS data on file (2022)[92]

Figure 33. League table for clinical response at induction in the bio-naive population (Ordinal, Unadjusted Random effects)



GOL = golimumab; IFX = infliximab; OZA = ozanimod; PBO = placebo; VEDO = vedolizumab.

Treatments are ordered from top-left to bottom-right by decreasing rank. For each pairwise comparison, the row treatment serves as the reference group. Pairwise comparisons from the best-fitting network meta-analysis model are shown in terms of odds ratios and 95% credible interval. An odds ratio > 1 favours the treatment in each column. Odds ratios with credible intervals that do not span unity are shown with a purple background to indicate significance.

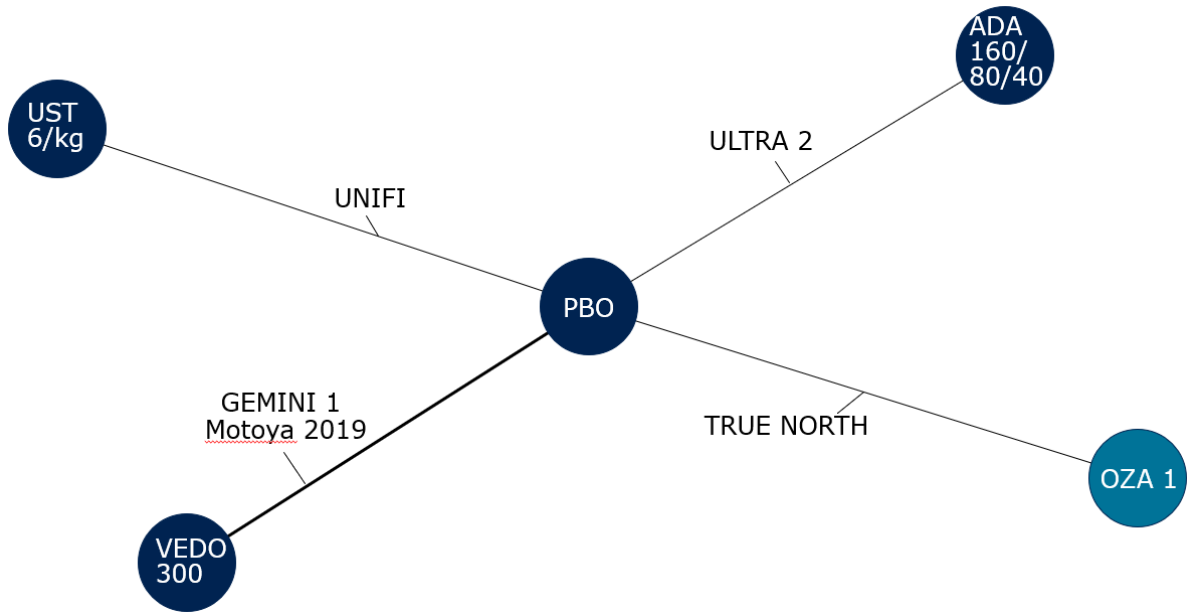
Source: BMS data on file (2022)[92]

7.2.14.2. Bio-experienced: clinical remission and clinical response at induction

7.2.14.2.1. Network of evidence

Data for the bio-experienced analyses were sparser than those in the bio-naive population since all data were retrieved from the bio-experienced subgroup in available mixed population trials (Figure 340). Of note, no data were available for golimumab and infliximab because these treatments were studied in entirely bio-naive populations. Of the remaining treatments, all were assessed in 1 or more placebo-controlled study, with some studies evaluating multiple doses of the same biologic. The network included one multiple study connection and random effects analysis was explored but models did not converge.

Figure 34. Evidence network for clinical remission and clinical response at induction in the bio-experienced population (Ordinal)



ADA = adalimumab; OZA = ozanimod; PBO = placebo; UST = ustekinumab; VEDO = vedolizumab.
Source: BMS data on file (2022)[92]

7.2.14.2.2. Model fit statistics

Table 22. Model fit statistics for clinical response and remission at induction (bio-experienced population)

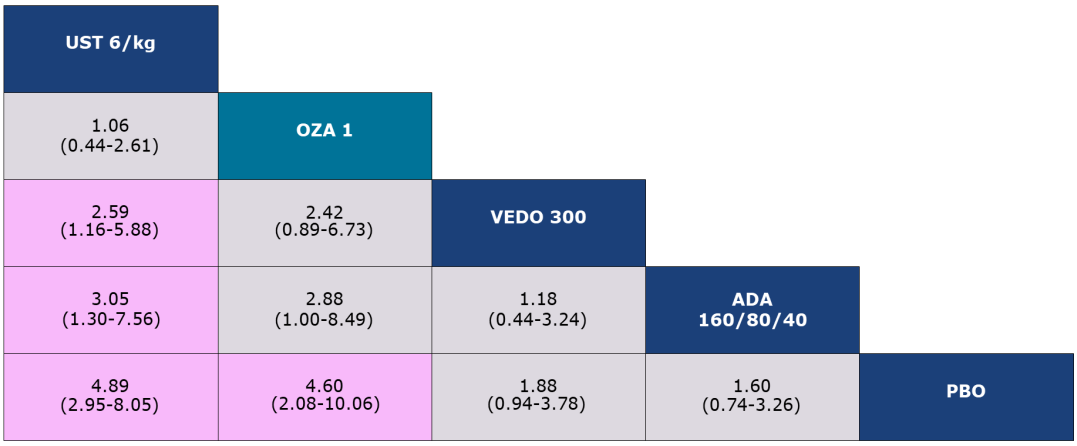
Diagnostic	Fixed effects model	Random effects model
DIC	**45.30**	Did not converge
ResDev (vs. 24 data points)	35.30	Did not converge
SDbt (95% CrI)	NA	Did not converge

CrI = credible interval; DIC = deviance information criterion; NA = not applicable; ResDev = residual deviance; SDbt = standard deviation between-trial heterogeneity.
Note: bold text denotes the preferred model
Source: BMS data on file (2022)[92]

7.2.14.2.3. Results

Both ozanimod and ustekinumab showed statistically significant improvements in clinical remission (Figure 350) and clinical response (Figure 36) over placebo. No statistically significant differences were found between ozanimod and other active therapies.

Figure 35. League table for clinical remission at induction in the bio-experienced population (Ordinal Unadjusted, Fixed Effect)

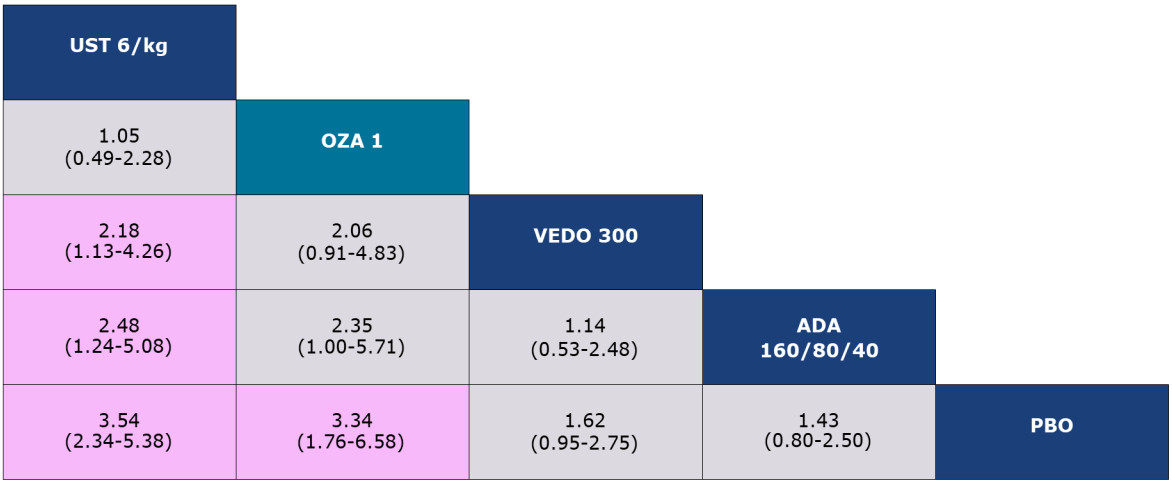


ADA = adalimumab; OZA = ozanimod; PBO = placebo; UST = ustekinumab; VEDO = vedolizumab.

Treatments are ordered from top-left to bottom-right by decreasing rank. For each pairwise comparison, the row treatment serves as the reference group. Pairwise comparisons from the best-fitting network meta-analysis model are shown in terms of odds ratios and 95% credible interval. An odds ratio > 1 favours the treatment in each column. Odds ratios with credible intervals that do not span unity are shown with a purple background to indicate significance.

Source: BMS data on file (2022)[92]

Figure 36. League table for clinical response at induction in the bio-experienced population (Ordinal Unadjusted, Fixed Effect)



ADA = adalimumab; OZA = ozanimod; PBO = placebo; UST = ustekinumab; VEDO = vedolizumab.

Treatments are ordered from top-left to bottom-right by decreasing rank. For each pairwise comparison, the row treatment serves as the reference group. Pairwise comparisons from the best-fitting network meta-analysis model are shown in terms of odds ratios and 95% credible interval. An odds ratio > 1 favours the treatment in each column. Odds ratios with credible intervals that do not span unity are shown with a purple background to indicate significance.

Source: BMS data on file (2022)[92]

7.2.15. Results from the comparative analysis at maintenance

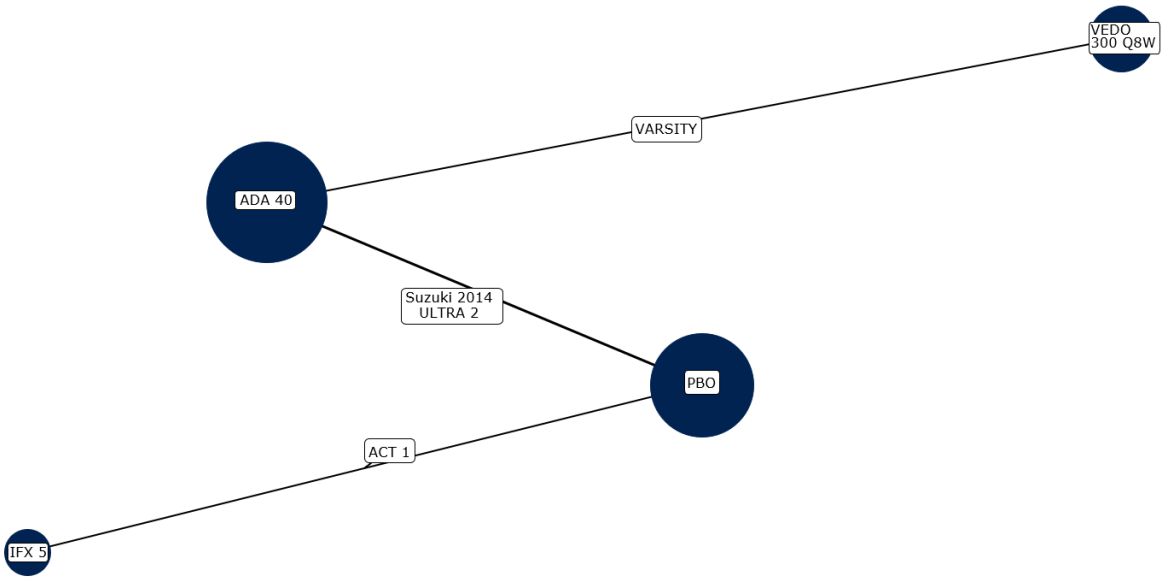
7.2.15.1. Bio-naive: Corticosteroid-free remission at maintenance

7.2.15.1.1. Network of evidence

As requested by DMC, TT and RR study designs have been analysed separately and therefore there are two network diagrams, model fit statistics tables and league tables for each outcome in the maintenance analyses.

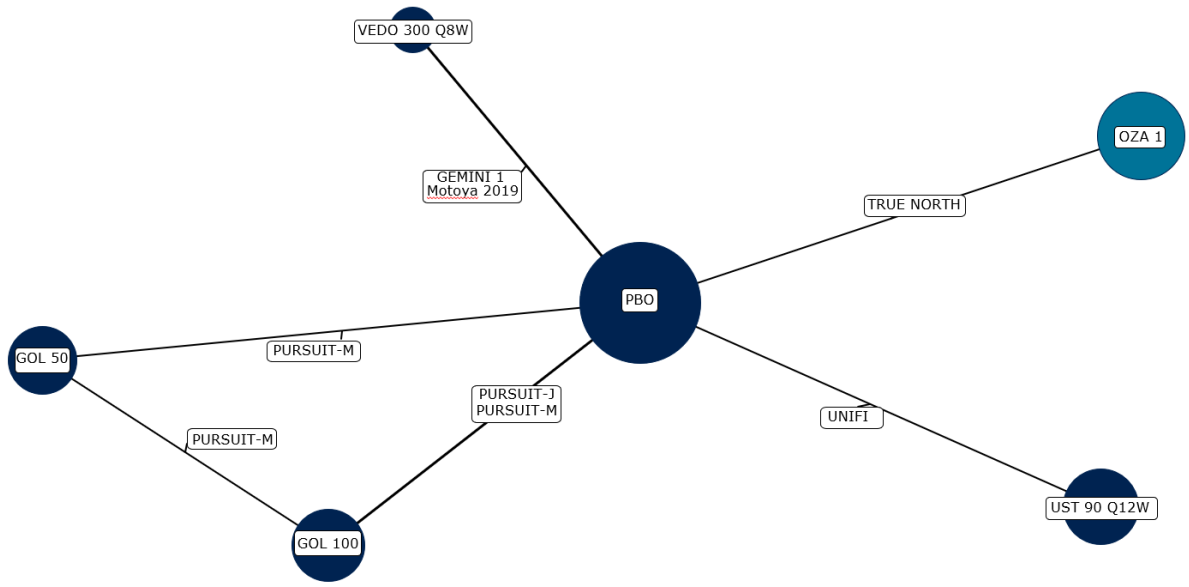
All interventions were assessed in 1 or more placebo-controlled studies. The analysis for the TT population includes the trials VARSITY, ACT 1, as well as Suzuki 2014 and ULTRA 2. Suzuki 2014 and ULTRA 2 are trials that investigate adalimumab in comparison to placebo in a bio-naïve population and therefore are not of relevance to Denmark. However, per the network diagram, adalimumab in comparison to placebo data are required to connect infliximab to vedolizumab and have therefore been included in this NMA (Figure 37). There is, however, also the option of evaluation of the TT population with regard to the ACT 1 trial only. The analysis for the RR population is presented in Figure 38.

Figure 37. Evidence network for corticosteroid-free remission at maintenance in the bio-naïve TT population (Binominal)



ADA = adalimumab; IFX = infliximab; PBO = placebo; TT = treat-through trial design ; VEDO = vedolizumab.
Source: BMS data on file (2022)[92]

Figure 38. Evidence network for corticosteroid-free remission at maintenance in the bio-naïve RR population (Binominal)



GOL = golimumab; UST = ustekinumab; OZA = ozanimod; PBO = placebo; RR = re-randomised trial design ; VEDO = vedolizumab.

Source: BMS data on file (2022)[92]

Table 23. Model fit statistics for corticosteroid-free remission at maintenance TT (bio-naïve population)

Diagnostic	Fixed effects model	Random effects model
DIC	**46.46**	47.29
ResDev (vs. 8 data points)	7.05	7.63
SDbt (95% CrI)	NA	0.65 (0.02-1.91)

CrI = credible interval; DIC = deviance information criterion; NA = not applicable; ResDev = residual deviance; SDbt = standard deviation between-trial heterogeneity; TT = treat-through trial design .

Note: bold text denotes the preferred model

Table 24. Source: BMS data on file (2022)[92]Model fit statistics for corticosteroid-free remission at maintenance RR (bio-naive population)

Diagnostic	Fixed effects model	Random effects model
DIC	**76.41**	76.13
ResDev (vs. 13 data points)	14.06	13.18
SDbt (95% CrI)	NA	0.86 (0.04-1.92)

CrI = credible interval; DIC = deviance information criterion; NA = not applicable; ResDev = residual deviance; RR = re-randomised trial design ; SDbt = standard deviation between-trial heterogeneity.

Note: bold text denotes the preferred model

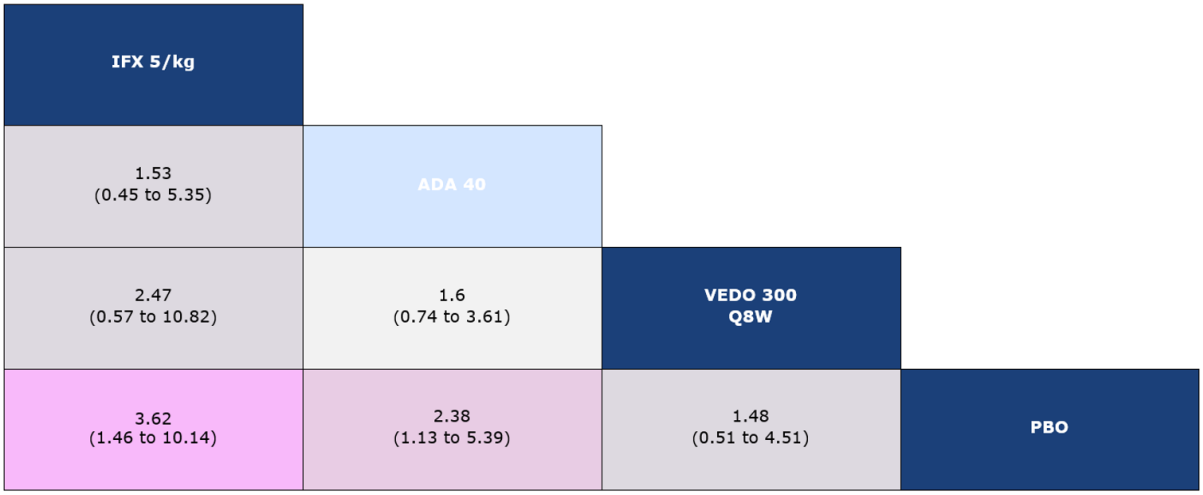
Source: BMS data on file (2022)[92]

7.2.15.1.2. Results

Only infliximab offered statistically significant improvement over placebo in corticosteroid-free remission for the bio-naïve TT studies (Figure 39). For the bio-naive RR studies, ozanimod, vedolizumab, and ustekinumab

offered statistically significant improvement in corticosteroid-free remission over placebo (Figure 40). Ozanimod was found to be numerically superior to all other active agents in the RR studies of a bio-naive population.

Figure 39. League table for corticosteroid-free remission at maintenance in the bio-naive TT population (Binominal, Unadjusted, Fixed Effect)

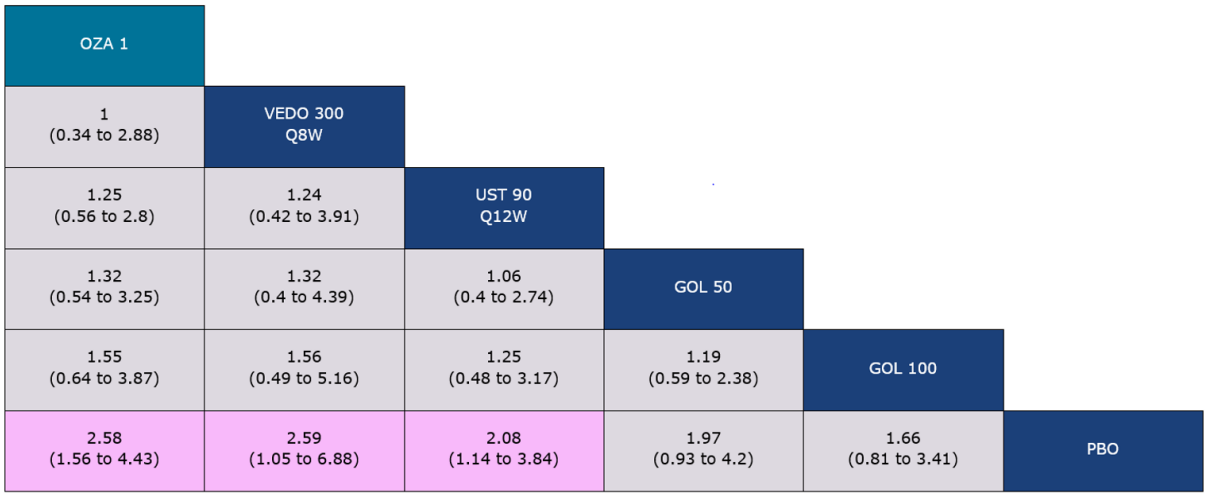


ADA = adalimumab; IFX = infliximab; OZA = ozanimod; PBO = placebo; TT = treat-through trial design ; VEDO = vedolizumab.

Treatments are ordered from top-left to bottom-right by decreasing rank. For each pairwise comparison, the row treatment serves as the reference group. Pairwise comparisons from the best-fitting network meta-analysis model are shown in terms of odds ratios and 95% credible interval. An odds ratio > 1 favours the treatment in each column. Odds ratios with credible intervals that do not span unity are shown with a purple background to indicate significance.

Source: BMS data on file (2022)[92]

Figure 40. League table for corticosteroid-free remission at maintenance in the bio-naïve RR population (Binominal, Unadjusted, Fixed Effect)



GOL = golimumab; IFX = infliximab; OZA = ozanimod; PBO = placebo; RR = re-randomised trial design ; VEDO = vedolizumab; UST = ustekinumab.

Treatments are ordered from top-left to bottom-right by decreasing rank. For each pairwise comparison, the row treatment serves as the reference group. Pairwise comparisons from the best-fitting network meta-analysis model are shown in terms of odds ratios and 95% credible interval. An odds ratio > 1 favours the treatment in each column. Odds ratios with credible intervals that do not span unity are shown with a purple background to indicate significance.

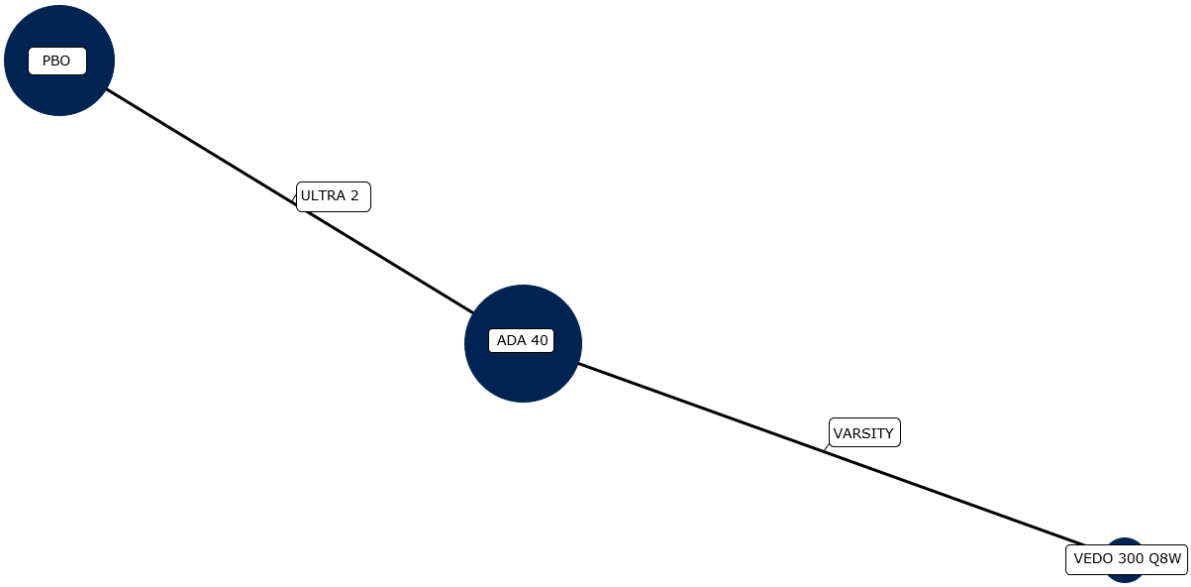
Source: BMS data on file (2022)[92]

7.2.15.2. Bio-experienced: corticosteroid-free remission at maintenance

7.2.15.2.1. Network of evidence

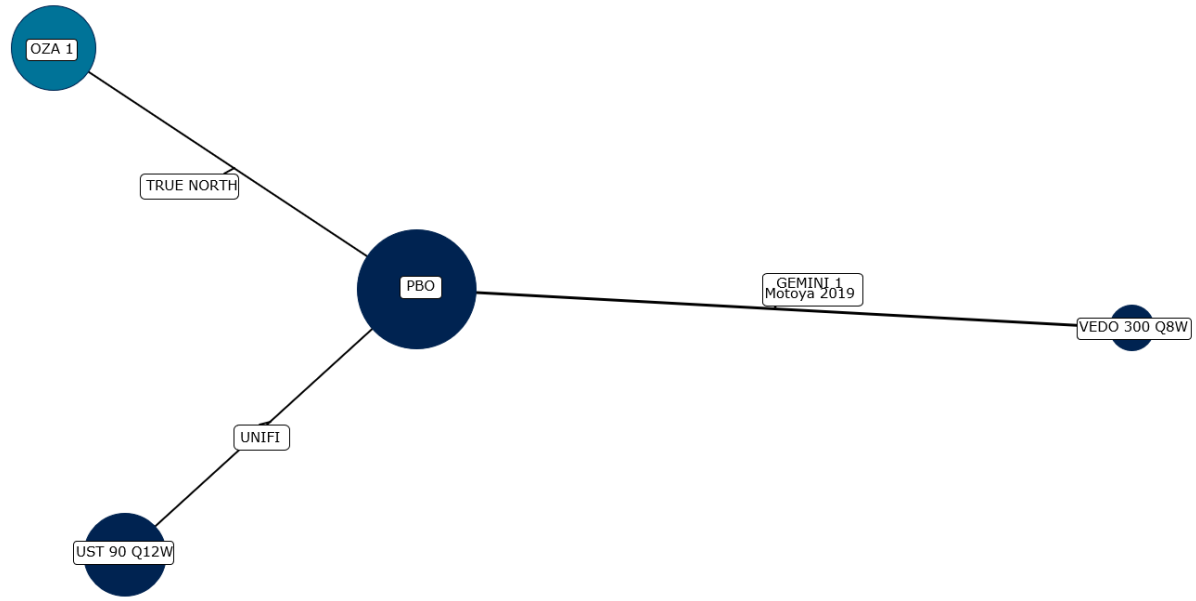
Data for the bio-experienced maintenance analyses were sparser than those in the bio-naive population since all data were retrieved from the bio-experienced subgroup in available mixed population trials. No data were available for golimumab and infliximab as these treatments were studied in entirely bio-naive populations (Figure 41).

Figure 41. Evidence network for corticosteroid-free remission at maintenance in the bio-experienced TT population (Binominal)



ADA = adalimumab; PBO = placebo; TT = treat-through trial design ; VEDO = vedolizumab.
Source: BMS data on file (2022)[92]

Figure 42. Evidence network for corticosteroid-free remission at maintenance in the bio-experienced RR population (Binominal)



OZA = ozanimod; PBO = placebo; RR = re-randomised trial design ; UST = ustekinumab; VEDO = vedolizumab.

7.2.15.2.2. Model fit statistics

The preferred model is the fixed effects model, shown in bold text in the table below.

Table 25. Model fit statistics for corticosteroid-free remission at maintenance TT (bio-experienced population)

Diagnostic	Fixed effects model	Random effects model
DIC	**19.85**	19.61
ResDev (vs. 4 data points)	4.31	4.23
SDbt (95% CrI)	NA	1.01 (0.06-1.95)

CrI = credible interval; DIC = deviance information criterion; NA = not applicable; ResDev = residual deviance; SDbt = standard deviation between-trial heterogeneity; TT = treat-through trial design .

Note: bold text denotes the preferred model

Source: BMS data on file (2022)[92]

Table 26. Model fit statistics for corticosteroid-free remission at maintenance RR (bio-experienced population)

Diagnostic	Fixed effects model	Random effects model
DIC	**40.06**	40.94
ResDev (vs. 8 data points)	7.29	7.62
SDbt (95% CrI)	NA	0.88 (0.03-1.93)

CrI = credible interval; DIC = deviance information criterion; NA = not applicable; ResDev = residual deviance; RR = re-randomised trial design ; SDbt = standard deviation between-trial heterogeneity.

Note: bold text denotes the preferred model

Source: BMS data on file (2022)[92]

7.2.15.2.3. Results

In the TT network of bio-experienced patients, adalimumab was significantly better than vedolizumab 300 Q8W in terms of corticosteroid-free remission (Figure 43). In the RR studies, vedolizumab and ozanimod offered statistically significant improvement in corticosteroid-free remission (Figure 44) over placebo in the bio-experienced maintenance period. Ozanimod was comparable to all other active agents and in favour of vedolizumab versus ozanimod..

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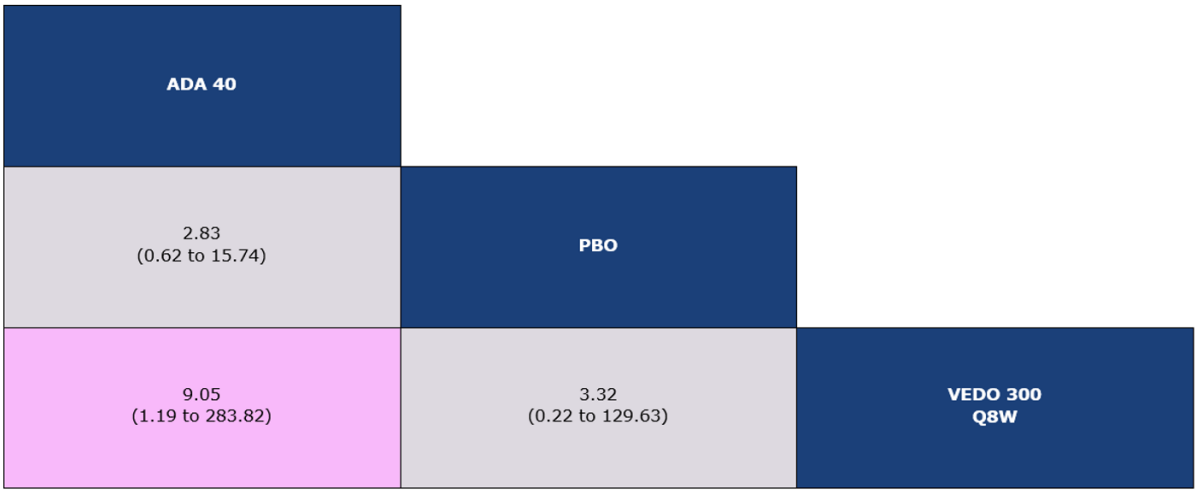
Figure 43. League table for corticosteroid-free remission at maintenance in the bio-experienced TT population (Binominal, Unadjusted, Fixed Effect)

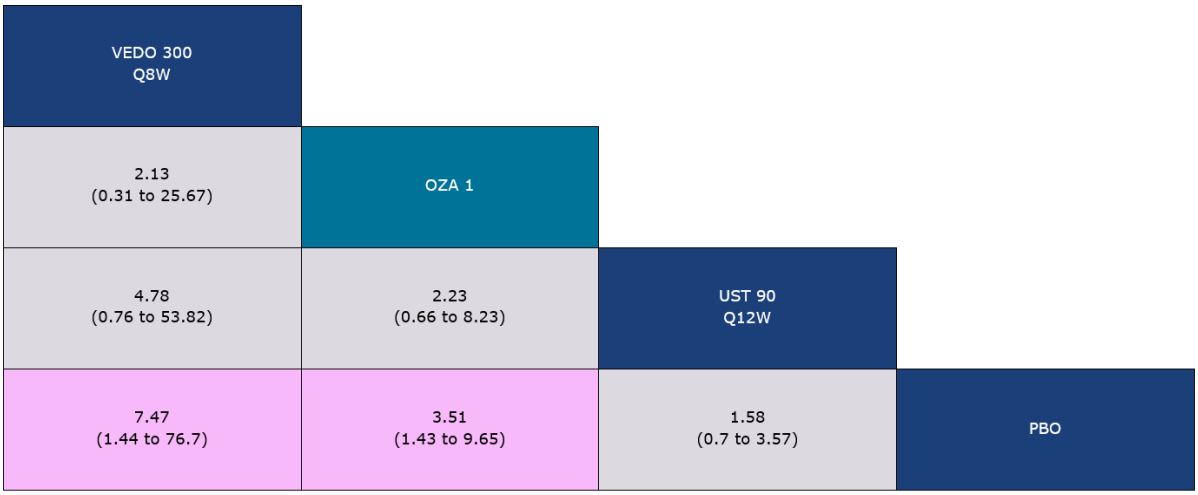


ADA = adalimumab; PBO = placebo; TT = treat-through trial design ; VEDO = vedolizumab.

Treatments are ordered from top-left to bottom-right by decreasing rank. For each pairwise comparison, the row treatment serves as the reference group. Pairwise comparisons from the best-fitting network meta-analysis model are shown in terms of odds ratios and 95% credible interval. An odds ratio > 1 favours the treatment in each column. Odds ratios with credible intervals that do not span unity are shown with a purple background to indicate significance.

Source: BMS data on file (2022)[92]

Figure 44. League table for corticosteroid-free remission at maintenance in the bio-experienced RR population (Binominal Unadjusted, Fixed Effect)



OZA = ozanimod; PBO = placebo; RR = re-randomised trial design ; UST = ustekinumab; VEDO = vedolizumab.

Treatments are ordered from top-left to bottom-right by decreasing rank. For each pairwise comparison, the row treatment serves as the reference group. Pairwise comparisons from the best-fitting network meta-analysis model are shown in terms of odds ratios and 95% credible interval. An odds ratio > 1 favours the treatment in each column. Odds ratios with credible intervals that do not span unity are shown with a purple background to indicate significance.

Source: BMS data on file (2022)[92]

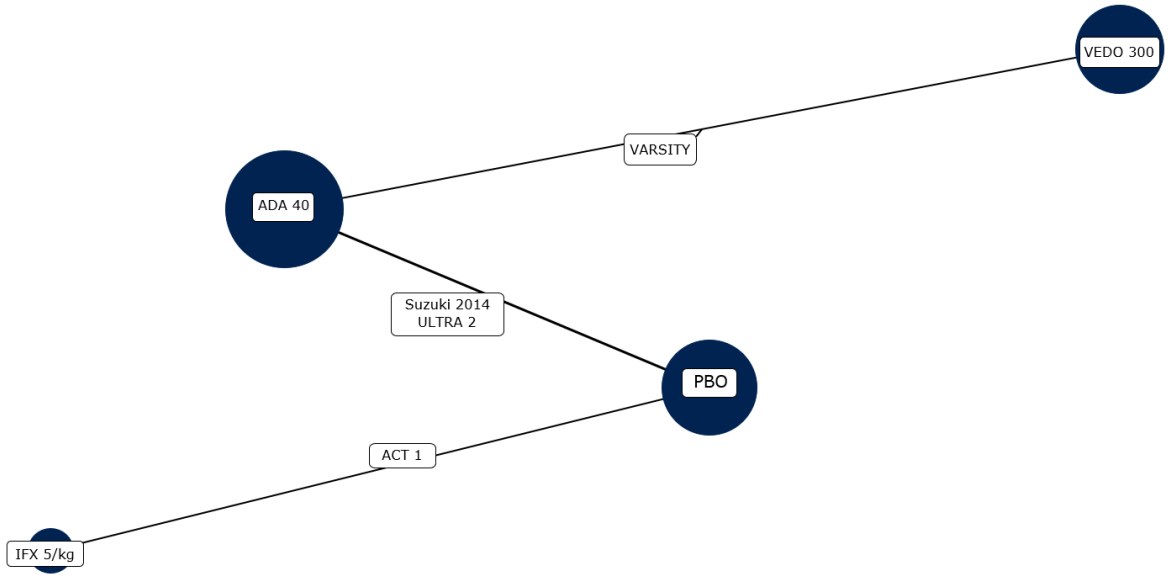
7.2.15.3. Bio-naïve population: endoscopic improvement at maintenance

7.2.15.3.1. Network of evidence

With the data available for endoscopic improvement in the naïve population treatments were assessed in 1 or more placebo-controlled studies. The analysis for the TT population includes the trials VARSITY, ACT 1, as well

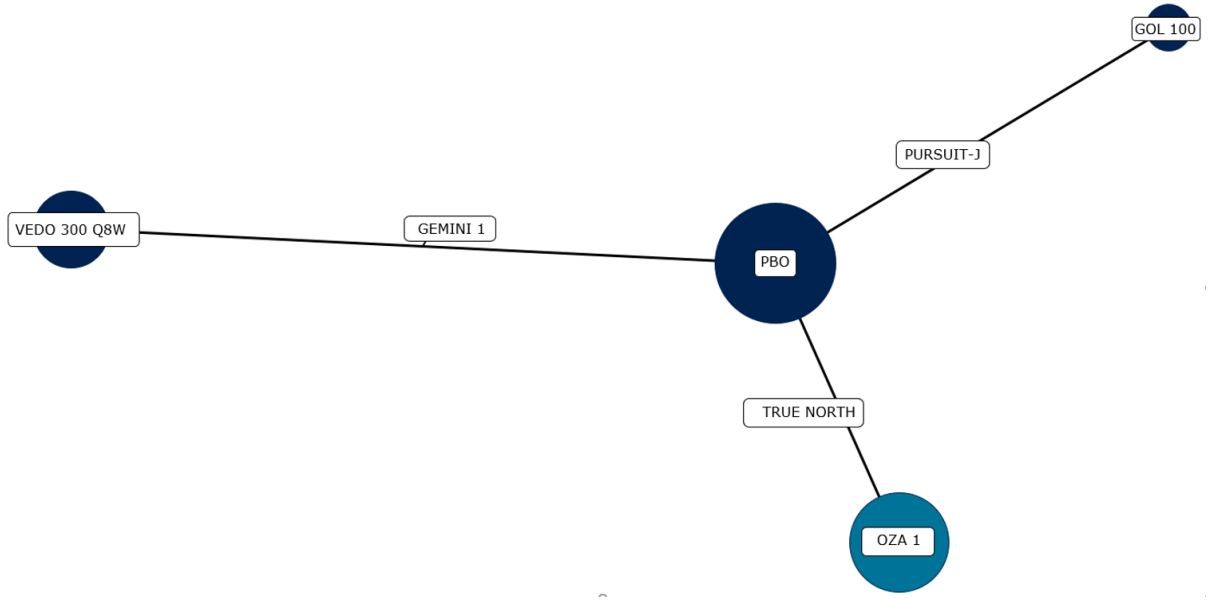
as Suzuki 2014 and ULTRA 2. Suzuki 2014 and ULTRA 2 are trials that investigate adalimumab in comparison to placebo in a bio-naïve population and therefore are not of relevance to Denmark. However, per the network diagram, adalimumab in comparison to placebo data are required to connect infliximab to vedolizumab and have therefore been included in this NMA (Figure 45). There is, however, also the option of evaluation of the TT population with regard to the ACT 1 trial only. The analysis for the RR population is presented in Figure 46.

Figure 45. Evidence network for endoscopic improvement at maintenance in the bio-naïve TT population (Binomial)



ADA = adalimumab; IFX = infliximab; PBO = placebo; TT = treat-through trial design ; VEDO = vedolizumab.
Source: BMS data on file (2022)[92]

Figure 46. Evidence network for endoscopic improvement at maintenance in the bio-naïve RR population (Binomial)



GOL = golimumab; OZA = ozanimod; PBO = placebo; RR = re-randomised trial design ; VEDO = vedolizumab.
Source: BMS data on file (2022)[92]

Table 27. Model fit statistics for endoscopic improvement at maintenance TT (bio-naive population)

Diagnostic	Fixed effects model	Random effects model
DIC	**56.39**	57.73
ResDev (vs. 8 data points)	7.13	7.59
SDbt (95% CrI)	NA	0.53 (0.02-1.87)

CrI = credible interval; DIC = deviance information criterion; NA = not applicable; ResDev = residual deviance; SDbt = standard deviation between-trial heterogeneity; TT = treat-through trial design .

Note: bold text denotes the preferred model

Source: BMS data on file (2022)[92]

Table 28. Model fit statistics for endoscopic improvement at maintenance RR (bio-naive population)

Diagnostic	Fixed effects model	Random effects model
DIC	**39.44**	39.11
ResDev (vs. 6 data points)	6.08	6.12
SDbt (95% CrI)	NA	1.0 (0.05-1.95)

CrI = credible interval; DIC = deviance information criterion; NA = not applicable; ResDev = residual deviance; RR = re-randomised trial design ; SDbt = standard deviation between-trial heterogeneity.

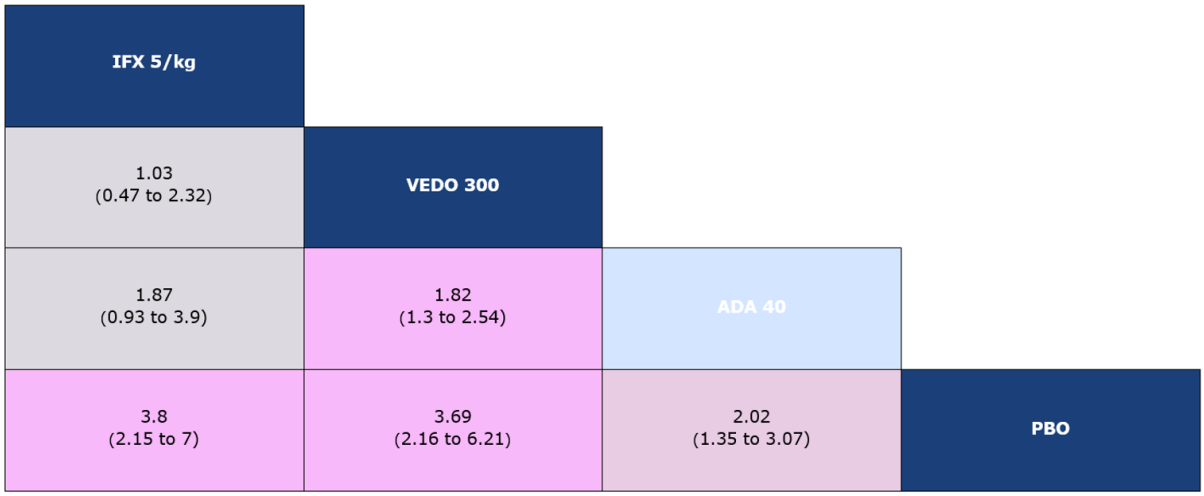
Note: bold text denotes the preferred model

Source: BMS data on file (2022)[92]

7.2.15.3.2. Results

All active agents offered statistically significant improvement in endoscopic improvement over placebo (Figure 47 and Figure 48).

Figure 47. League table for endoscopic improvement at maintenance in the bio-naive TT population (Binomial, Unadjusted, Fixed Effect)

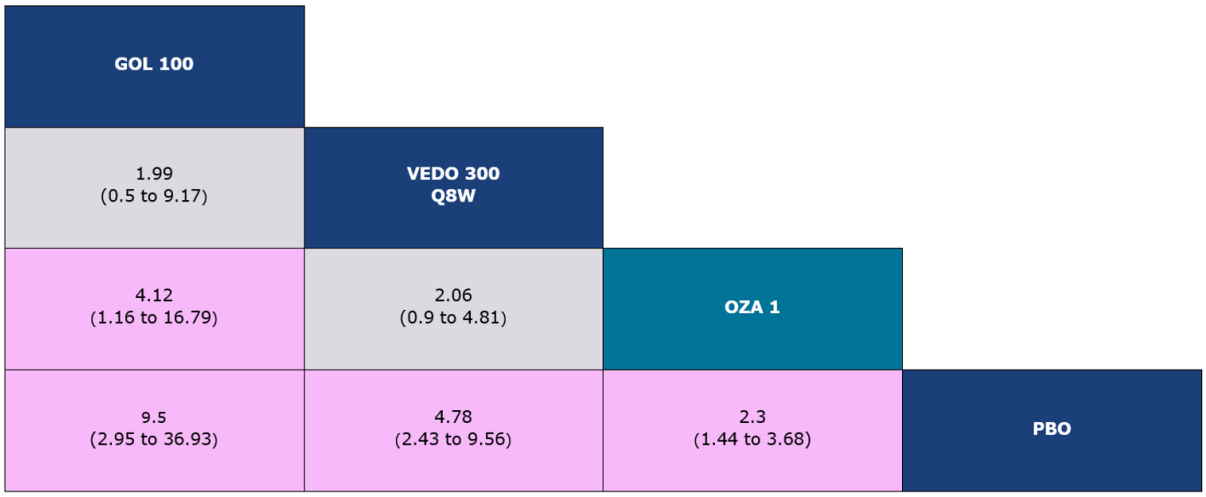


ADA = adalimumab;IFX = infliximab; PBO = placebo; TT = treat-through trial design ; VEDO = vedolizumab.

Treatments are ordered from top-left to bottom-right by decreasing rank. For each pairwise comparison, the row treatment serves as the reference group. Pairwise comparisons from the best-fitting network meta-analysis model are shown in terms of odds ratios and 95% credible interval. An odds ratio > 1 favours the treatment in each column. Odds ratios with credible intervals that do not span unity are shown with a purple background to indicate significance.

Source: BMS data on file (2022)[92]

Figure 48. League table for endoscopic improvement at maintenance in the bio-naive RR population (Binomial, Unadjusted, Fixed Effect)



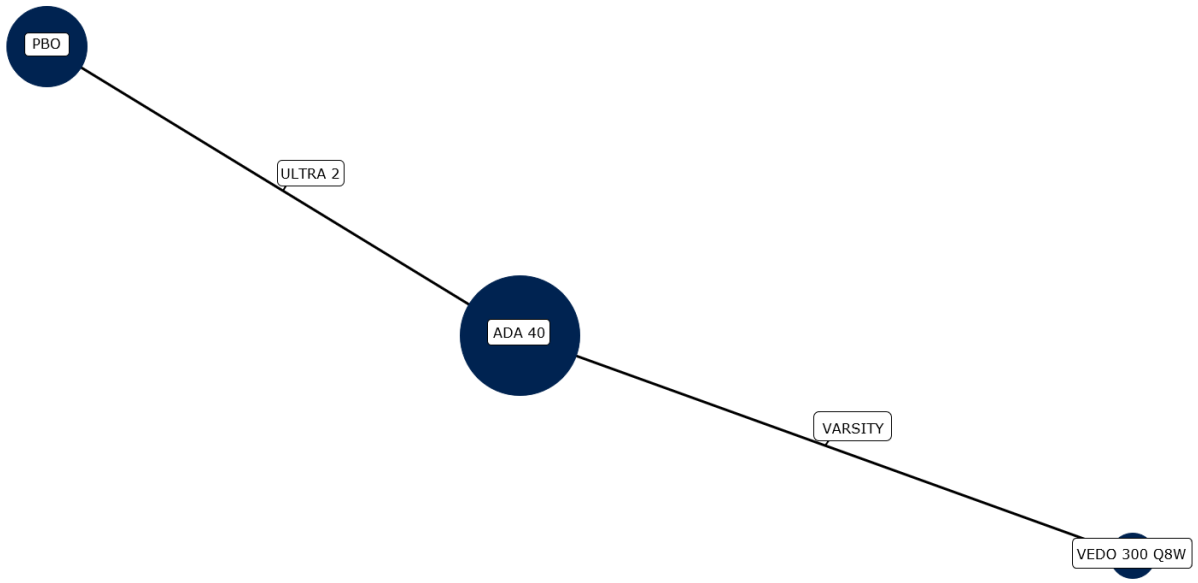
GOL = golimumab; OZA = ozanimod; PBO = placebo; RR = re-randomised trial design ; VEDO = vedolizumab.
Treatments are ordered from top-left to bottom-right by decreasing rank. For each pairwise comparison, the row treatment serves as the reference group. Pairwise comparisons from the best-fitting network meta-analysis model are shown in terms of odds ratios and 95% credible interval. An odds ratio > 1 favours the treatment in each column. Odds ratios with credible intervals that do not span unity are shown with a purple background to indicate significance.
Source: BMS data on file (2022)[92]

7.2.15.4. Bio-experienced population: endoscopic improvement at maintenance

7.2.15.4.1. Network of evidence

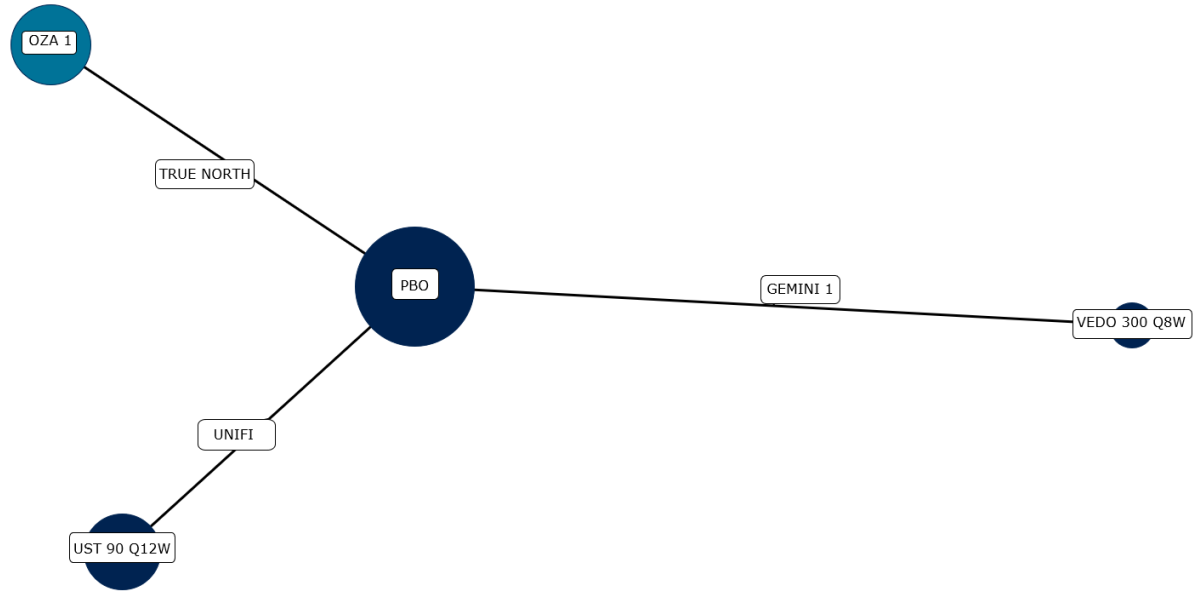
With the data available for endoscopic improvement in the bio-experienced population treatments, all were assessed in 1 or more placebo-controlled studies. The analysis for the TT population includes the trials VARSITY and ULTRA 2; they are trials that investigate adalimumab in comparison to placebo and adalimumab in comparison to vedolizumab in a bio-experienced population. This NMA has been requested by the DMC and has therefore been included (Figure 49). The NMA for the RR population is presented in Figure 50.

Figure 49. Evidence network for endoscopic improvement at maintenance in the bio-experienced TT population (Binomial)



ADA = adalimumab; PBO = placebo; TT = treat-through trial design ; UST = ustekinumab; VEDO = vedolizumab.
Source: BMS data on file (2022)[92]

Figure 50. Evidence network for endoscopic improvement at maintenance in the bio-experienced RR population (Binomial)



OZA = ozanimod; PBO = placebo; RR = re-randomised trial design ; UST = ustekinumab; VEDO = vedolizumab.
Source: BMS data on file (2022)[92]

7.2.15.4.2. Model fit statistics

Table 29. Model fit statistics for endoscopic improvement at induction TT (bio-experienced population)

Diagnostic	Fixed effects model	Random effects model
DIC	**25.28**	25.47
ResDev (vs. 4 data points)	4.02	4.07
SDbt (95% CrI)	NA	1.01 (0.05-1.95)

CrI = credible interval; DIC = deviance information criterion; NA = not applicable; ResDev = residual deviance; SDbt = standard deviation between-trial heterogeneity; TT = treat-through trial design .
Note: bold text denotes the preferred model
Source: BMS data on file (2022)[92]

Table 30. Model fit statistics for endoscopic improvement at induction RR (bio-experienced population)

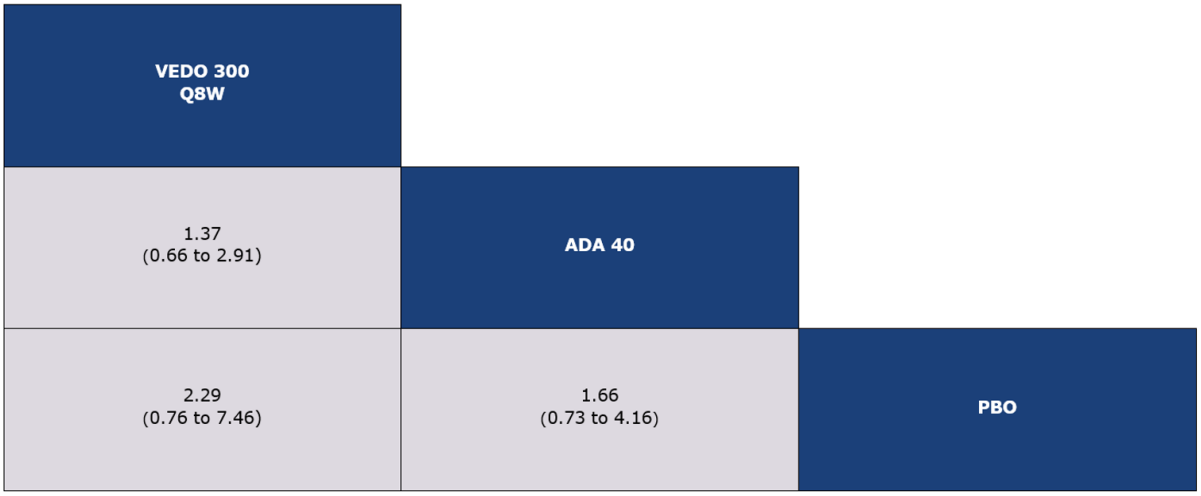
Diagnostic	Fixed effects model	Random effects model
DIC	**36.92**	37.0
ResDev (vs. 6 data points)	6.15	6.06
SDbt (95% CrI)	NA	0.98 (0.04-1.95)

CrI = credible interval; DIC = deviance information criterion; NA = not applicable; ResDev = residual deviance; RR = re-randomised trial design ; SDbt = standard deviation between-trial heterogeneity.
Note: bold text denotes the preferred model
Source: BMS data on file (2022)[92]

7.2.15.4.3. Results

In the TT analysis, the active agents (adalimumab and vedolizumab) did not show a statistically significant benefit in endoscopic improvement over placebo (Figure 51). For the RR population, ozanimod and vedolizumab show statistically significant improvement over placebo (Figure 52).

Figure 51. League table for endoscopic improvement at maintenance in the bio-experienced TT population (Binomial, Unadjusted, Fixed Effect)

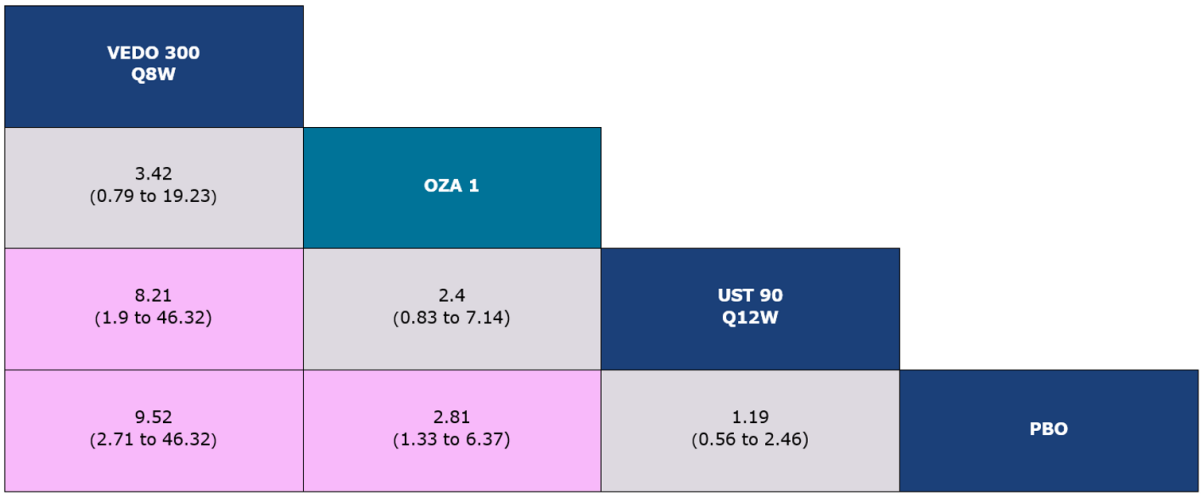


ADA = adalimumab; PBO = placebo; TT = treat-through trial design ; VEDO = vedolizumab.

Treatments are ordered from top-left to bottom-right by decreasing rank. For each pairwise comparison, the row treatment serves as the reference group. Pairwise comparisons from the best-fitting network meta-analysis model are shown in terms of odds ratios and 95% credible interval. An odds ratio > 1 favours the treatment in each column. Odds ratios with credible intervals that do not span unity are shown with a purple background to indicate significance.

Source: BMS data on file (2022)[92]

Figure 52. League table for endoscopic improvement at maintenance in the bio-experienced RR population (Binomial, Unadjusted, Fixed Effect)



OZA = ozanimod; PBO = placebo; RR = re-randomised trial design ; UST = ustekinumab; VEDO = vedolizumab.

Treatments are ordered from top-left to bottom-right by decreasing rank. For each pairwise comparison, the row treatment serves as the reference group. Pairwise comparisons from the best-fitting network meta-analysis model are shown in terms of odds ratios and 95% credible interval. An odds ratio > 1 favours the treatment in each column. Odds ratios with credible intervals that do not span unity are shown with a purple background to indicate significance.

Source: BMS data on file (2022)[92]

7.2.16. Safety results from the comparative analysis

The DMC requested that the safety analysis be presented by biologic exposure (naive and experienced) rather than by treatment phases (induction and maintenance). However, it was deemed not an appropriate analysis as this effectively treats the bio-naive and bio-experienced populations as separate studies, and outcomes can differ between induction and maintenance. Also, the trials included in the NMA included both "treat-through" and "re-randomised" trial designs. If we were to pool the safety data based on biologic exposure, there is potential to have patients in re-randomised trial designs that were on treatment drug at induction but switched to placebo at the maintenance phase. Although this analysis is not deemed appropriate, an analysis of the combined treatment phases for the overall population is presented at the end of this section.

The main comparative safety analysis presented is also limited to the overall population due to data availability. These analyses include the induction analysis of SAEs regardless of prior bio exposure, the maintenance analysis of SAEs regardless of prior bio exposure (with RR and TT study designs combined) and a combined induction/maintenance network (includes all studies regardless of design and bio experience).. Many of the treatments, including ozanimod, had low event rates across several safety outcomes. The use of low event rates to inform binomial models leads to high levels of uncertainty in the NMA results and often results in overlap in pairwise 95% credible intervals between most treatments. Therefore, results from safety analyses should be interpreted with caution in the context of the NMA being underpowered because of the rarity of outcomes.[17]

The model selection rationale is detailed throughout. Similar to the clinical efficacy analysis models for each analysis were selected by inspecting model fit statistics (see Table 30, Table 31, and Table 32). Preferred models are highlighted in bold. For each analysis, the default preference was for random effects models over fixed effect when possible, to acknowledge the heterogeneity identified in the networks. When model fit statistics disagree substantially, preference should be given to the model with lower DIC and lower ResDev, provided posterior SD was reasonably estimated. In this case, fits were generally similar for all models. However, despite similar fits between fixed and random effects models, in several analyses the random effects models produced improbably wide credible intervals for pairwise treatment comparisons. This was due to the limited size of these networks, which were reduced by removing entire trials, or removing treatment arms from some included trials, to accommodate specific comparator, dosage, and follow-up time requirements for Denmark. This resulted in the majority of links in the treatment networks consisting of single trials, necessitating fixed effects models, which are more appropriate under those constraints.

7.2.16.1. Network meta-analysis safety: induction period

7.2.16.1.1. Network of evidence

In the induction period, analyses for SAEs used an unadjusted, fixed effects model owing to a sparse network structure (Figure 53). Ozanimod consistently demonstrated comparable SAEs to all other agents (Figure 54).

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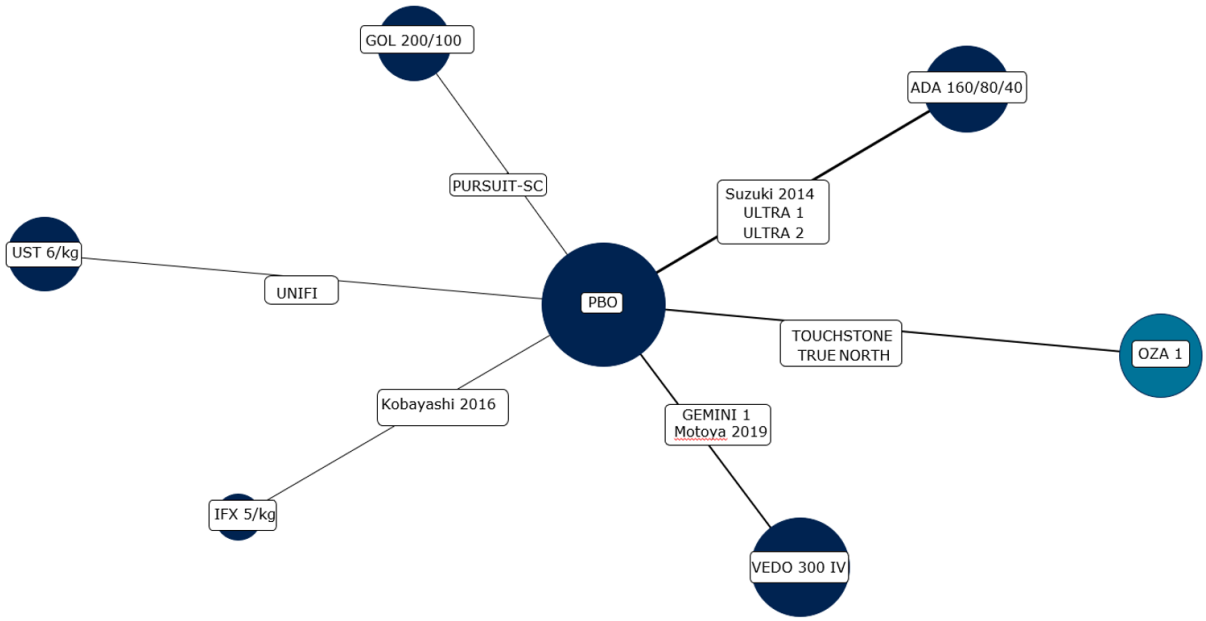
Figure 53. Evidence network for serious adverse events at induction in the overall population (Binomial)



ADA = adalimumab; GOL = golimumab; IFX = infliximab; OZA = ozanimod; PBO = placebo; UST = ustekinumab; VEDO = vedolizumab.

Source: BMS data on file (2022)[92]

Table 31. Model fit statistics for serious adverse events at induction (overall population)

Diagnostic	Fixed effects model	Random effects model
DIC	**117.07**	118.67
ResDev (vs. 20 data points)	19.32	19.25
SDbt (95% CrI)	NA	0.35 (0.01-1.5)

CrI = credible interval; DIC = deviance information criterion; NA = not applicable; ResDev = residual deviance; SDbt = standard deviation between-trial heterogeneity.

Note: bold text denotes the preferred model

Source: BMS data on file (2022)[92]

7.2.16.1.2. Results

Figure 54. Serious adverse events at induction in the overall population (fixed effects)

GOL 200/100						
0.9 (0.29 to 2.7)	**UST 6/kg**					
0.7 (0.26 to 1.77)	0.79 (0.31 to 1.88)	**ADA 160/80/40**				
0.64 (0.19 to 2.2)	0.72 (0.22 to 2.34)	0.92 (0.33 to 2.6)	**IFX 5/kg**			
0.63 (0.21 to 1.74)	0.7 (0.25 to 1.83)	0.9 (0.39 to 1.97)	0.98 (0.31 to 2.94)	**VEDO 300 IV**		
0.42 (0.13 to 1.25)	0.47 (0.16 to 1.36)	0.6 (0.23 to 1.46)	0.64 (0.19 to 2.16)	0.67 (0.24 to 1.74)	**OZA 1**	
0.42 (0.18 to 0.93)	0.48 (0.22 to 0.97)	0.6 (0.37 to 0.98)	0.66 (0.26 to 1.64)	0.67 (0.36 to 1.34)	1.01 (0.48 to 2.23)	**PBO**

ADA = adalimumab; GOL = golimumab; IFX = infliximab; OZA = ozanimod; PBO = placebo; UST = ustekinumab; VEDO = vedolizumab.

Note: Treatments are ordered from top-left to bottom-right by decreasing rank. For each pairwise comparison, the row treatment serves as the reference group. Pairwise comparisons from the best-fitting network meta-analysis model are shown in terms of odds ratios and 95% credible intervals. An odds ratio < 1 favours the treatment in each column.

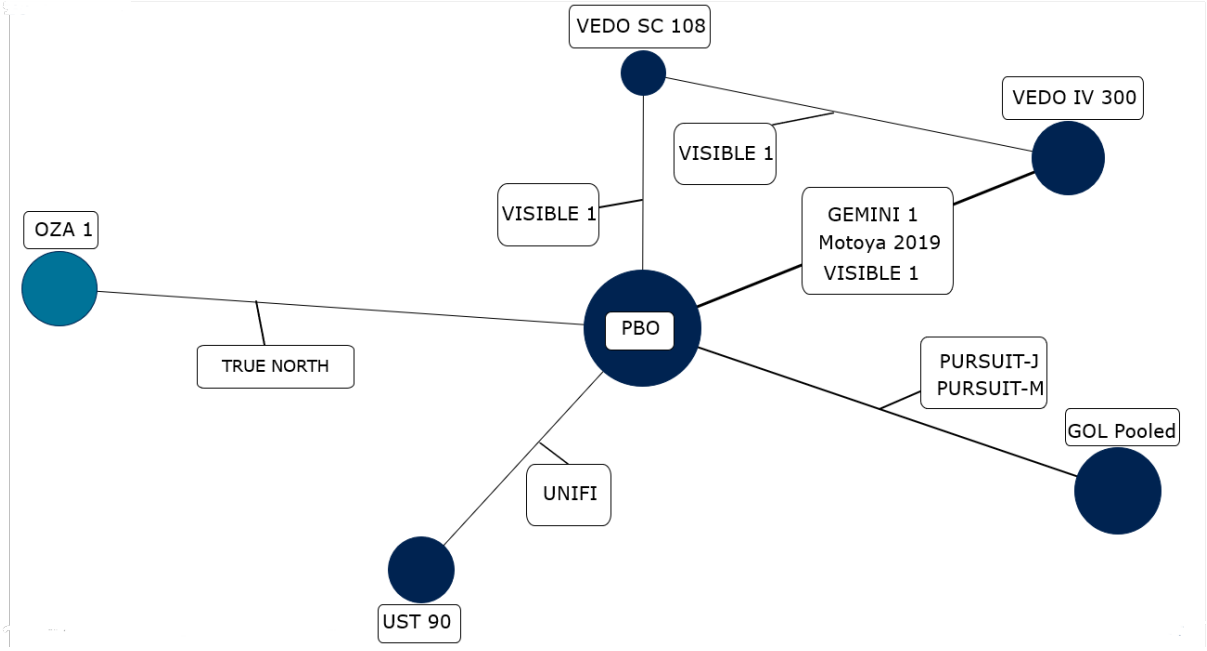
Source: BMS data on file (2022)[92]

7.2.16.2. Network meta-analysis safety: maintenance period

7.2.16.2.1. Network of evidence

In the maintenance period, the analysis for SAEs used an unadjusted fixed effects model owing to sparse network structures (Figure 55). Within the NMA, ozanimod offered comparable SAEs to all other agents (Figure 56).

Figure 55. Evidence network for serious adverse events at maintenance in the overall population (Binomial)



GOL = golimumab; OZA = ozanimod; PBO = placebo; UST = ustekinumab; VEDO = vedolizumab.

Source: BMS data on file (2022)[92]

Table 32. Model fit statistics for serious adverse events at maintenance (overall population)

Diagnostic	Fixed effects model	Random effects model
DIC	**88.57**	87.74
ResDev (vs. 15 data points)	18.03	15.38
SDbt (95% CrI)	NA	0.86 (0.07-1.9)

CrI = credible interval; DIC = deviance information criterion; NA = not applicable; ResDev = residual deviance; SDbt = standard deviation between-trial heterogeneity.

Note: bold text denotes the preferred model

Source: BMS data on file (2022)[92]

7.2.16.2.2. Results

Figure 56. Serious adverse events at maintenance in the overall population (fixed effects)

OZA 1					
0.94 (0.28 to 3.11)	VEDO SC 108				
0.88 (0.32 to 2.31)	0.92 (0.36 to 2.42)	VEDO IV 300			
0.84 (0.28 to 2.43)	0.89 (0.27 to 2.9)	0.96 (0.37 to 2.55)	UST 90		
0.63 (0.29 to 1.32)	0.67 (0.26 to 1.7)	0.72 (0.39 to 1.31)	0.75 (0.35 to 1.61)	PBO	
0.5 (0.18 to 1.29)	0.53 (0.17 to 1.59)	0.57 (0.24 to 1.35)	0.59 (0.21 to 1.59)	0.79 (0.41 to 1.47)	GOL Pooled

GOL = golimumab; OZA = ozanimod; PBO = placebo; UST = ustekinumab; VEDO = vedolizumab.

Note: Treatments are ordered from top-left to bottom-right by decreasing rank. For each pairwise comparison, the row treatment serves as the reference group. Pairwise comparisons from the best-fitting network meta-analysis model are shown in terms of odds ratios and 95% credible intervals. An odds ratio < 1 favours the treatment in each column.

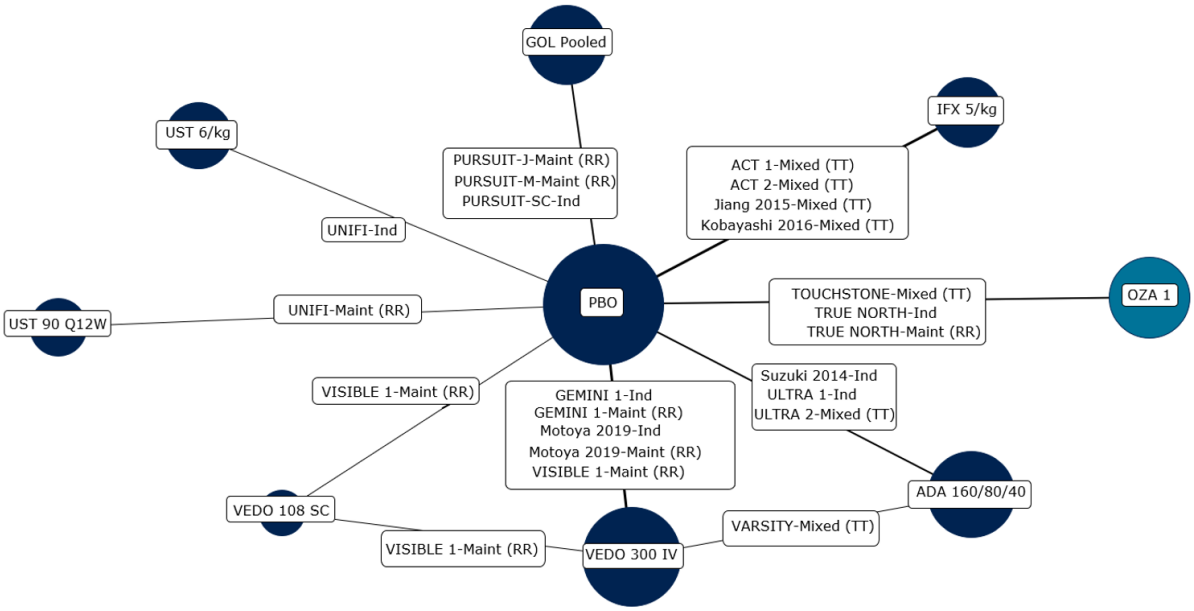
Source: BMS data on file (2022)[92]

7.2.16.3. Network meta-analysis safety: combined treatment phases

7.2.16.3.1. Network of evidence

The combined analysis for all treatment phases) used an unadjusted fixed effects model (Figure 57). This analysis showed that ozanimod offered comparable SAEs to all other agents (Figure 58).

Figure 57. Evidence network for serious adverse events in combined treatment phases in the overall population (Binomial)



ADA = adalimumab; GOL = golimumab; IFX = infliximab; OZA = ozanimod; PBO = placebo; UST = ustekinumab; VEDO = vedolizumab.

Source: BMS data on file (2022)[92]

7.2.16.3.2. Model fit statistics

Table 33. Model fit statistics for serious adverse events at maintenance (overall population)

Diagnostic	Fixed effects model	Random effects model
DIC	**255.16**	**Did not converge**
ResDev (vs. 15 data points)	47.2	Did not converge
SDbt (95% CrI)	NA	Did not converge

CrI = credible interval; DIC = deviance information criterion; NA = not applicable; ResDev = residual deviance; SDbt = standard deviation between-trial heterogeneity.

Note: bold text denotes the preferred model

Source: BMS data on file (2022)[92]

7.2.16.3.3. Results

Figure 58. Serious adverse events in combined treatment phases in the overall population (fixed effects)

UST 6/kg								
0.71 (0.3 to 1.64)	**VEDO 300 IV**							
0.74 (0.23 to 2.4)	1.03 (0.42 to 2.64)	**VEDO 108 SC**						
0.64 (0.27 to 1.48)	0.91 (0.54 to 1.54)	0.88 (0.32 to 2.31)	**IFX 5/kg**					
0.62 (0.21 to 1.81)	0.87 (0.37 to 2.09)	0.85 (0.25 to 2.71)	0.96 (0.4 to 2.28)	**UST 90 Q12W**				
0.6 (0.24 to 1.52)	0.84 (0.45 to 1.57)	0.82 (0.28 to 2.3)	0.93 (0.5 to 1.76)	0.97 (0.38 to 2.48)	**OZA 1**			
0.58 (0.25 to 1.32)	0.81 (0.57 to 1.14)	0.79 (0.3 to 1.96)	0.89 (0.53 to 1.49)	0.93 (0.39 to 2.14)	0.96 (0.52 to 1.78)	**ADA 160/80/40**		
0.56 (0.23 to 1.37)	0.79 (0.43 to 1.4)	0.76 (0.26 to 2.08)	0.87 (0.48 to 1.56)	0.9 (0.37 to 2.24)	0.93 (0.47 to 1.84)	0.97 (0.54 to 1.72)	**GOL Pooled**	
0.47 (0.22 to 1)	0.66 (0.46 to 0.94)	0.64 (0.25 to 1.54)	0.73 (0.5 to 1.06)	0.76 (0.35 to 1.63)	0.78 (0.46 to 1.31)	0.82 (0.57 to 1.15)	0.84 (0.53 to 1.35)	**PBO**

ADA = adalimumab; GOL = golimumab; IFX = infliximab; OZA = ozanimod; PBO = placebo; UST = ustekinumab; VEDO = vedolizumab.

Note: Treatments are ordered from top-left to bottom-right by decreasing rank. For each pairwise comparison, the row treatment serves as the reference group. Pairwise comparisons from the best-fitting network meta-analysis model are shown in terms of odds ratios and 95% credible intervals. An odds ratio < 1 favours the treatment in each column.

Source: BMS data on file (2022)[92]

7.3. Safety of ozanimod in moderately to severely active UC

As of 19 September 2020, a total of 5,180 patients received ozanimod in company-sponsored clinical trials, with approximately 16,200 patient-years of exposure/observation in patients with MS, UC, or Crohn's disease who received the therapeutic dose.[93]

7.3.1. Relevant studies: pooled safety data in ulcerative colitis

- D'Haens et al. (2021)[13] conducted a pooled safety analysis from the clinical development programme of ozanimod in UC. Table 33 presents details of the study methodology; further details on design, endpoints, and statistical analysis are described in Section 7.3.1.1. For detailed study characteristics, please refer to
- Appendix B. For baseline characteristics of patients included in each study, refer to Appendix C. For details on statistical testing, refer to Appendix G.

Table 34. Pooled safety data in ulcerative colitis: summary of trial methodology

Study	Safety of ozanimod in patients with moderately to severely active ulcerative colitis over time: pooled analysis from phase 2, phase 3, and open-label extension trials
Key publications	D'Haens G, Colombel J, Lichtenstein GR, Charles L, Petersen A, Ather S, et al. Safety of ozanimod in patients with moderately to severely active ulcerative colitis over time: pooled analysis from phase 2, phase 3, and open-label extension trials. Presented at the Digestive Disease Week (DDW); 21-23 May 2021. Virtual. Rieder F, Wolf DC, Charles L, Kollengode K, Hsu K, Patel A, et al. Fr513 Incidence of infections in patients with moderately to severely active ulcerative colitis treated with ozanimod and relationship to significant lymphopenia: results form a pooled safety analysis. Gastroenterology. 2021;160(6):S339-40.
Sample size (n)	1,666
Study design	Pooled safety analysis from 32-week TOUCHSTONE trial (phase 2), 52-week TRUE NORTH study (phase 3), and the respective open-label extension trials
Location	Worldwide
Patient population	Patients with moderate-to-severe active UC
Intervention(s)	▪ Ozanimod 1 mg – Controlled UC induction period[a]: n = 496 – All UC studies[b]: n = 1,158
Comparator(s)	▪ Placebo – Controlled UC induction period[a]: n = 281 – All UC studies[b]: n = 508
Follow-up period	716 patients (61.8%) were treated with ozanimod 1 mg for ≥ 1 year, and 322 (27.8%) for ≥ 2 years

UC = ulcerative colitis.

[a] Patients in TOUCHSTONE and those in cohort 1 of TRUE NORTH treated in the induction period.

[b] Includes all patients in TOUCHSTONE, TRUE NORTH, and/or the open-label extension trials.

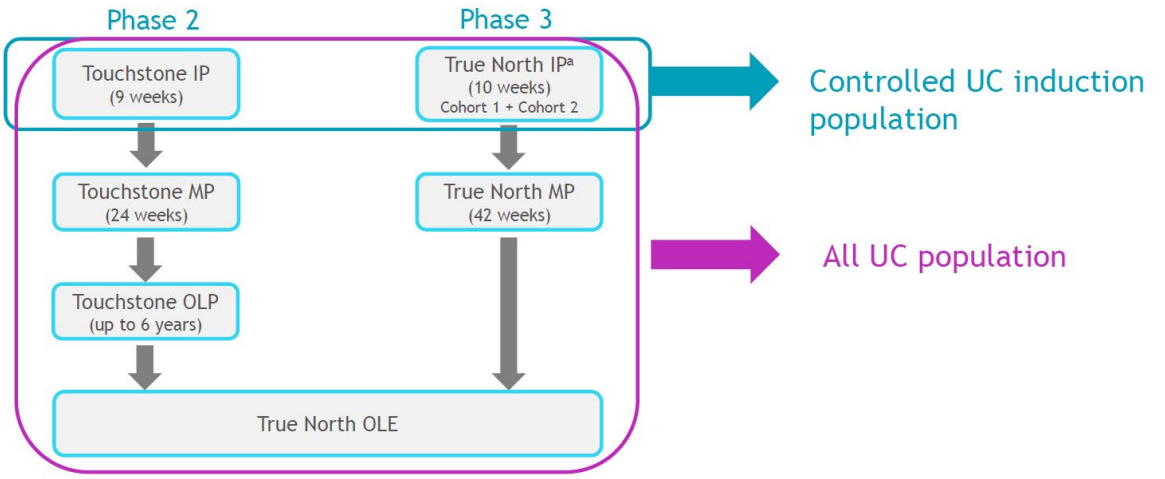
7.3.1.1. Pooled safety data in ulcerative colitis: study design

The objective of this pooled safety analysis was to assess the safety of ozanimod (1 mg) exposure in patients with UC from all clinical trials.[13] Figure 59 presents the study designs for all clinical trials in the UC populations, which include 2 randomised trials. The 2 randomised trials are a phase 2 RCT (TOUCHSTONE),[10] which included an OLE period,[11,12] and a phase 3 RCT (TRUE NORTH).[9] Patients in the TRUE NORTH study were eligible to enter a separate OLE study (RPC01-3102) if they completed the induction period but did not have a clinical response at week 10 (cohort 1 or 2), experienced disease relapse during the maintenance period, or completed the

maintenance period.[9] The TOUCHSTONE OLE ended in 2019 after all active patients had completed at least 4 years of follow-up. All active patients at the point of study closure were invited to enrol into the TRUE NORTH OLE (RPC01-3102).[11] This pooled safety analysis combined all safety data from the ozanimod-treated patients from all UC trials, including the TRUE NORTH OLE.[13]

The pooled safety analysis included 2 analyses: the induction period for TOUCHSTONE and TRUE NORTH (controlled UC induction population) and all patients from TOUCHSTONE, TRUE NORTH, and/or the OLE (all UC population) (Figure 59).[13]

Figure 59. Study designs for all company-sponsored clinical trials in ulcerative colitis populations



IP = induction period; MP = maintenance period; OLE = open-label extension; OLP = open-label period.

[a] Responders assigned to ozanimod 1 mg (cohort 1 and cohort 2) in the IP were re-randomised to receive ozanimod or placebo in a 1:1 ratio and in a double-blinded manner when entering the MP. Adult subjects in clinical response at week 10 of the IP who were randomised to placebo (cohort 1) continued to receive placebo in the MP in a double-blinded manner.

Source: D'Haens et al. (2021)[13]

7.3.2. Pooled safety data in ulcerative colitis: safety results

A total of 1,666 patients (ozanimod and placebo) were included in the pooled analysis (Table 34); of these, 61.8% (n = 716) received ozanimod 1 mg for ≥ 1 year and 27.8% (n = 322) for ≥ 2 years.[13]

Table 35. Ozanimod exposure during induction and for all ulcerative colitis trials

	Controlled UC induction period[a]		All UC studies[b]	
	Ozanimod 1 mg	Placebo	Ozanimod 1 mg	Placebo
No. of patients	496	281	1,158	508
Median treatment duration (range), weeks	10.14 (0.1-17.9)	10.14 (0.6-17.1)	65.79 (0.17-358.09)	17.21 (0.56-60.27)
Patient-years of treatment exposure	97.5	53.9	1,841.7	242.8

UC = ulcerative colitis.

[a] Patients in TOUCHSTONE and those in cohort 1 of TRUE NORTH treated in the induction period.

[b] Includes all patients in TOUCHSTONE, TRUE NORTH, and/or the open-label extension.

Source: D'Haens et al. (2021)[13]

A similar rate of TEAEs occurred in the ozanimod (37.9%) and placebo (36.3%) arms during the controlled induction period (Table 35). The most common TEAE was anaemia in both treatment arms (ozanimod, 3.6% and placebo, 5.7%).[13]

Table 36. Incidence and incidence rate of most common treatment-emergent adverse events with ozanimod 1 mg during induction

	Controlled UC induction period			
	Ozanimod 1 mg (n = 496) PY = 101.4[a]		Placebo (n = 281) PY = 57.3[a]	
	n (%)	IR[b], per 100 PYs	n (%)	IR[b], per 100 PYs
Patients with ≥ 1 TEAE	188 (37.9)	251.42	102 (36.3)	226.61
TEAEs in ≥ 2% of patients treated with ozanimod				
Anaemia	18 (3.6)	18.22	16 (5.7)	28.69
Nasopharyngitis	15 (3.0)	15.04	3 (1.1)	5.25
Headache	15 (3.0)	15.12	7 (2.5)	12.37
Nausea	14 (2.8)	14.11	5 (1.8)	8.82
Pyrexia	14 (2.8)	14.06	3 (1.1)	5.28
ALT increased	12 (2.4)	11.95	0	0
Arthralgia	12 (2.4)	12.01	3 (1.1)	5.25

ALT = alanine aminotransferase; IR = incidence rate; PY = patient-year; TEAE = treatment-emergent adverse event; UC = ulcerative colitis.

Note: Analysis was based on the treatment group to which a patient was assigned when the event occurred, including patients who were re-randomised to placebo.

[a] Total PYs equals the sum of the number of years on study contributed by each patient from time of first dose per treatment group in the pool to last date on study per treatment group in the pool. The algorithm for the last date on study is dependent on patient disposition and whether the patient enrolled into an extension study.

[b] Incidence rate per 100 PYs, calculated as number of patients/PY × 100 for specific system organ class category or preferred term subcategory.

Source: D'Haens et al. (2021)[13]

There was a 28% difference between treatment arms reporting ≥ 1 TEAE in the all-study analysis. A total of 68.7% of patients in the ozanimod arm reported ≥ 1 TEAE compared with 40.7% in the placebo arm (Table 36). However, application of exposure-adjusted incidence rates of TEAEs across the pooled UC study groups showed that ozanimod was associated with lower rates compared with placebo. The most frequent TEAE was lymphopenia (8.9%) in the ozanimod arm, which is to be expected owing to the mode of action for ozanimod. Anaemia (4.1%) was the most frequent TEAE in the placebo arm.[13]

Table 37. Incidence and incidence rate of most common treatment-emergent adverse events with ozanimod 1 mg at any time during all ulcerative colitis studies

	All UC studies			
	Ozanimod 1 mg (n = 1,158) PY = 1,922.5[a]		Placebo (n = 508) PY = 249.2[a]	
	n (%)	IR[b], per 100 PYs	n (%)	IR[b], per 100 PYs
Patients with ≥ 1 TEAE	796 (68.7)	94.9	207 (40.7)	112.1
TEAEs in ≥ 5% of patients treated with ozanimod				
Lymphopenia	103 (8.9)	5.71	0	0
Nasopharyngitis	86 (7.4)	4.74	10 (2.0)	4.07
Anaemia	85 (7.3)	4.67	21 (4.1)	8.53
ALT increased	72 (6.2)	3.98	2 (0.4)	0.81
Lymphocyte count decreased	71 (6.1)	3.85	0	0
Headache	69 (6.0)	3.76	8 (1.6)	3.25

	All UC studies			
	Ozanimod 1 mg (n = 1,158) PY = 1,922.5[a]		Placebo (n = 508) PY = 249.2[a]	
	n (%)	IR[b], per 100 PYs	n (%)	IR[b], per 100 PYs
Arthralgia	62 (5.4)	3.38	12 (2.4)	4.89
Upper respiratory tract infection	59 (5.1)	3.19	11 (2.2)	4.50

ALT = alanine aminotransferase; IR = incidence rate; PY = patient-year; TEAE = treatment-emergent adverse event; UC = ulcerative colitis.

Note: Analysis was based on the treatment group to which a patient was assigned when the event occurred, including patients who were re-randomised to placebo.

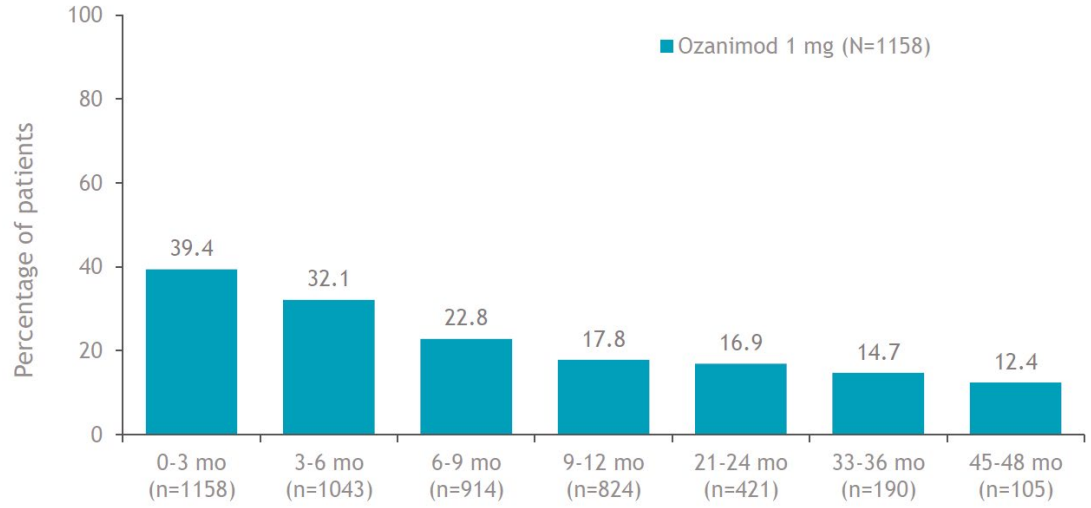
[a] Total PYs equals the sum of the number of years on study contributed by each patient from time of first dose per treatment group in the pool to last date on study per treatment group in the pool. The algorithm for the last date on study is dependent on patient disposition and whether the patient enrolled into an extension study.

[b] Incidence rate per 100 PYs, calculated as number of patients/PY × 100 for specific system organ class category or preferred term subcategory.

Source: D'Haens et al. (2021)[13]

Across the whole analysis, the proportion of patients treated with ozanimod reporting a TEAE was highest during the first 3 months of treatment and decreased over time (Figure 60).[13]

Figure 60. Incidence of newly emergent treatment-emergent adverse events in patients on ozanimod 1 mg over time (all ulcerative colitis studies)



Source: D'Haens et al. (2021)[13]

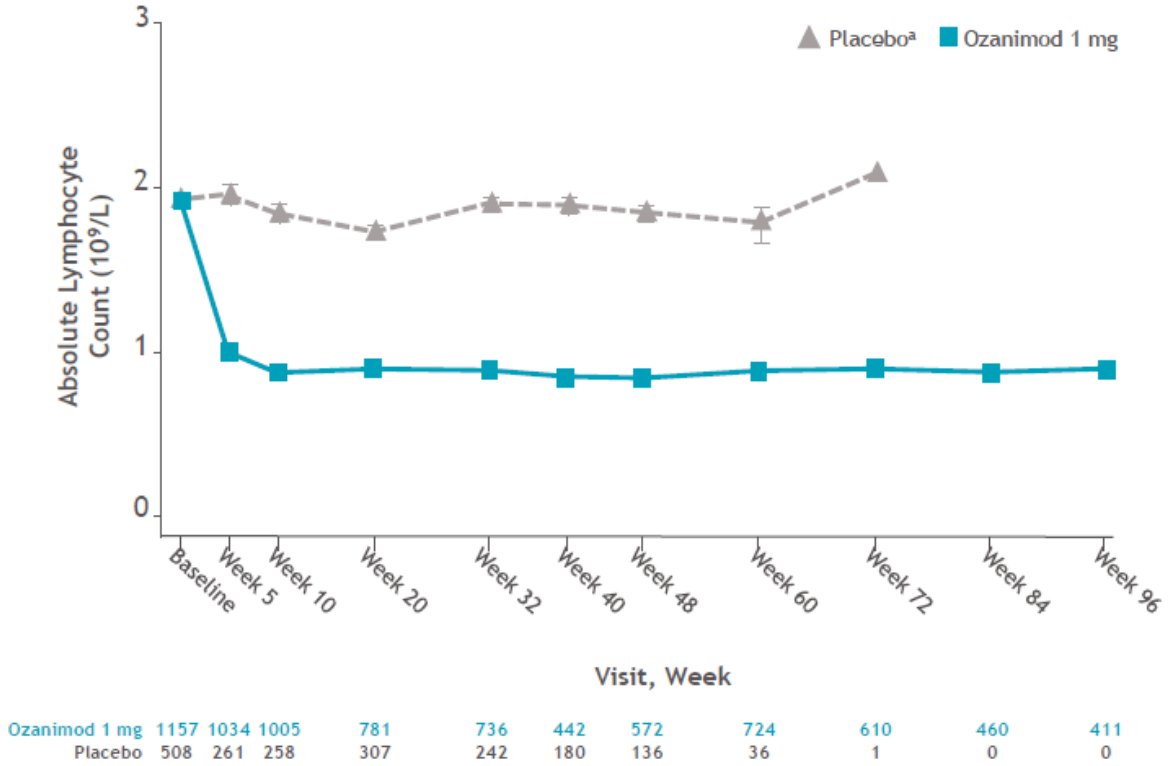
7.3.2.1. Infections

Reductions in ALC are expected because of ozanimod's mode of action. Reductions in ALC are associated with immunosuppression and the rare condition of PML, which is a subacute progressive demyelinating disease of the central nervous system. The disease is caused by infection with the ubiquitous human polyomavirus John Cunningham virus.[94] PML is associated with certain diseases and immunosuppressant therapies, in particular natalizumab, which is an alpha-4 integrin antagonist licensed for the treatment of relapsing remitting multiple sclerosis (RRMS).[95] Natalizumab is associated with a 1 in 44 chance, of developing PML[96]; therefore, there is a general concern around immunosuppressant therapies and the risk of PML.

Patients who received ozanimod had a mean ALC reduction of 47% from baseline at the last on-treatment assessment. Baseline mean ALC was 1.93 cells × 10^9/L and 0.84 cells × 10^9/L at the last on-treatment

assessment. In patients treated with ozanimod, the mean ALC decreased from baseline to week 5 and remained stable through to week 96 (Figure 61).[14]

Figure 61. Mean absolute lymphocyte count by visit through 24 months



[a] Patients may be included in both placebo and ozanimod treatment groups. The total count in the placebo group includes 227 patients who were treated with ozanimod in the induction period and were re-randomised to placebo in the maintenance period of TRUE NORTH.

Source: Rieder et al. (2021)[14]

A total of 5.3% of patients (n = 60) experienced an ALC < 0.2 × 10^9/L at least once during ozanimod treatment (Table 37). However, in most patients (98.3%; n = 59), ALC levels had returned to ≥ 0.2 × 10^9/L at the time of the database cut. In 89.8% of patients, ALC levels returned to ≥ 0.2 × 10^9/L while continuing treatment with ozanimod.[14]

Table 38. Minimum absolute lymphocyte count by threshold for patients treated with ozanimod

Minimum absolute lymphocyte count value, 10^9/L	Ozanimod 1 mg (n = 1,158), n (%)
< LLN	1,004 (88.3)
< 0.8	877 (77.1)
< 0.5	556 (48.9)
< 0.2	60 (5.3)

LLN = lower limit of normal (1.02 × 10^9/L).
Source: Rieder et al. (2021)[14]

Table 38 presents the infection rates for both the induction phase and across all UC trials, with no serious or opportunistic infections concurrent with ALC < 0.2 × 10^9/L.[13]

Table 39. S1PR modulator class-related adverse events of special interest: infections during induction versus all ulcerative colitis trials

	Controlled UC induction period				All UC studies			
Any infection	49 (9.9)	51.63	30 (10.7)	55.18	337 (29.1)	22.81	71 (14.0)	31.43
Infections in ≥ 5% of patients								
Nasopharyngitis	15 (3.0)	15.04	3 (1.1)	5.25	86 (7.4)	4.74	10 (2.0)	4.07
Upper respiratory tract infection	6 (1.2)	5.96	3 (1.1)	5.25	59 (5.1)	3.19	11 (2.2)	4.50
Any opportunistic infection	3 (0.6)	2.97	0	0	28 (2.4)	1.48	2 (0.4)	0.81
Herpes zoster	2 (0.4)	1.98	0	0	25 (2.2)	1.32	2 (0.4)	0.81
Any serious infection	4 (0.8)	3.96	1 (0.4)	1.75	25 (2.2)	1.32	7 (1.4)	2.84
Serious infections in ≥ 2 patients treated with ozanimod								
Appendicitis	1 (0.2)	—	0	—	6 (0.5)	0.31	1 (0.2)	0.40
Pneumonia	0	—	0	—	4 (0.3)	0.21	0	—
Clostridium difficile infection	0	—	0	—	2 (0.2)	0.10	0	—
Gastroenteritis	0	—	0	—	2 (0.2)	0.10	0	—
Urinary tract infection	0	—	0	—	2 (0.2)	0.10	0	—

S1PR = sphingosine 1-phosphate receptor; UC = ulcerative colitis.
Source: D'Haens et al. (2021)[13]

To place the infection rate data reported in Table 38 into context, Table 39 presents infection rates across comparator therapies. Across the follow-up period, ozanimod had the lowest rate of serious infection per 100 patient-years.

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Table 40. Serious infection rates for ozanimod and comparator therapies (per 100 patient-years)

Therapy	Any serious infection, per 100 PYs			Total PYs of exposure		
	Induction period, intervention	Maintenance period, intervention	Across follow-up, intervention	Across follow-up, placebo	Intervention	Placebo
Ozanimod[13]	3.96	Not available	1.32	2.84	1,922.50	249.20
Adalimumab[97]	Not available	Not available	3.5	Not available	3,397	Not available
Golimumab[98]	Not available	Not available	2.44	0.95	1,601	105
Infliximab[99]	Not available	Not available	5.05	2.87	831	209
Tofacitinib[100]	4.83	1.35	1.70	1.38[a]	2,581.3	145.2
Ustekinumab[101]	1.50[a]	4.34	3.19	4.00	627	250
Vedolizumab (IV)[102]	Not available	Not available	1.8	Not available	3,451	Not available
Vedolizumab (IV)[103]	Not available	Not available	2.7	5.0	2,083	214

IV = intravenous; PY = patient-year.

[a] Estimated from event counts/patient-years follow-up.

In addition to the pooled safety data in UC reported by D'Haens et al. (2021)[13], a pooled safety analysis to assess the safety of extended ozanimod exposure in patients with RMS has also been conducted. The analysis compared data from all company-sponsored clinical trials of ozanimod in RMS with phase 3 trial data; Appendix E presents these results.[58] In March 2021, 1 case of PML was reported in a patient enrolled in the DAYBREAK study for MS. DAYBREAK is an OLE study to assess the long-term safety and tolerability of ozanimod 0.92 mg in patients with RMS from 4 parent studies (a phase 1 study, phase 2 RADIANCE study, and phase 3 RADIANCE and SUNBEAM studies). All patients received ozanimod 0.92 mg.[104] [redacted]

The PML rate for ozanimod is low and similar to other immunosuppressant treatments for UC.Card et al. (2018)[105] reported that the risk of developing of PML with vedolizumab is small and unlikely to be higher than 6.75 cases per 100,000 patient-years. Ozanimod currently has 1 case per 16,200 patient-years, which is equivalent to 6.17 per 100,000 patient-years. In a pooled safety analysis of ustekinumab, no cases of PML were reported in 1,733 patient-years of follow-up.[101] Patients on ozanimod will undergo regular ALC monitoring. Absolute lymphocyte counts < 0.2×10^9/L, if confirmed, should lead to interruption of ozanimod therapy until the level reaches > 0.5×10^9/L, when re-initiation of ozanimod can be considered. Reports have shown that, in cases in which ozanimod has been discontinued owing to low ALC, levels have risen to normal values within 30 days,[106] thus avoiding the risk of infection.

7.3.2.2. Malignancies

Some biologics and small molecule inhibitor therapies approved for use in moderate-to-severe UC are associated with an increased risk of malignancy.[52-55,107] Over the 1,922 patient-years of exposure, ozanimod showed a low incidence of malignancy, with an incidence rate of 0.63 per 100 patient-years (Table 40).[13]

Table 41. S1PR modulator class-related adverse events of special interest: malignancies across all ulcerative colitis studies

	All UC studies			
	Ozanimod 1 mg (n = 1,158) PYs = 1,922.5		Placebo (n = 508) PYs = 249.2	
	n (%)	IR, per 100 PYs	n (%)	IR, per 100 PYs
Malignancies	12 (1.0)	0.63	2 (0.4)[a]	0.81
Non-cutaneous malignancy	6 (0.5)	—	2 (0.4)	—
Adenocarcinoma	1 (< 0.1)	0.05	0	0
Adenocarcinoma of the colon	0	0	1 (0.2)	0.40
Breast cancer	1 (< 0.1)	0.05	1 (0.2)	0.40
Lung neoplasm malignant	1 (< 0.1)	0.05	0	0
Prostate cancer	1 (< 0.1)	0.05	0	0
Rectal adenocarcinoma	1 (< 0.1)	0.05	0	0
Rectal cancer stage II	1 (< 0.1)	0.05	0	0
Cutaneous malignancy	6 (0.5)	—	0	—
Basal cell carcinoma	5 (0.4)	0.26	0	0
Squamous cell carcinoma	1 (< 0.1)	0.05	0	0

IR = incidence rate; PY = patient-year; S1PR = sphingosine 1-phosphate receptor; UC = ulcerative colitis.

[a] Both patients in the placebo arm had prior ozanimod treatment.

Source: D'Haens et al. (2021)[13]

When comparing malignancy rates with comparator therapies, ozanimod had the lowest incidence rate per 100 patient-years when excluding non-melanoma skin cancer malignancies (0.31) and when assessing the incidence rate for all malignancies incidence (0.63 per 100 patient-years) (Table 41).

Table 42. Malignancy rates for ozanimod and comparator therapies (per 100 patient-years)

Therapy	All malignancies, per 100 patient-years		Excluding NMSC malignancies, per 100 patient-years		Total patient-years of exposure	
	Across follow-up, intervention	Across follow-up, placebo	Across follow-up, intervention	Across follow-up, placebo	Intervention	Placebo
Ozanimod[13]	0.63	0.81	0.31[a]	0.81	1,922.50	249.20
Adalimumab[97]	1.0	Not available	0.79[a]	Not available	3,397	Not available
Golimumab[98]	0.82	0	0.57	0	1,601	105
Infliximab[99]	Not available	Not available	0.6	0	831	209
Tofacitinib[108,109]	1.65[a]	Not available	Not available	Not available	2,186	Not available
	Not available	Not available	0.75	0	2,656.37	148.77
Ustekinumab[101]	1.12	0.4	0.64	0.4	627	250
Vedolizumab (IV)[102,103]	0.98	Not available	Not available	Not available	3,451	Not available
	N/A	0.47[a]	0.48[a]	0	2,083	214

IV = intravenous; NMSC = non-melanoma skin cancer.

[a] Estimated from event counts/patient-years follow-up.

7.3.3. Relevant studies: Pooled safety data in ulcerative colitis and relapsing multiple sclerosis

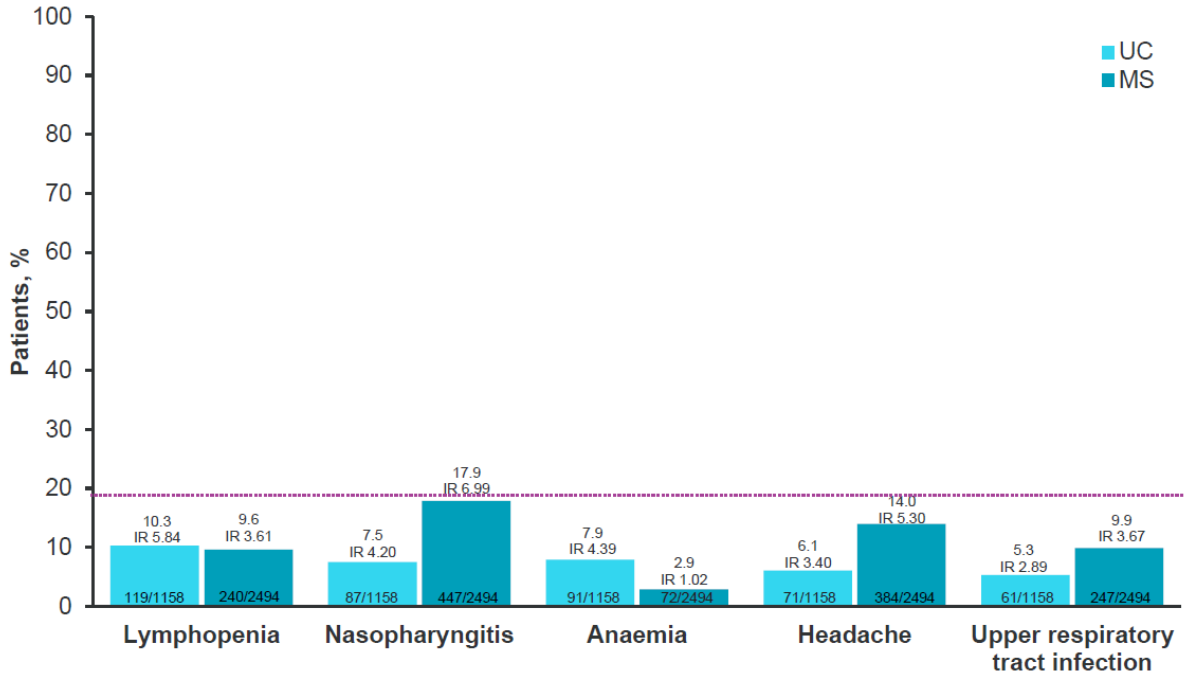
Danese et al. (2021)[59] reported a pooled safety analysis to assess the safety of extended ozanimod exposure in participants with RMS and UC combined. The pooled analysis reported TEAEs, most commonly reported TEAEs, and AESIs. The pooled analysis was based on the UC controlled and uncontrolled studies (TRUE NORTH, TOUCHSTONE, and the OLE) and the MS uncontrolled OLE study (DAYBREAK).[59] The baseline characteristics are reported in Appendix C.

In the pooled UC studies, 1,158 patients were evaluated. The mean duration of ozanimod exposure was 22 months, with a total of 2,196.4 patient-years of exposure. A total of 760 patients (65.5%) were treated with ozanimod 1 mg for ≥ 1 year, and 432 patients (37.3%) were treated for ≥ 2 years. In the MS DAYBREAK study, 2,494 patients were enrolled and received at least 1 dose of ozanimod 0.92 mg. The mean duration of ozanimod exposure was 1,077 days (35 months), with a total exposure of 7,161.0 patient-years. A total of 2,395 patients (96.0%) were treated with ozanimod 1 mg for ≥ 1 year, and 2,285 patients (91.6%) were treated for ≥ 2 years.[59]

7.3.3.1. Treatment-emergent adverse events

Among patients with UC and MS, respectively, TEAEs occurred in 70.8% and 81.8%, severe TEAEs occurred in 10.2% and 6.1%, and serious TEAEs occurred in 14.0% and 9.5%. TEAEs led to treatment discontinuation in 8.0% of patients in the UC studies and 2.2% of patients in the MS study. The most commonly reported TEAEs in the UC studies were lymphopenia (10.3%), anaemia (7.9%), and nasopharyngitis (7.5%); exposure-adjusted incidence rates per 100 patient-years were 5.84, 4.39, and 4.20, respectively (Figure 62). The most commonly reported TEAEs in the MS study were nasopharyngitis (17.9%), headache (14.0%), upper respiratory tract infection (9.9%), and lymphopenia (9.6%); exposure-adjusted incidence rates per 100 patient-years were 6.99, 5.30, 3.67, and 3.61, respectively (Figure 62).

Figure 62. **Most commonly reported treatment-emergent adverse events in the ulcerative colitis and multiple sclerosis studies**



IR = incidence rate; MS = multiple sclerosis; UC = ulcerative colitis.
Source: Danese et al. (2021)[59]

7.3.3.2. Adverse events of special interest (based on prior associations with S1P receptor modulation)

Adverse events of special interest included bradycardia, heart conduction abnormalities (second degree and higher atrioventricular block), macular oedema, malignancy, serious or opportunistic infection, pulmonary effects, dyspnoea, and hepatic effects. In the UC and MS data sets, respectively, incidence rates per 100 patient-years were 21.48 and 26.49 for any infections and 1.29 and 0.72 for serious infections. Incidence rates per 100 patient-years for AESIs were low (Table 42). Dose escalation mitigated first-dose cardiac effects, and there were no findings of second-degree type 1 atrioventricular block or higher. Pulmonary events, including small changes in pulmonary function tests, did not increase over time. Most confirmed cases of macular oedema were associated with pre-existing risk factors or comorbid conditions. Most hepatic events were transient and resolved while continuing treatment and did not result in study drug discontinuation; there were no cases of severe drug-induced liver injury or Hy's law. Increased ALT to > 5 times the upper limit of normal was reported in 2.1% of patients with UC and 0.7% of patients with MS.[59]

Table 43. Adverse events of special interest

	UC studies Ozanimod 0.92 mg (N = 1,158) Total PY = 2,196.4		MS study Ozanimod 0.92 mg (N = 2,494) Total PY = 7,161.0	
Characteristic	n (%)	IR per 100 PY	n (%)	IR per 100 PY
Malignancy	14 (1.2)	6.4	NR	NR
Pulmonary effect	12 (1.0)	5.5	NR	NR
Opportunistic infection	31 (2.7)	1.4	117 (4.7)	1.7
Serious infection	28 (2.4)	1.3	51 (2.0)	0.72
Herpes zoster	28 (2.4)	1.3	29 (1.2)[a]	0.41
Bradycardia	7 (0.6)	0.69	1 (< 0.1)	0.07
Macular oedema	7 (0.6)[b,c]	0.32	8 (0.3)[b]	0.11

AESI = adverse events of special interest; IR = incident rate; MS = multiple sclerosis; NR = not reported; PY = patient-years, UC = ulcerative colitis.

Note: AESIs include bradycardia, heart conduction abnormalities (second degree and higher atrioventricular block), macular oedema, malignancy, serious or opportunistic infection, pulmonary effects, dyspnoea, and hepatic effects and have been adjudicated by the safety review team per the safety management plan.

[a] In addition, varicella zoster virus infection was reported in 3 patients (0.1%; IR per 100 PY = 0.04) in the MS study.

[b] All patients in the UC studies and only 3 patients in the MS study were confirmed to have macular oedema by a panel of specialists (Macular Oedema Review Panel).

[c] Treatment-emergent adverse events of macular oedema include preferred terms of macular oedema and cystoid macular oedema.

Source: Danese et al. (2021)[59]

In conclusion, TEAEs were similar and consistent in UC and MS studies, and rates were low, with no new safety signals determined with long-term treatment. Low rates of treatment discontinuation due to TEAEs were seen in both the UC and MS studies. Hence, long-term exposure to ozanimod 0.92 mg/day in patients with moderately to severely active UC and in patients with relapsing forms of MS was well tolerated.[59]

8. Health economic analysis

8.1. Cost-minimisation analysis

As presented in Section 7, the result of the NMA shows that ozanimod has at least non-inferior efficacy and at least non-inferior safety compared with existing treatments in both the induction and maintenance phase of treatment.

Based on this premise of clinical equivalence, a cost-minimisation analysis was deemed the most appropriate for comparing ozanimod with other currently existing treatments from the perspective of the Danish healthcare system for the treatment of adults with moderately to severely active UC who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biologic agent.

The results presented from the analysis are based on the list prices for all pharmaceutical, including ozanimod, in accordance with national guidelines. However, a confidential net price is in place.

8.2. Summary of analysis

The base-case cost-minimisation analysis was based on drug acquisition costs, drug administration costs, monitoring costs, societal costs, and AE costs. The rationale behind adding treatment-related costs (drug

acquisition costs, drug administration costs, monitoring costs and AE costs) and societal costs is that they are expected to differ during the induction phase and maintenance phase. Therefore, the model is programmed to estimate cost of therapy associated with both induction phase and maintenance phase total costs over the model time horizon for drug administration, monitoring, and AEs are estimated based on the induction phase and the maintenance phase.

Patients achieving treatment response or remission at the end of the induction phase transition to the maintenance phase of the treatment, where they remain for the remainder of the model time horizon. We assume all patients transition from the induction phase to the maintenance phase of treatment. We further assume in our base case that patients are offered the SmPC approved dosages. However, based on interviews with local clinical experts, it is anticipated that some patients may receive an escalated dose of therapy in the maintenance phase based on their response to therapy during the induction phase. This potential dose escalation will be explored in a scenario analysis.

A summary of the base-case assumptions of the cost-minimisation approach is shown in Table 43. A working version of cost-minimisation analysis is presented in the form of an Excel file.

Table 44. Model overview

Decision problem	
Perspective	Societal perspective[a]
Time horizon	1.5 years
Discounting	3.5%
Population	Adult patients with moderate-to-severe active UC (reflecting the average patient enrolled in the TRUE NORTH clinical trial for ozanimod) The model provides the option to conduct analysis for the following subgroups based on their treatment exposure: ▪ Bio-naive ▪ Bio-experienced Note: bio refers to anti-tumour necrosis factor therapy (infliximab), and vedolizumab
Intervention	Ozanimod oral therapy Induction: ▪ Days 1-4: 0.23 mg once daily ▪ Days 5-7: 0.46 mg once daily Maintenance: ▪ Days 8 and thereafter: 0.92 mg once daily
Comparators	▪ Bio-naive: infliximab and vedolizumab ▪ Bio-experienced: ustekinumab, adalimumab, and vedolizumab Both vedolizumab (IV) and subcutaneous (SC) therapies are included in the model as comparators in the 2 subgroups
Cost categories	Drug acquisition costs, drug administration costs for SC and IV therapies, treatment monitoring costs, adverse event costs, and societal costs
Model output	Discounted per-patient costs stratified by category (i.e., drug acquisition costs, drug administration costs, treatment monitoring costs, adverse event costs, and societal costs), and incremental per-patient costs versus comparator

IV = intravenous; SC = subcutaneous.

[a] The societal perspective includes cost incurred to patients for treatment administration and monitoring. This is estimated based on time spent for treatment administration and monitoring, and time spent for travel.

8.3. Resource use and costs

This section provides an overview of model parameters and inputs used in the cost-minimisation analysis.

8.3.1. Drug acquisition costs and dosing

Treatment cost of each therapy included in the analysis was based on the recommended dose and list price of each therapy for both the induction and maintenance therapy. Information on dosage, drug administration, and treatment schedules was obtained using the respective SmPC and an overview of the dosing of ozanimod and included comparators is provided in Table 44. The drug consumption in our base-case analysis matches 1:1 the calculations reported by the DMC in the cost analysis within IBD.[110] Pharmacy purchase price for comparators is used in the analysis in Table 45. Based on the Danish guidelines for treatment of UC, a patient weight of 75 kg was assumed to be reflective of the Danish clinical setting and thus used for dose calculations.[111] This assumption of patient weight was tested in scenario analyses where the weight was increased and decreased by 20%.

Table 45. Dose of treatments in the induction and maintenance phase

Treatment		Dose mg (induction)	Dose mg (maintenance)
Ozanimod (oral)[112]		0.23 mg on days 1-4, 0.46 mg on days 5-7; followed by 0.92 mg QD	0.23 mg on days 1-4, 0.46 mg on days 5-7; followed by 0.92 mg QD
Adalimumab (SC)		160 mg at Week 0 (given as four 40 mg injections in 1 day or as two 40 mg injections per day for 2 consecutive days) and 80 mg at Week 2 (given as two 40 mg injections in 1 day)	40 mg every other week via subcutaneous injection
Infliximab (IV)[113]		5 mg/kg at 0, 2, and 6 weeks	5 mg/kg at 0, 2, and 6 weeks
Ustekinumab (SC)[55]	Ustekinumab (IV induction)	390 mg at 0 weeks	Not Applicable
	Ustekinumab (SC)	Not Applicable	90 mg Q12W (8 weeks after the IV dose)
Vedolizumab (SC)[114]	Vedolizumab (IV induction)[115]	300 mg at 0 and 2 weeks	NA
	Vedolizumab (SC)	108 mg at week 6	108 mg once every 2 weeks
Vedolizumab (IV)[115]		300 mg at 0, 2, and 6 weeks	300 mg Q8W

IV = intravenous; NA = not applicable; Q12W = every 12 weeks; Q8W = every 8 weeks; QD = once daily; SC = subcutaneous.

Table 46. Price per pack of treatments included in the model

Product	Price per pack
Ozanimod (starter pack) 0.23 mg/0.46 mg	DKK 2,715.51
Ozanimod (standard pack) 0.92 mg	DKK 10,753.67
Adalimumab (40 mg/0.4 mL)	DKK 7,151.09
Infliximab (IV) 100 mg)	DKK 3,683.00
Ustekinumab (IV) 130 mg	DKK 25,094.36
Ustekinumab (SC) 90 mg	DKK 21,557.78
Vedolizumab (SC) 108 mg	DKK 3,654.04
Vedolizumab (IV) 300 mg	DKK 16,920.58

IV = intravenous; SC = subcutaneous.

8.3.2. Dose escalation

There is evidence from clinical trials of ustekinumab and vedolizumab (IV) therapies that a proportion of patients may be prescribed a higher dose during the maintenance phase.[55,79,115] Similar dose escalation is also expected for infliximab, as confirmed by clinical experts. Dose escalation is assumed to be similar for adalimumab. Based on clinical input, dose escalation is also standard in clinical practice; however, to allow the economic analysis to mirror the evidence included in the NMA supporting non-inferiority, dose escalation is not applied in the base case. However, as a scenario analysis, dose escalation for patients on infliximab, ustekinumab, and vedolizumab during the maintenance phase was investigated.

The dose escalation schedule and proportion of patients as applied in the scenario analysis is presented in Table 46.

Table 47. Dose escalation for therapies in the maintenance phase

Treatment	Dose	Proportion of patients
Infliximab[a]	10 mg/kg Q8W	30%
Adalimumab (SC)	80 mg Q2W	30%
Ustekinumab (SC)[b,55]	90 mg Q8W	70%
Vedolizumab (SC)	108 mg Q1W	17.5%
Vedolizumab (IV)[b,115]	300 mg Q4W	30%

IV = intravenous; Q1W = every 1 week; Q2W = every 2 weeks; Q4W = every 4 weeks; Q8W = every 8 weeks; SC = subcutaneous.

[a] Dose of infliximab is assumed to be increased from 5 mg/kg to 10 mg/kg for dose escalation.

[b] Frequency of administration for ustekinumab and vedolizumab IV are expected to increase for dose escalation.

8.3.3. Drug wastage

In the base case, 100% vial sharing is assumed for IV therapies and no wastage is applied for oral or SC therapies. However, to investigate this assumption a scenarios analysis was conducted to explore the impact of this assumption on the results. In this scenario, end of treatment wastage is applied for oral and SC therapy, where we assume that a portion of the last month's therapy is wasted. For the IV treatments, a portion of every vial is assumed wasted depending on the dose of IV therapy and the vial strength (e.g., for a dose of 375 mg infliximab, 25 mg of infliximab is wasted based on a vial strength of 100 mg). It is of note that, due to the vedolizumab IV dosing schedule, no wastage occurs with this treatment.

8.3.4. Duration of therapy

Based on the premise of equivalence of treatment effect, the overall treatment duration (induction + maintenance) for all treatments included in the analysis were assumed to be the same and equal to the time horizon selected for the analysis. However, the induction period is defined per the posology of treatments in moderate-to-severe UC and differ across the included treatments, as described in the respective SmPCs.[46,55,113-115] The duration of both induction and maintenance therapy applied in the analysis for the base-case time horizon of 1.5 years are presented in Table 47.

Table 48. Duration of therapy

Treatment	Induction duration (weeks)	Time to maintenance (weeks)[a]	Maintenance duration (weeks)
Ozanimod[116]	10	10	68
Adalimumab	8	8	70
Infliximab[113]	6	14	64
Ustekinumab[55]	8	8	70
Vedolizumab (IV)[115]	6	14	64
Vedolizumab (SC)[114]	6	8	70

IV = intravenous; SC = subcutaneous.

[a] Time to maintenance includes the time from treatment initiation to the first dose of maintenance treatment.

8.3.5. Drug administration costs

Cost of drug administration was included in the model dependent on mode of administration for each therapy. Ozanimod is an oral therapy, and therefore possible to self-administer. Based on the SmPC for ozanimod, few patients (~5%) with cardiac complications are likely to receive additional cardiac monitoring at the first dose (monitored initiation).[106,116] This is included as a one-off cost for ozanimod therapy during treatment initiation, at a cost of DKK 1,173. Similarly, it was assumed that 85% of patients self-administer SC therapy and 15% will require assistance; therefore, administration cost would be associated with these patients. For SC assistance, a unit cost of DKK 348.41 and a patient cost of DKK 232.81 were used. For IV therapy, an outpatient office visit cost is applied for each IV administration (DKK 2,277).[117]

8.3.6. Monitoring costs

Treatment monitoring parameters included in the model were based on the SmPCs and physician interviews for ozanimod, infliximab, ustekinumab, and vedolizumab (IV and SC).[55,113-116] Treatment monitoring resource use in the induction and maintenance treatment phases is summarised in Table 48 and Table 49.[106,116] For ozanimod, 4 blood tests per year were included in the maintenance period based on the SmPC statement that in the absence of clinical symptoms, liver transaminases, and bilirubin levels should be monitored at months 1, 3, 6, 9, and 12 and periodically thereafter. For infliximab, ustekinumab, and vedolizumab (IV and SC), clinicians were shown the tables below and asked to enter the frequency of treatment monitoring that they would anticipate. The unit costs for each of the treatment monitoring parameters are summarised in Table 50.

Table 49. Treatment monitoring parameters (induction period)

Treatment	Duration (weeks)	Standard blood test[a]	Chest x-ray	Tuberculosis test[b]	Hepatitis B and C test	VZV IgG test	ECG	Pneumovax + Influvac Tetra vaccination	Varivax vaccination	Blood test for anti-drug antibodies to anti-TNF-α	Faeces sample	Colonoscopy	Pregnancy test
Ozanimod	10	2.00	1.00	1.00	1.00	0.50	1.00	0.50	0.025	0.00	1.00	1.00	0.50
Adalimumab	8	1.00	1.00	1.00	1.00	0.50	0.00	0.50	0.025	0.00	1.00	1.00	0.00
Infliximab	6	1.00	1.00	1.00	1.00	0.50	0.00	0.50	0.025	0.00	1.00	1.00	0.00
Ustekinumab	8	1.00	1.00	1.00	1.00	0.50	0.00	0.50	0.025	0.00	1.00	1.00	0.00
Vedolizumab (IV)	6	1.00	1.00	1.00	1.00	0.50	0.00	0.50	0.025	0.00	1.00	1.00	0.00
Vedolizumab (SC)	6	1.00	1.00	1.00	1.00	0.50	0.00	0.50	0.025	0.00	1.00	1.00	0.00

CBC = complete blood count; ECG = electrocardiogram; IV = intravenous; SC = subcutaneous; TNF = tumour necrosis factor; VZV IgG = Varicella zoster virus antibody.

[a] Blood test including gastro-profile, CBC, and liver enzymes test.

[b] Tuberculosis test QuantiFERON.

Table 50. Treatment monitoring parameters and annual frequency of monitoring (maintenance period)

Treatment	Duration (weeks)	Standard blood test[a]	Chest x-ray	Tuberculosis test[b]	Hepatitis B and C test	VZV IgG test	ECG	Pneumovax + Influvac Tetra vaccination	Varivax vaccination	Blood test for anti-drug antibodies to anti-TNF-α	Faeces sample	Colonoscopy	Pregnancy test
Ozanimod	10	4.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	2.00	0.00	0.00
Adalimumab	8	3.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	2.00	0.00	0.00
Infliximab	14	3.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	2.00	0.00	0.00
Ustekinumab	8	3.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	2.00	0.00	0.00
Vedolizumab (IV)	14	3.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	2.00	0.00	0.00
Vedolizumab (SC)	8	3.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	2.00	0.00	0.00

CBC = complete blood count; ECG = electrocardiogram; IV = intravenous; SC = subcutaneous; TNF = tumour necrosis factor; VZV IgG = Varicella zoster virus antibody.

[a] Blood test including gastro-profile, CBC, and liver enzymes test.

[b] Tuberculosis test QuantiFERON.

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Table 51. Unit costs for treatment monitoring parameters

Parameter	Unit cost	Reference
Treatment monitoring		
Standard blood test[a]	DKK 129.00	65TE01, DRG takster 2021
Chest X-ray	DKK 505.00	30PR18 Røntgenundersøgelse (alm), ukompliceret, Ambulante DAGS 2021
Tuberculosis test QuantiFERON[b]	DKK 563.00	Statens Serum Insititut: Interferon gamma release (TB-related) (Mycobacterium tuberculosis) (R-No 178)
Hepatitis B and C Test[b]	DKK 1,326.00	LMV Labortoriemedicinsk Vejledning
Blood test for VZV IgG	DKK 761.00	Statens Serum Insititut: Human alphavirus 3 (Varicella zoster virus) antibody (R-No 277)
Electrocardiogram (ECG)	DKK 174.00	LMV Labortoriemedicinsk Vejledning
Pneumovax + Influvac Tetra vaccination	DKK 286.77	MEDICINPRISER.DK
Varivax vaccination	DKK 796.00	MEDICINPRISER.DK
Blood Test for anti-drug antibodies to anti-TNF-α	DKK 405.00	LMV Labortoriemedicinsk Vejledning
Faeces sample	DKK 233.00	LMV Labortoriemedicinsk Vejledning
Colonoscopy	DKK 5,485.00	06PR03, DRG takster 2021
Pregnancy test[b]	DKK 28.00	LMV Labortoriemedicinsk Vejledning

TNF = tumour necrosis factor; VZV IgG = Varicella zoster virus antibody.

[a] Cost of liver function test, comprehensive metabolic panel, and complete blood count is assumed to be costed under one category for "standard blood test."

[b] Added to standard blood test.

8.3.7. Adverse events costs

Patients receiving treatment can experience treatment-related AEs in both the induction and maintenance phases. Adverse events were included based on a review of efficacy and safety evidence conducted by BMS and included serious infections and malignancy because these AEs were identified as potentially costly. However, as the event rates show, there is little difference between treatments and the overall impact on total costs is small. Therefore, BMS also provides a scenario without the inclusion of costs of treatment-related AEs.

Treatment-specific AE incidence rates for the induction and maintenance phases were obtained and calculated as a 2-week probability of experiencing each AE based on the clinical trial data identified through the review. Annual probabilities were converted to 2-week probabilities by dividing the annual probability by 26. The 2-week probability of AEs are presented in Table 51.

Table 52. Two-week probability of adverse events in the bio-naive population

	Induction & Maintenance phase	
Treatment	**Serious infections**	**Malignancy**
Ozanimod[118]	0.05%	0.05%
Infliximab[67,69]	0.19%	0.03%
Ustekinumab[73]	0.12%	0.12%
Vedolizumab (IV)[63,71,72]	0.07%	0.04%
Vedolizumab (SC)[71]	0.07%	0.04%

IV = intravenous; SC = subcutaneous.

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The cost of serious infection was derived as a weighted average of the costs of sepsis, tuberculosis, pneumonia, soft tissue infection, bone and joint infections, and urinary tract infections. The distribution of patients experiencing infections was based on data from the ozanimod pivotal trials within UC and MS and applied across all therapies assuming that the ozanimod frequencies were a relevant proxy for the other therapies. These costs and patient distributions are presented in Table 52.

Table 53. Cost and distribution of serious infections

Serious infection	Proportion of patients	Cost	Cost reference
Appendicitis	0.24	DKK 28,367.17	06MP17 & 06MP18, DRG takster 2021
Clostridium difficile infection	0.08	DKK 22,115.00	06MA10, DRG takster 2021
Pneumonia	0.16	DKK 36,514.00	04MA13, DRG takster 2021
Miscellaneous infections[a]	0.24	DKK 35,768.00	18MA08, DRG takster 2021
Gastroenteritis	0.08	DKK 22,115.00	06MA10, DRG takster 2021
Urinary tract infections	0.08	DKK 24,431.00	11MA07, DRG takster 2021
Upper respiratory tract infection	0.12	DKK 23,756.00	03MA04, DRG takster 2021

[a] Yersinia infection, measles, nasopharyngitis, otitis externa, pyelonephritis, vestibular neuronitis, etc.

In the model, we anchor the malignancies on the events observed in the TRUE NORTH trial (i.e., colorectal cancer and breast cancer) for costing purposes. A weighted average of the cost of these malignancies was considered for all treatments in moderate-to-severe UC. The malignancy costs and patient distributions are presented in Table 53.

Table 54. Cost and distribution of malignancies

Malignancies	Proportion of patients	Cost	Cost reference
Colorectal cancer	0.25	DKK 94,133.00	06MP10, DRG takster 2021
Breast cancer	0.08	DKK 36,865.00	09MA08, DRG takster 2021
Prostate cancer	0.08	DKK 93,124.00	11MP12, DRG takster 2021
Basal cell, or squamous cell, carcinomas	0.50	DKK 3,978.00	09PR03, DRG takster 2021
Lung neoplasms	0.08	DKK 96,211.00	04MP02, DRG takster 2021

8.3.8. Societal costs

Societal costs are included in the model for drug administration (i.e., physician-administered SC therapy, IV infusion administration, and treatment monitoring for ozanimod and comparators).

Societal costs were calculated based on patient visits in accordance with "Cost analysis concerning equivalent BTSDs for the treatment of ulcerative colitis and Crohn's disease, 2021."[110] The analysis estimates that the cost to patients per hour spent at the treatment facility is DKK 179/h, and the travel cost per visit is DKK 98.56 (assuming 90 minutes of 2-way travel for a distance of 28 km at a rate of DKK 3.52/km).[110]

We assumed that chest X-rays, colonoscopies, and faeces samples were performed as standalone. The Pneumovax + Influvac Tetra vaccination required a single visit and was also performed as standalone, whereas the Varivax vaccination requires 2 visits. The first visit was assumed to occur in connection with other vaccinations and the second visit as standalone; therefore, the model only assumed patient cost of 1 visit. Standard blood work was assumed to include a complete blood test, a tuberculosis test (QuantiFERON test), a varicella zoster virus antibody test, a pregnancy test, and an electrocardiogram test.

Table 54 presents the societal costs incurred per patient. Patient costs were calculated based on the cost to patient per hour spent (DKK 179/h) at the treatment-related facility, with a travel cost per visit of DKK 98.56 (assuming 90 minutes of 2-way travel for a distance of 28 km at a rate of DKK 3.52/km). We assumed time spent at each visit is 90 minutes.

Table 55. Societal costs

Parameters	Hours (per visit)	Societal costs (per visit)
Drug administration		
Consultants visit for SC injection	0.75	DKK 232.81
Outpatient office visit for IV infusion	1.5	DKK 367.06
Monitored initiation		
Day care visit	6	DKK 1,173
Treatment monitoring		
Liver function test, comprehensive metabolic panel, complete blood count	1.5	DKK 367.06
Chest X-ray	1.5	DKK 367.06
HBV test	1.5	DKK 0.00
ECG	1.5	DKK 0.00

ECG = electrocardiogram; HBV = hepatitis B virus; IV = intravenous; SC = subcutaneous.

8.4. Results

8.4.1. Biologic-naive

8.4.1.1. Base-case results

The base-case results indicate that vedolizumab (IV) (DKK 229,841) is associated with higher costs than ozanimod (DKK 225,024), infliximab (DKK 196,983), and vedolizumab (SC) (DKK 188,572). The costs associated with vedolizumab (IV) were minimally higher than ozanimod. Drug acquisition costs are the main driver of these results. Ozanimod has the lowest drug administration costs compared with infliximab, vedolizumab (SC), and vedolizumab (IV). The base-case results are presented Table 55.

Table 56. Base-case results

	Treatment			
Cost category	**Ozanimod**	**Infliximab**	**Vedolizumab (IV)**	**Vedolizumab (SC)**
Drug acquisition cost	DKK 208,532	DKK 151,158	DKK 185,189	DKK 164,577
Drug administration cost	DKK 168	DKK 24,921	DKK 25,047	DKK 6,424
Monitoring cost	DKK 10,378	DKK 9,959	DKK 9,959	DKK 9,959
Adverse event cost	DKK 999	DKK 2,742	DKK 1,443	DKK 1,443
Total direct cost	DKK 220,076	DKK 188,779	DKK 221,637	DKK 182,402
Societal cost	DKK 4,948	DKK 8,204	DKK 8,204	DKK 6,170
Total cost	DKK 225,024	DKK 196,983	DKK 229,841	DKK 188,572
Incremental cost vs. ozanimod	N/A	DKK 28,041	−DKK 4,817	DKK 36,452

IV = intravenous; N/A = not applicable; SC = subcutaneous.

8.4.1.2. Scenario analyses

Scenario analyses were conducted by varying the model time horizon, discount rate, drug wastage, dose escalation, excluding AEs, and excluding societal costs. The results of the scenario analyses are summarised in Table 56. The results from the scenarios are mostly consistent with the base-case results. The model time horizon has the largest impact on results. Varying patient weight had an impact on results versus infliximab.

In the dose escalation scenario, the results are more favourable for ozanimod versus infliximab and versus vedolizumab (IV) than for the base case. In this scenario, ozanimod therapy is associated with less costs than infliximab, the key driver being an increase in infliximab drug acquisition costs. Additionally, an increase in the cost differential is seen in favour of ozanimod versus vedolizumab (IV).

A 20% increase in patient weight (90 kg) sees a reduction in incremental costs for ozanimod versus infliximab, while a 20% reduction in patient weight (60 kg) sees an increase in incremental costs for ozanimod versus infliximab. These results are primarily driven by drug acquisition costs associated with infliximab; these vary due to the change in infliximab dosing, which is weight based (5 mg/kg).

Incremental costs of ozanimod versus comparators are seen to increase over longer time horizons. These are driven primarily by accumulation of per-patient drug acquisition costs against infliximab and vedolizumab (SC). The cost differential versus vedolizumab (IV) remains higher for ozanimod but societal costs remain low.

Table 57. Summary of scenario analyses in the bio-naive population

	Treatment		
Incremental cost of ozanimod vs:	**Infliximab**	**Vedolizumab (IV)**	**Vedolizumab (SC)**
Base-case result	DKK 28,041	−DKK 4,817	DKK 36,452
Scenario analyses			
1-year time horizon	DKK 12,232	−DKK 10,994	DKK 15,454
3-year time horizon	DKK 73,868	DKK 12,343	DKK 97,322
5-year time horizon	DKK 131,406	DKK 32,160	DKK 173,747
10-year time horizon	DKK 259,064	DKK 67,801	DKK 343,310
0% discount rate	DKK 28,315	−DKK 4,581	DKK 36,817
Include drug wastage	DKK 23,249	DKK 469	DKK 38,146
Include dose escalations[a]	−DKK 4,876	−DKK 46,020	DKK 14,001
Adverse events excluded	DKK 29,783	−DKK 4,373	DKK 36,896
Societal costs excluded	DKK 31,297	−DKK 1,561	DKK 37,675
Patient weight 60 kg (−20%)	DKK 58,273	−DKK 4,817	DKK 36,452
Patient weight 90 kg (+20%)	−DKK 2,191	−DKK 4,817	DKK 36,452

IV = intravenous; SC = subcutaneous.

[a] Dose escalation applies only to infliximab and vedolizumab (SC & IV) and is based on feedback from Danish clinicians.

8.4.2. Biologic-experienced

8.4.2.1. Base-case results

The base-case results indicate that ozanimod therapy is more expensive than ustekinumab, adalimumab, and vedolizumab (IV) and marginally less expensive than vedolizumab (SC). The key driver of this result is the associated drug acquisition cost. Ozanimod therapy has the lowest drug administration costs but higher monitoring costs than other therapies. This result is aligned with the analysis in the bio-naive subgroup. The base-case results are presented in Table 57.

Table 58. Base-case results

Cost category	Treatment				
	Ozanimod	Ustekinumab	Vedolizumab (IV)	Vedolizumab (SC)	Adalimumab (SC)
Drug acquisition cost	DKK 208,532	DKK 200,240	DKK 185,189	DKK 164,577	DKK 145,805
Drug administration cost	DKK 168	DKK 2,580	DKK 25,047	DKK 6,424	DKK 4,147
Monitoring cost	DKK 10,378	DKK 9,926	DKK 9,959	DKK 9,959	DKK 9,926
Adverse event cost	DKK 999	DKK 2,148	DKK 1,443	DKK 1,443	DKK 1,624
Total direct cost	DKK 220,076	DKK 214,894	DKK 221,637	DKK 182,402	DKK 161,502
Societal cost	DKK 4,948	DKK 4,685	DKK 8,204	DKK 6,170	DKK 5,732
Total cost	DKK 225,024	DKK 219,580	DKK 229,841	DKK 188,572	DKK 167,234
Incremental cost	N/A	DKK 5,444	−DKK 4,817	DKK 36,452	DKK 57,790

IV = intravenous; N/A = not applicable; SC = subcutaneous.

8.4.2.2. Scenario analyses

The results from the scenarios are mostly consistent with the base-case results in the bio-experienced population. These results are summarised in Table 58. The 5- and 10-years' time horizon scenarios have the largest impact on results.

When the model time horizon is reduced to 1-year, ozanimod therapy is associated with lower costs than ustekinumab and vedolizumab IV therapies. When longer time horizons are assumed, the cost and frequency of the ustekinumab SC therapy offsets the cost of induction. This is not the case during a 1-year time horizon and thus costs for ustekinumab are higher.

Table 59. Summary of scenario analyses in the bio-experienced population

Incremental cost of ozanimod vs:	Treatment			
	Ustekinumab	Vedolizumab (IV)	Vedolizumab (SC)	Adalimumab (SC)
Base-case result	DKK 5,444	−DKK 4,817	DKK 36,452	DKK 57,790
Scenario analyses				
1-year time horizon	−DKK 17,030	−DKK 10,994	DKK 15,454	DKK 35,710
3-year time horizon	DKK 70,593	DKK 12,343	DKK 97,322	DKK 121,795
5-year time horizon	DKK 152,391	DKK 32,160	DKK 173,747	DKK 202,156
10-year time horizon	DKK 333,875	DKK 67,801	DKK 343,310	DKK 380,453
0% discount rate	DKK 5,834	−DKK 4,581	DKK 36,817	DKK 58,173
Include drug wastage	DKK 7,198	DKK 469	DKK 38,146	DKK 59,560
Include dose escalations[a]	−DKK 38,362	−DKK 46,020	DKK 14,001	DKK 20,484
Adverse events excluded	DKK 6,593	−DKK 4,373	DKK 36,896	DKK 58,415
Societal costs excluded	DKK 5,182	−DKK 1,561	DKK 37,675	DKK 58,574
Patient weight 60 kg (−20%)	DKK 5,444	−DKK 4,817	DKK 36,452	DKK 57,790
Patient weight 90 kg (+20%)	DKK 5,444	−DKK 4,817	DKK 36,452	DKK 57,790

IV = intravenous; SC = subcutaneous.

[a] Dose escalation applies only to ustekinumab and vedolizumab (SC & IV) and is based on feedback from Danish clinicians.

9. Budget impact

The impact of introducing ozanimod in the treatment landscape of moderate-to-severe UC was estimated using a 5-year budget-impact model. The bio-naive and bio-experienced populations were analysed separately.

A cohort of patients start treatment each year (n = 500 for the bio-naive subgroup and n = 300 for the bio-experienced subgroup).[119,120] The budget-impact model only considers incident patients over time. We further assume that the cohort of patients starting treatment each year will stay on treatment until progression. This assumption is aligned with the cost-minimisation analysis. Costs for each treatment are accrued for up to 5 years and are estimated as a function of cost per patient and the expected epidemiological data. Costs per patients are estimated using the same assumptions used in the cost-minimisation analyses. Given the assumption regarding incident patients in the model, the variation in costs by treatment is driven by market shares for the treatments.

The budget impact in each year is captured as the sum of costs in that year. The model estimates undiscounted results.

9.1. Market share

This section provides an overview of market shares Table 59 and Table 60 used in the budget-impact analysis. It is anticipated that ozanimod therapy captures market shares from vedolizumab (IV and SC) therapy.

Table 60. Market shares in the treatment landscape of moderate-to-severe UC in the bio-naive population

Bio-naive population	Year 1	Year 2	Year 3	Year 4	Year 5
Situation without ozanimod					
Ozanimod	0	0	0	0	0
Infliximab	70%	70%	70%	70%	70%
Vedolizumab (IV)	15%	15%	15%	15%	15%
Vedolizumab (SC)	15%	15%	15%	15%	15%
Situation with ozanimod					
Ozanimod	25%	25%	25%	25%	25%
Infliximab	70%	70%	70%	70%	70%
Vedolizumab (IV)	2.5%	2.5%	2.5%	2.5%	2.5%
Vedolizumab (SC)	2.5%	2.5%	2.5%	2.5%	2.5%

IV = intravenous; SC = subcutaneous.

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Table 61. Market shares in the treatment landscape of moderate-to-severe UC in the bio-experienced population

Bio-experienced population	Year 1	Year 2	Year 3	Year 4	Year 5
Situation without ozanimod					
Ozanimod	0	0	0	0	0
Ustekinumab	25%	25%	25%	25%	25%
Vedolizumab (IV)	25%	25%	25%	25%	25%
Vedolizumab (SC)	25%	25%	25%	25%	25%
Adalimumab (SC)	25%	25%	25%	25%	25%
Situation with ozanimod					
Ozanimod	70%	70%	70%	70%	70%
Ustekinumab	7.5%	7.5%	7.5%	7.5%	7.5%
Vedolizumab (IV)	7.5%	7.5%	7.5%	7.5%	7.5%
Vedolizumab (SC)	7.5%	7.5%	7.5%	7.5%	7.5%
Adalimumab (SC)	7.5%	7.5%	7.5%	7.5%	7.5%

IV = intravenous; SC = subcutaneous.

Table 61 and Table 62 show the number of patients based on the market share in the bio-naive and bio-experienced population. Ozanimod is expected to take the market share of vedolizumab (IV and SC) in the bio-naive population, whereas in the bio-experienced population, ozanimod is expected to take the market share of all the comparators.

Table 62. Number of patients based on market share in bio-naive population

Bio-naive population	Year 1	Year 2	Year 3	Year 4	Year 5
Situation without ozanimod					
Ozanimod	0	0	0	0	0
Infliximab	350	350	350	350	350
Vedolizumab (IV)	75	75	75	75	75
Vedolizumab (SC)	75	75	75	75	75
Situation with ozanimod					
Ozanimod	125	125	125	125	125
Infliximab	350	350	350	350	350
Vedolizumab (IV)	13	13	13	13	13
Vedolizumab (SC)	13	13	13	13	13

IV = intravenous; SC = subcutaneous.

Table 63. Number of patients based on market share in bio-experienced population

Bio-experienced population	Year 1	Year 2	Year 3	Year 4	Year 5
Situation without ozanimod					
Ozanimod	0	0	0	0	0
Ustekinumab	75	75	75	75	75
Vedolizumab (IV)	75	75	75	75	75
Vedolizumab (SC)	75	75	75	75	75

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Bio-experienced population	Year 1	Year 2	Year 3	Year 4	Year 5
Adalimumab (SC)	75	75	75	75	75
Situation with ozanimod					
Ozanimod	210	210	210	210	210
Ustekinumab	23	23	23	23	23
Vedolizumab (IV)	23	23	23	23	23
Vedolizumab (SC)	23	23	23	23	23
Adalimumab (SC)	23	23	23	23	23

IV = intravenous; SC = subcutaneous.

Table 63 and Table 64 shows the cost per patient based on the market shares in both the bio-naive and bio-experienced population.

Table 64. Cost per patient in bio-naive population

Bio-naive population	Year 1	Year 2	Year 3	Year 4	Year 5
Ozanimod	DKK 150,557	DKK 141,450	DKK 141,450	DKK 141,450	DKK 141,450
Infliximab	DKK 136,061	DKK 107,265	DKK 107,265	DKK 107,265	DKK 107,265
Vedolizumab (IV)	DKK 159,288	DKK 126,605	DKK 126,605	DKK 126,605	DKK 126,605
Vedolizumab (SC)	DKK 134,147	DKK 98,184	DKK 98,184	DKK 98,184	DKK 98,184

IV = intravenous; SC = subcutaneous.

Table 65. Cost per patient in bio-experienced population

Bio-naive population	Year 1	Year 2	Year 3	Year 4	Year 5
Ozanimod	DKK 150,557	DKK 141,450	DKK 141,450	DKK 141,450	DKK 141,450
Ustekinumab	DKK 134,223	DKK 105,427	DKK 105,427	DKK 105,427	DKK 105,427
Vedolizumab (IV)	DKK 159,288	DKK 126,605	DKK 126,605	DKK 126,605	DKK 126,605
Vedolizumab (SC)	DKK 134,147	DKK 98,184	DKK 98,184	DKK 98,184	DKK 98,184
Adalimumab (SC)	DKK 114,328	DKK 95,983	DKK 95,983	DKK 95,983	DKK 95,983

IV = intravenous; SC = subcutaneous.

9.2. Budget impact

9.2.1. Biologic-naive

9.2.1.1. Base-case analysis

The introduction of ozanimod therapy leads to an increase in budgets over all 5 years compared with a situation without ozanimod therapy (Table 65). Ozanimod is expected to take up market shares only from vedolizumab (IV and SC) therapies, while infliximab accounts for 70% of the market shares in the treatment landscape of moderate-to-severe UC in bio-experienced patients. As vedolizumab (SC) is a less expensive therapy (see Section 8.4.2) a reduction in the market share for this therapy would lead to an increase in budget. As the cost differential between ozanimod and vedolizumab (SC) is higher compared with the cost differential between ozanimod and vedolizumab (IV) therapy, a reduction in market shares for vedolizumab (SC) is expected to have a larger impact on the overall budgets.

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Table 66. Base-case results – budget impact in bio-naive population

Budget years	Year 1	Year 2	Year 3	Year 4	Year 5
Situation with ozanimod	DKK 70,109,119	DKK 128,142,868	DKK 186,176,617	DKK 244,210,366	DKK 302,244,114
Situation without ozanimod	DKK 69,629,109	DKK 124,030,936	DKK 178,432,763	DKK 232,834,589	DKK 287,236,416
Budget impact	DKK 480,010	DKK 4,111,932	DKK 7,743,854	DKK 11,375,776	DKK 15,007,699

9.2.1.2. Scenario analyses

As a scenario, the proportion of patients on an escalated dose of infliximab and vedolizumab (IV) was varied as per input from Danish clinical expert (see Table 46). In the dose escalation scenario, the impact of introducing ozanimod to the treatment landscape of moderate-to-severe UC was favourable in every year when compared with the existing market mix.

The budget-impact results over 5 years for the scenarios without and with patients on escalated dose are presented in Table 66.

Table 67. Scenario analyses – budget impact in bio-naive population

Budget years	Year 1	Year 2	Year 3	Year 4	Year 5
Base-case budget impact	DKK 480,010	DKK 4,111,932	DKK 7,743,854	DKK 11,375,776	DKK 15,007,699
Budget impact including dose escalation	−DKK 1,906,232	−DKK 1,375,624	−DKK 845,015	−DKK 314,406	DKK 216,203

9.2.2. Biologic-experienced

9.2.2.1. Base-case analysis

Introduction of ozanimod to the treatment landscape in moderate-to-severe UC led to an increase in budgets compared with a scenario without ozanimod in all years (Table 67). As ozanimod therapy takes up market shares from all therapies (ustekinumab, vedolizumab IV, vedolizumab SC, and adalimumab SC), the cost of ustekinumab and vedolizumab induction therapies which are more expensive are replaced in part by the relatively lower induction costs of ozanimod therapy.

Table 68. Base-case results – budget impact in bio-experienced population

Budget years	Year 1	Year 2	Year 3	Year 4	Year 5
Situation with ozanimod	DKK 44,565,953	DKK 83,646,344	DKK 122,726,734	DKK 159,647,496	DKK 193,995,869
Situation without ozanimod	DKK 43,163,019	DKK 74,416,205	DKK 105,669,391	DKK 136,922,577	DKK 159,601,135
Budget impact	DKK 1,402,934	DKK 9,230,138	DKK 17,057,343	DKK 22,724,919	DKK 34,394,734

9.2.2.2. Scenario analysis

As a scenario, the proportion of ustekinumab and vedolizumab (IV) patients on an escalated dose was varied to 50%.

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In a scenario where patients were on an escalated dose for infliximab (IV), Ustekinumab (SC), Adalimumab (SC), Vedolizumab (SC) and Vedolizumab (IV), a negative budget impact is observed in year 1 and year 2.

The budget-impact results over 5 years for the scenario with patients on escalated dose are presented in Table 68.

Table 69. Scenario analyses – budget impact in bio-experienced population

Budget years	Year 1	Year 2	Year 3	Year 4	Year 5
Base case	DKK 1,402,934	DKK 9,230,138	DKK 17,057,343	DKK 22,724,919	DKK 34,394,734
Budget impact (Dose escalation)	DKK −3,292,891	DKK −1,251,514	DKK 789,863	DKK 44,104	DKK 6,539,510

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10. Discussion on the submitted documentation

Summary

- The clinical and economic evidence in this application strongly supports the case for at least non-inferior efficacy, with similar rates of AEs of ozanimod than with currently existing therapies for UC in Denmark.
- Ozanimod offers a new mode of action for treatment of moderately to severely active UC and constitutes a safe, once daily, oral alternative to the existing therapies recommended by the Danish Medicines Council.

10.1. Interpretations and conclusions of the clinical evidence

The approval of ozanimod is based a phase 3 placebo-controlled TRUE NORTH trial,[9] supported by the phase 2 placebo-controlled TOUCHSTONE trial,[10] and the respective OLE trials and pooled analyses.[11-14] Results from both studies are likely to be generalisable to the anticipated population in Denmark. Both studies included patients from Europe.

10.1.1. Strengths and limitations of the clinical evidence

10.1.1.1. TRUE NORTH

TRUE NORTH is generally considered a high-quality study, based on a quality assessment using the University of York Centre for Reviews and Dissemination criteria for assessment of risk of bias in RCTs.[121] These criteria include questions on randomisation scheme, allocation concealment, balance of prognostic factors, blinding of patients, care providers, outcome assessors, imbalances in dropouts between groups, selective outcome reporting, and ITT analysis/handling of missing data.

A possible limitation to the TRUE NORTH study was the use of the 3-component Mayo Score to assess the primary and key secondary endpoints, when previous studies have used the 4-component Mayo Score. The rationale for using the 3-component Mayo Score was to be consistent with health authority guidance for UC development programmes. The 3-component Mayo Score does not use the PGA (physician's global assessment of disease activity) because of its uncertain added value in the assessment of treatment effect.

10.1.1.2. Indirect treatment comparison

As a head-to-head trial was not available, an indirect treatment comparison was performed to compare the efficacy and safety of ozanimod with currently available therapies for UC. The NMA of ozanimod versus currently existing therapies used the best quality evidence available to inform the network and was based on a comprehensive and robust SLR. In total, 121 publications reporting on 26 unique trials met the inclusion criteria, with 25 studies meeting the NMA eligibility criteria. The current review and analyses were associated with certain strengths and limitations. These included the following considerations:

- High-quality systematic review and report
  - A major strength of this report was that it adhered to best practices for the conduct and reporting of systematic reviews. Notably, all the searches were performed and peer-reviewed by experienced information specialists. All systematic reviews also reported detailed search strategies, PRISMA flow diagrams, full included/excluded study lists, and risk of bias assessments using appropriate tools, as per PRISMA Guidelines.[122,123] Although this review was restricted to English-language articles at the study selection stage, it did not restrict the search itself to English-only articles.
- Limited network structures for inconsistency assessment
  - An important assumption underlying NMA is that the analysed network is consistent, meaning that there is no evidence of disagreement between the direct and indirect evidence being combined. An unrelated mean effects model (i.e., an inconsistency model) was used to test for inconsistency; however, all independent closed loops in the evidence network were informed entirely by multi-arm trials or by a mixture of designs that make separating inconsistency and heterogeneity difficult. Regardless, no evidence of significant inconsistency was observed for key outcomes.
- Clinically relevant subgroup analyses
  - Analyses in the overall population combined data from patients without previous exposure to biologic treatments (bio-naive) and those who had received previous biologic treatment (bio-experienced) to explore the effects of treatment regardless of previous exposure to biologics. Additional analyses restricted to patients who were bio-naive or bio-experienced were performed to compare whether the effects of therapies varied in patients with or without previous biologic treatment, an important consideration for clinicians and payers deciding whether a treatment is appropriate for a patient with moderate-to-severe UC.
- Rigorous exploration of heterogeneity and sensitivity analyses
  - A thorough exploration of the various sources of heterogeneity associated with clinical trials in moderate-to-severe UC was conducted to evaluate the potential influence on NMA results. As a result of this assessment, several sensitivity analyses were explored to control for the various sources of heterogeneity, including analyses conducted in previous NMAs in UC. Overall, a conservative approach to trial and data inclusion was taken to limit the influence of the heterogeneity described throughout.
- Models selected
  - In general, the best-fitting model selected was the result of an assessment of model fits and face validity of findings. Despite the fact that random effects models would be favourable a priori due to the clinical heterogeneity established, these models often resulted in highly uncertain estimates that lacked face validity by showing that several active agents would be considered comparable to placebo, demonstrated by overlap of the pairwise 95% credible intervals with unity. As a result, random effects models were only leveraged for the bio-naive analyses during the induction period, wherein estimates from the random effects models were reasonable. Applying an informative half-normal prior on the between-trial heterogeneity parameter was explored through a sensitivity analysis but did not offer significant improvement in the face validity of estimates and therefore was not leveraged for the base-case models.
  - Use of a fixed effect model when clinical heterogeneity has been established is not ideal, as outlined by the ERG in recent UC submissions to NICE. In such cases, a fixed effect model likely generates overly precise estimates. Despite this limitation, the recent UC evidence report

published by ICER leveraged a fixed effect model in the maintenance period due to the sparsity of network in their analyses, aligning with our model selection approach and showing a preference for the fixed effect model in the latest UC NMAs despite the limitations listed above because the lack of uncertainty caused by the random effects models undermines the validity of the NMAs performed. Regardless, conclusions should be interpreted in the context of these limitations.

10.1.1.3. TOUCHSTONE

TOUCHSTONE is generally considered a high-quality study, based on a quality assessment using the University of York Centre for Reviews and Dissemination criteria for assessment of risk of bias in RCTs.[121] This phase 2 study was associated with some limitations. The 8-week time period for the induction phase may not be long enough for drugs that target lymphocyte migration; this is supported by the enhanced benefits seen in maintenance phase. This short time period and small number of patients makes it difficult to fully assess the safety of ozanimod. TOUCHSTONE was restricted to patients receiving ozanimod as monotherapy or in combination with glucocorticoids or aminosalicylates.

10.2. Interpretation and conclusions of economic evidence

The base-case results indicate that ozanimod therapy is associated with higher per-patient costs than infliximab and vedolizumab (SC & IV) therapies in bio-naive patients; and ustekinumab, adalimumab (SC), and vedolizumab (SC & IV) therapies in bio-experienced patients. However, the cost-minimisation analyses were carried out using the PPP as per DMC guidelines.

10.2.1. Strengths and limitations of the economic evaluation

A thorough cost-minimisation model has been submitted based on a methodologically robust NMA indicating that ozanimod is non-inferior to comparators of interest. A key strength of the economic evaluation is that extensive scenario analyses have been explored to identify the impact of each input parameter in the model and the results appear to be robust. One drawback of the results of economic evaluation is that these results are based on the list prices (PPP) of pharmaceuticals in question.

11. List of experts

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13. List of appendices

- Appendix A: Literature search
  - Please see the separate attachment.
- Appendix B: Main characteristics of included studies
  - Please see the separate attachment.
- Appendix C: Baseline characteristics of patients in studies used for the comparative analysis of efficacy and safety
  - Please see the separate attachment. Parts of this document contain confidential information and have been highlighted accordingly.
- Appendix D: Efficacy and safety results per study
  - Please see the separate attachment. Parts of this document contain confidential information and have been highlighted accordingly.
- Appendix E: Safety data for intervention and comparator(s)
  - Please see the separate attachment. Parts of this document contain confidential information and have been highlighted accordingly.
- Appendix F: Comparative analysis of efficacy and safety
  - Please see the separate attachment. Parts of this document contain confidential information and have been highlighted accordingly.
- Appendix G: TRUE NORTH and TOUCHSTONE additional study details
  - Please see the separate attachment. Parts of this document contain confidential information and have been highlighted accordingly.
- Appendix H: Summary of product characteristics (SmPC) for ozanimod
  - Please see the separate attachment.
- Appendix I: Description of comparators
  - Please see the separate attachment.
- Appendix J: Extrapolation
  - Not applicable as a cost-minimisation approach was used.
- Appendix K: Literature search for HRQoL data

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  - Not applicable because HRQoL data are not used in economic evaluation due to the cost-minimisation approach.

- Appendix L: Mapping of HRQoL data
  - Not applicable because a cost-minimisation approach was used.
- Appendix M: Probabilistic sensitivity analyses
  - Probabilistic sensitivity analyses were not conducted because a cost-minimisation approach was used.
- Appendix N: NMA additional details
  - Please see the separate attachment. Parts of this document contain confidential information and have been highlighted accordingly.

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Medicinrådet

Appendices for the assessment of ozanimod (ZEPOSIA®) for the treatment of moderately to severely active ulcerative colitis

FINAL Updated 16 June 2022

[redacted]

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Table of contents

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Appendix A. Literature search for efficacy and safety of intervention and comparator(s)

Appendix A.1 Introduction

The SLR was performed in accordance with the Cochrane Handbook for Systematic Reviews of Interventions[1] and reported in alignment with the Preferred Reporting Items for Systematic Literature Reviews and Meta-Analyses (PRISMA) statement.[2,3] The Population, Intervention, Comparator, Outcome, Study (PICOS) framework was used to develop the search strategy.

Objective of the literature search: How do agents approved for moderate-to-severe UC compare in terms of key clinical efficacy (clinical response, clinical remission, and endoscopic improvement) and safety (adverse events, serious adverse events, withdrawals due to adverse events, and serious infections) outcomes evaluated at induction and maintenance of phase 2 and 3 randomised controlled trials?

Databases: Using the Ovid platform, Ovid MEDLINE® including Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Embase, Cochrane Central Register of Controlled Trials, and the Database of Abstracts of Reviews of Effects were searched. Separate searches were performed for trials and systematic reviews/meta-analyses. All searches were performed on October 21, 2020.

Strategies used a combination of controlled vocabulary (e.g., "Colitis, Ulcerative," "Infliximab," "Tumour Necrosis Factor Inhibitors") and keywords (e.g., "ulcerative colitis," "Remicade," "anti-TNF"). Vocabulary and syntax were adjusted across the databases. Results were limited to the publication years 2000 to the present and, where possible, animal-only, opinion pieces, and case reports were removed. Only conference abstracts published in 2019 or later were retained.

Table A-1. Bibliographic databases included in the literature search

Database	Platform	Relevant period for the search	Date of search completion
Embase	Ovid	1974 to 20 October 2020	21 October 2020
Medline	Ovid	1946 to October 20, 2020	21 October 2020
Medline In-Process and Epub Ahead of Print	Ovid	1946 to October 20, 2020	21 October 2020
Cochrane CENTRAL	Ovid	September 2020	21 October 2020
DARE[a]	Ovid	1st Quarter 2016	21 October 2020

DARE = Database of Abstracts of Reviews of Effects

[a] DARE were discontinued in 2015; therefore, only the archived databases (until 2015) were searched. CRD is maintaining versions of the DARE until at least 2021, when the current process will be reviewed

Appendix A.2 Additional sources

Additional searches were performed, including a targeted grey literature search of ClinicalTrials.gov, hand searches of identified conferences of interest from 2019-2020 (Crohn's & Colitis, American College of Gastroenterology, European Crohn's and Colitis Organisation, Digestive Disease Week, Biennial World Congress of Gastroenterology, Annual United European Gastroenterology Week, Annual Advances in Inflammatory Bowel Diseases) and bibliographies of relevant SLRs identified via the original database search. These targeted searches facilitated cross-referencing of the included

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study list with registered clinical trials and existing reviews. The following HTA agencies were also searched:

- National Institute for Clinical Excellence (NICE)
- Canadian Agency for Drugs and Technologies in Health (CADTH)
- Institute for Clinical and Economic Review (ICER)

Appendix A.3 Eligibility criteria

The clinical SLR focused on phase 2 and 3 RCTs in patients with moderate-to-severe UC. The prespecified PICOS criteria described were used to identify studies relevant for inclusion in this review.

Table A-2. PICOS criteria

	Inclusion criteria	Exclusion criteria
Population	▪ Adults (≥ 18 years) with moderate-to-severe UC ▪ Subgroups of interest: biologic treatment failure and biologic treatment non-failure with and without prior corticosteroid use	▪ Non-adults (≤ 18 years) ▪ Animals, in vitro studies ▪ Patients with mild UC
Interventions	▪ ozanimod ▪ ustekinumab ▪ infliximab ▪ certolizumab ▪ adalimumab ▪ vedolizumab ▪ tofacitinib ▪ golimumab ▪ filgotinib ▪ etrasimod ▪ filgotinib ▪ etrasimod ▪ or biosimilar versions of these therapies	▪ Treatments not related to UC ▪ etrolizumab (withdrawn) ▪ Medical devices ▪ Non-pharmacological interventions
Comparators	▪ The above therapies alone or in combination with SOC; or SOC alone (including approved or recommended immunosuppressants, corticosteroids, and 5-ASAs)	
Outcomes	▪ Clinical remission ▪ Clinical response ▪ Endoscopic improvement / mucosal healing ▪ Histologic remission ▪ Steroid-free remission ▪ Adverse events ▪ Serious adverse events ▪ AEs leading to discontinuation ▪ Specific AE categories ▪ HRQoL outcomes ▪ Patient-reported outcomes ▪ Resource use ▪ Productivity ▪ Mortality	▪ Outcomes not related to UC (e.g., outcomes related to another population or disease)
Study design	▪ Phase 2, phase 3, and phase 2/3 RCTs, including published studies, conference abstracts/posters, and grey literature	▪ Phase 1, phase 1/3 and phase 4 RCTs ▪ Non-RCTs ▪ Single-arm studies

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	Inclusion criteria	Exclusion criteria
	▪ Systematic reviews, meta-analyses, and network meta-analyses	▪ Open-label extension trials ▪ Study protocols ▪ Opinion pieces, commentaries, letters, editorials, case reports ▪ Economic/cost-effectiveness evaluations ▪ Narrative reviews (i.e., non-systematic)
Location	▪ Global	▪ None
Language	▪ English only	▪ Non-English
Date limit	▪ Full-text articles: 2000-2020	▪ Full-text articles prior to 2000

ASA = acetylsalicylic acid; AE = adverse event; HRQoL = health-related quality of life; RCT = randomised controlled trial; SOC = standard of care; UC = ulcerative colitis.

Appendix A.3.1 Study selection

Study screening was conducted by 2 reviewers who independently reviewed the study records, citation titles, and abstracts identified in the clinical literature search to assess study eligibility based on the prespecified PICOS criteria. Study screening was performed using the systematic review software DistillerSR (Evidence Partners, Ottawa, Canada).[4] Reviewers documented their reasons for exclusion and presented the results in the form of a PRISMA flow diagram.[3] Citations considered to describe potentially eligible articles were independently reviewed by 2 reviewers in full-text form for formal inclusion in the final review. Any discrepancies between the 2 reviewers were resolved by consensus or were referred to and resolved by a third independent reviewer not involved in the data collection process. Included full-text articles were further validated for inclusion during the data extraction phase. This involved reviewing the study design details, baseline population characteristics, efficacy, safety endpoints, and assessing risk of bias.

Appendix A.4 Search strategy

Table A-3. Search strategy for RCTs

No.	Query	Results
1	Colitis, Ulcerative/ (62483)	62483
2	((colitis or colorectitis or proctocolitis or procto colitis) adj3 (ulcer* or mucosa* or gravis or idiopathic*)).tw,kf. (110538)	110538
3	(((colon or colonic) adj3 ulceration) and chronic*).tw,kf. (128)	128
4	(UC and (ulcer* or colitis*)).tw,kf. (43814)	43814
5	or/1-4 [UC] (127053)	127053
6	(severe* or acute* or intensive* or moderate*).tw,kf. (6909831)	6909831
7	5 and 6 [MODERATE OR SEVERE UC] (28378)	28378
8	(exp Child/ or exp Infant/) not (Adolescent/ or exp Adult/) (2910517)	2910517
9	7 not 8 [CHILD-, INFANT-ONLY REMOVED] (27448)	27448
10	(ozanimod or rpc 1063 or rpc1063 or HSDB 7852 or OZM or Zeposia$2 or UNII-Z80293URPV or Z80293URPV or 1306760-87-1).tw,kf,rn. (548)	548
11	Adalimumab/ (40380)	40380
12	(adalimumab or ADA or "abp 501" or abp501 or "abt d2e7" or abtd2e7 or adaly$2 or amgevita$2 or amjevita$2 or "avt 02" or "avt 02" or "bat 1406" or bat1406 or "bax 2923" or bax2923 or "bax 923" or bax923 or "bi 695501" or bi695501 or "chs 1420" or chs1420 or "ct p17" or ctp17 or cyltezo$2 or "da 3113" or da3113 or "dmb 3113" or dmb3113 or exemptia$2 or "fkb 327" or fkb327 or fyzoclad$2 or	72642

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No.	Query	Results
	"gp 2017" or gp2017 or hadlima$2 or halimato$2 or hefiya$2 or "hlx 03" or hlx03 or hulio$2 or humira$2 or hyrimoz$2 or "ibi 303" or ibi303 or imraldi$2 or kromeya$2 or lu 200134 or lu200134 or "m 923" or m923 or mabura$2 or (monoclonal adj3 antibod$ adj3 D2E7) or "msb 11022" or msb11022 or "ons 3010" or ons3010 or "pf 06410293" or "pf 6410293" or pf06410293 or pf6410293 or raheara$2 or "sb 5" or sb5 or solymbic$2 or trudexa$2 or "zrc 3197" or zrc3197 or FYS6T7F842 or 331731-18-1 or 1446410-95-2).tw,kf,rn. (72642)	
13	(etrasimod or APD334 or UNII-6WH8495MMH or 6WH8495MMH or 1206123-37-6).tw,kf,rn. (109)	109
14	(etrolizumab or pro 145223 or pro145223 or rhumab beta7 or UNII-I2A72G2V3J or I2A72G2V3J or 1044758-60-2).tw,kf,rn. (433)	433
15	(filgotinib or "g 146034" or "g 146034 101" or g146034 or "g146034 101" or "glpg 0634" or glpg0634 or "gs 6034" or gs6034 or Jyseleca$2).tw,kf,rn. (744)	744
16	(golimumab or CNTO-148 or CNTO148 or Simponi$2 or UNII-91X1KLU43E or 91X1KLU43E or 476181-74-5).tw,kf,rn. (9232)	9232
17	Infliximab/ (62466)	62466
18	(infliximab or CT-P13 or CTP13 or SB2 or "abp 710" or abp710 or avakine$2 or flixabi$2 or "gp 1111" or gp1111 or inflectra$2 or ixifi$2 or "pf 06438179" or "pf 6438179" or pf06438179 or pf6438179 or remicade$2 or remsima$2 or renflexis$2 or revellex$2 or "ta 650" or ta650 or zessly$2).tw,kf,rn. (70728)	70728
19	(tofacitinib or "cp 690 550" or "cp 690550" or "cp690 550" or cp690550 or HSDB 8311 or xeljanz$2 or UNII-87LA6FU830 or 87LA6FU830 or 477600-75-2 or 540737-29-9).tw,kf,rn. (7366)	7366
20	Ustekinumab/ (8582)	8582
21	(ustekinumab or "cnto 1275" or cnto1275 or stelara$2 or UNII-FU77B4U5Z0 or FU77B4U5Z0 or 15610-63-0).tw,kf,rn. (10415)	10415
22	(vedolizumab or entyvio$2 or "ldp 02" or ldp02 or "mln 0002" or mln0002 or "mln 02" or mln02 or "ldp 02" or UNII-9RV78Q2002 or 9RV78Q2002 or 943609-66-3).tw,kf,rn. (5606)	5606
23	Tumour Necrosis Factor Inhibitors/ (12295)	12295
24	(anti TNF or anti TNFs or antiTNF or antiTNFs or anti tumour necrosis factor? or antitumour necrosis factor?).tw,kf. (42747)	42747
25	((TNF or TNFs or tumour necrosis factor?) adj3 inhibitor?).tw,kf. (21475)	21475
26	((TNF or TNFs or tumour necrosis factor?) adj3 (antagonist* or blocker?)).tw,kf. (10691)	10691
27	Sphingosine 1 Phosphate Receptor Modulators/ (98)	98
28	(sphingosine adj3 (receptor? adj1 modulat*)).tw,kf. (618)	618
29	(sphingosine adj3 receptor affecting agent?).tw,kf. (0)	0
30	((S1P or S1P5 or S1PR) adj3 (immomodulator? or agonist?)).tw,kf. (845)	845
31	((lysosphingolipid? or sphingolipid?) adj3 (receptor? adj1 modulat*)).tw,kf. (9)	9
32	((lysosphingolipid? or sphingolipid?) adj3 receptor affecting agent?).tw,kf. (0)	0
33	((lysosphingolipid? or sphingolipid?) adj3 (immomodulator? or agonist?)).tw,kf. (13)	13
34	Receptors, Lysosphingolipid/ (1936)	1936
35	or/10-34 [AGENTS OF INTEREST] (175510)	175510
36	9 and 35 [MODERATE OR SEVERE UC - AGENTS OF INTEREST] (6538)	6538
37	(controlled clinical trial or randomized controlled trial or equivalence trial or pragmatic clinical trial).pt. (1197052)	1197052
38	clinical trials as topic/ (306247)	306247
39	exp Randomized Controlled Trials as Topic/ (337812)	337812
40	(randomi#ed or randomi#ation? or randomly or RCT or placebo*).tw,kf. (3483717)	3483717

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No.	Query	Results
41	((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw,kf. (697702)	697702
42	trial.ab. (1748716)	1748716
43	groups.ab. (5528289)	5528289
44	dt.fs. [drug therapy] (6242983)	6242983
45	or/37-44 [RCTS - MODIFIED COCHRANE HSSS - BROAD] (13611037)	13611037
46	36 and 45 (4381)	4381
47	clinical trial, phase ii/ (33587)	33587
48	clinical trial, phase iii/ (17369)	17369
49	(trial? adj3 (phase 2 or phase ii or phase 3 or phase iii or "phase 2/3" or "phases 2/3" or "phase ii/iii" or "phases ii/iii")).tw,kf. (189964)	189964
50	open label*.tw,kf. (190236)	190236
51	or/47-50 (390518)	390518
52	36 and 51 (823)	823
53	46 or 52 [UC - AGENTS OF INTEREST - RCTS, INCL PHASE 2-3, OPEN LABEL] (4473)	4473
54	exp Animals/ not Humans/ (17360395)	17360395
55	53 not 54 [ANIMAL-ONLY REMOVED] (3022)	3022
56	(comment or editorial or newspaper article or news or case reports).pt. (4238923)	4238923
57	(letter not (letter and randomized controlled trial)).pt. (2247021)	2247021
58	55 not (56 or 57) [OPINION PIECES REMOVED] (2845)	2845
59	limit 58 to yr="2000-current" (2834)	2834
60	59 use ppez [MEDLINE RECORDS] (830)	830
61	ulcerative colitis/ (110332)	110332
62	((colitis or colorectitis or proctocolitis or procto colitis) adj3 (ulcer* or mucosa* or gravis or idiopathic*)).tw,kw. (111979)	111979
63	(((colon or colonic) adj3 ulceration) and chronic*).tw,kw. (128)	128
64	(UC and (ulcer* or colitis*)).tw,kw. (44008)	44008
65	or/61-64 [UC] (138604)	138604
66	(severe* or acute* or intensive* or moderate*).tw,kw. (6936165)	6936165
67	65 and 66 [MODERATE OR SEVERE UC] (29642)	29642
68	exp juvenile/ not exp adult/ (2225183)	2225183
69	67 not 68 [UNDER 18 POPULATION-ONLY REMOVED] (28357)	28357
70	ozanimod/ (294)	294
71	(ozanimod or rpc 1063 or rpc1063 or HSDB 7852 or OZM or Zeposia$2 or UNII-Z80293URPV or Z80293URPV or 1306760-87-1).tw,kw,rn. (550)	550
72	adalimumab/ (40380)	40380
73	(adalimumab or ADA or "abp 501" or abp501 or "abt d2e7" or abtd2e7 or adaly$2 or amgevita$2 or amjevita$2 or "avt 02" or "avt 02" or "bat 1406" or bat1406 or "bax 2923" or bax2923 or "bax 923" or bax923 or "bi 695501" or bi695501 or "chs 1420" or chs1420 or "ct p17" or ctp17 or cyltezo$2 or "da 3113" or da3113 or "dmb 3113" or dmb3113 or exemptia$2 or "fkb 327" or fkb327 or fyzoclad$2 or "gp 2017" or gp2017 or hadlima$2 or halimato$2 or hefiya$2 or "hlx 03" or hlx03 or hulio$2 or humira$2 or hyrimoz$2 or "ibi 303" or ibi303 or imraldi$2 or kromeya$2 or lu 200134 or lu200134 or "m 923" or m923 or mabura$2 or (monoclonal adj3 antibod$ adj3 D2E7) or "msb 11022" or msb11022 or "ons 3010" or ons3010 or "pf 06410293" or "pf 6410293" or pf06410293 or pf6410293 or raheara$2	72912

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No.	Query	Results
	or "sb 5" or sb5 or solymbic$2 or trudexa$2 or "zrc 3197" or zrc3197 or FYS6T7F842 or 331731-18-1 or 1446410-95-2).tw,kw,rn. (72912)	
74	etrasimod/ (64)	64
75	(etrasimod or APD334 or UNII-6WH8495MMH or 6WH8495MMH or 1206123-37-6).tw,kw,rn. (109)	109
76	etrolizumab/ (291)	291
77	(etrolizumab or pro 145223 or pro145223 or rhumab beta7 or UNII-I2A72G2V3J or I2A72G2V3J or 1044758-60-2).tw,kw,rn. (435)	435
78	filgotinib/ (429)	429
79	(filgotinib or "g 146034" or "g 146034 101" or g146034 or "g146034 101" or "glpg 0634" or glpg0634 or "gs 6034" or gs6034 or Jyseleca$2).tw,kw,rn. (744)	744
80	golimumab/ (7110)	7110
81	(golimumab or CNTO-148 or CNTO148 or Simponi$2 or UNII-91X1KLU43E or 91X1KLU43E or 476181-74-5).tw,kw,rn. (9271)	9271
82	infliximab/ (62466)	62466
83	(infliximab or CT-P13 or CTP13 or SB2 or "abp 710" or abp710 or avakine$2 or flixabi$2 or "gp 1111" or gp1111 or inflectra$2 or ixifi$2 or "pf 06438179" or "pf 6438179" or pf06438179 or pf6438179 or remicade$2 or remsima$2 or renflexis$2 or revellex$2 or "ta 650" or ta650 or zessly$2).tw,kw,rn. (70989)	70989
84	tofacitinib/ (4744)	4744
85	(tofacitinib or "cp 690 550" or "cp 690550" or "cp690 550" or cp690550 or HSDB 8311 or xeljanz$2 or UNII-87LA6FU830 or 87LA6FU830 or 477600-75-2 or 540737-29-9).tw,kw,rn. (7409)	7409
86	ustekinumab/ (8582)	8582
87	(ustekinumab or "cnto 1275" or cnto1275 or stelara$2 or UNII-FU77B4U5Z0 or FU77B4U5Z0 or 15610-63-0).tw,kw,rn. (10464)	10464
88	vedolizumab/ (3939)	3939
89	(vedolizumab or entyvio$2 or "ldp 02" or ldp02 or "mln 0002" or mln0002 or "mln 02" or mln02 or "ldp 02" or UNII-9RV78Q2002 or 9RV78Q2002 or 943609-66-3).tw,kw,rn. (5634)	5634
90	tumour necrosis factor inhibitor/ (14885)	14885
91	(anti TNF or anti TNFs or antiTNF or antiTNFs or anti tumour necrosis factor? or antitumour necrosis factor?).tw,kw. (43643)	43643
92	((TNF or TNFs or tumour necrosis factor?) adj3 inhibitor?).tw,kw. (21836)	21836
93	((TNF or TNFs or tumour necrosis factor?) adj3 (antagonist* or blocker?)).tw,kw. (10894)	10894
94	sphingosine 1 phosphate receptor modulator/ (95)	95
95	(sphingosine adj3 (receptor? adj1 modulat*)).tw,kw. (627)	627
96	(sphingosine adj3 receptor affecting agent?).tw,kw. (0)	0
97	((S1P or S1P5 or S1PR) adj3 (immomodulator? or agonist?)).tw,kw. (843)	843
98	((lysosphingolipid? or sphingolipid?) adj3 (receptor? adj1 modulat*)).tw,kw. (9)	9
99	((lysosphingolipid? or sphingolipid?) adj3 receptor affecting agent?).tw,kw. (0)	0
100	((lysosphingolipid? or sphingolipid?) adj3 (immomodulator? or agonist?)).tw,kw. (13)	13
101	lysophospholipid receptor affecting agent/ (2)	2
102	or/70-101 [AGENTS OF INTEREST] (174954)	174954
103	69 and 102 [MODERATE OR SEVERE UC - AGENTS OF INTEREST] (6746)	6746
104	exp randomized controlled trial/ (1145313)	1145313
105	controlled clinical trial/ (559383)	559383

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No.	Query	Results
106	"clinical trial (topic)"/ (109337)	109337
107	"randomized controlled trial (topic)"/ (189305)	189305
108	(randomi#ed or randomi#ation? or randomly or RCT or placebo*).ti,ab,kw. (3544905)	3544905
109	((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).ti,ab,kw. (725334)	725334
110	trial.ab. (1748716)	1748716
111	groups.ab. (5528289)	5528289
112	dt.fs. [drug therapy] (6242983)	6242983
113	or/104-112 [RCTS - MODIFIED COCHRANE HSSS - BROAD] (13609027)	13609027
114	103 and 113 (4702)	4702
115	phase 2 clinical trial/ (83853)	83853
116	phase 3 clinical trial/ (49395)	49395
117	(trial? adj3 (phase 2 or phase ii or phase 3 or phase iii or "phase 2/3" or "phases 2/3" or "phase ii/iii" or "phases ii/iii")).tw,kw. (212203)	212203
118	open label*.tw,kw. (190268)	190268
119	or/115-118 [PHASE 2/3, OPEN LABEL TRIALS] (442874)	442874
120	103 and 119 (1048)	1048
121	114 or 120 [UC - AGENTS OF INTEREST - RCTS, INCL PHASE 2-3, OPEN LABEL] (4788)	4788
122	exp animal/ or exp animal experimentation/ or exp animal model/ or exp animal experiment/ or nonhuman/ or exp vertebrate/ (52245601)	52245601
123	exp human/ or exp human experimentation/ or exp human experiment/ (40915815)	40915815
124	122 not 123 (11331441)	11331441
125	121 not 124 [ANIMAL-ONLY REMOVED] (4750)	4750
126	editorial.pt. (1215638)	1215638
127	case report/ (4666955)	4666955
128	letter.pt. not (letter.pt. and randomized controlled trial/) (2246897)	2246897
129	125 not (126 or 127 or 128) [OPINION PIECES REMOVED] (4316)	4316
130	limit 129 to yr="2000-current" (4303)	4303
131	conference abstract.pt. (3906990)	3906990
132	130 not 131 [CONFERENCE ABSTRACTS REMOVED] (3142)	3142
133	130 and 131 (1161)	1161
134	limit 133 to yr="2019-current" (254)	254
135	132 or 134 [MOST RECENT 2 YRS CONFERENCE ABSTRACTS RETAINED] (3396)	3396
136	135 use oemezd [EMBASE RECORDS] (1909)	1909
137	Colitis, Ulcerative/ (62483)	62483
138	((colitis or colorectitis or proctocolitis or procto colitis) adj3 (ulcer* or mucosa* or gravis or idiopathic*)).ti,ab,kw. (111979)	111979
139	(((colon or colonic) adj3 ulceration) and chronic*).ti,ab,kw. (128)	128
140	(UC and (ulcer* or colitis*)).ti,ab,kw. (44008)	44008
141	or/137-140 [UC] (128912)	128912
142	(severe* or acute* or intensive* or moderate*).ti,ab,kw. (6936123)	6936123
143	141 and 142 [MODERATE OR SEVERE UC] (28687)	28687
144	(exp Child/ or exp Infant/) not (Adolescent/ or exp Adult/) (2910517)	2910517

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No.	Query	Results
145	143 not 144 [CHILD-, INFANT-ONLY REMOVED] (27753)	27753
146	(ozanimod or rpc 1063 or rpc1063 or HSDB 7852 or OZM or Zeposia$2 or UNII-Z80293URPV or Z80293URPV or 1306760-87-1).ti,ab,kw. (401)	401
147	Adalimumab/ (40380)	40380
148	(adalimumab or ADA or "abp 501" or abp501 or "abt d2e7" or abtd2e7 or adaly$2 or amgevita$2 or amjevita$2 or "avt 02" or "avt 02" or "bat 1406" or bat1406 or "bax 2923" or bax2923 or "bax 923" or bax923 or "bi 695501" or bi695501 or "chs 1420" or chs1420 or "ct p17" or ctp17 or cyltezo$2 or "da 3113" or da3113 or "dmb 3113" or dmb3113 or exemptia$2 or "fkb 327" or fkb327 or fyzoclad$2 or "gp 2017" or gp2017 or hadlima$2 or halimato$2 or hefiya$2 or "hlx 03" or hlx03 or hulio$2 or humira$2 or hyrimoz$2 or "ibi 303" or ibi303 or imraldi$2 or kromeya$2 or lu 200134 or lu200134 or "m 923" or m923 or mabura$2 or (monoclonal adj3 antibod$ adj3 D2E7) or "msb 11022" or msb11022 or "ons 3010" or ons3010 or "pf 06410293" or "pf 6410293" or pf06410293 or pf6410293 or raheara$2 or "sb 5" or sb5 or solymbic$2 or trudexa$2 or "zrc 3197" or zrc3197 or FYS6T7F842 or 331731-18-1 or 1446410-95-2).ti,ab,kw. (55407)	55407
149	(etrasimod or APD334 or UNII-6WH8495MMH or 6WH8495MMH or 1206123-37-6).ti,ab,kw. (73)	73
150	(etrolizumab or pro 145223 or pro145223 or rhumab beta7 or UNII-I2A72G2V3J or I2A72G2V3J or 1044758-60-2).ti,ab,kw. (290)	290
151	(filgotinib or "g 146034" or "g 146034 101" or g146034 or "g146034 101" or "glpg 0634" or glpg0634 or "gs 6034" or gs6034 or Jyseleca$2).ti,ab,kw. (535)	535
152	(golimumab or CNTO-148 or CNTO148 or Simponi$2 or UNII-91X1KLU43E or 91X1KLU43E or 476181-74-5).ti,ab,kw. (5694)	5694
153	Infliximab/ (62466)	62466
154	(infliximab or CT-P13 or CTP13 or SB2 or "abp 710" or abp710 or avakine$2 or flixabi$2 or "gp 1111" or gp1111 or inflectra$2 or ixifi$2 or "pf 06438179" or "pf 6438179" or pf06438179 or pf6438179 or remicade$2 or remsima$2 or renflexis$2 or revellex$2 or "ta 650" or ta650 or zessly$2).ti,ab,kw. (43309)	43309
155	(tofacitinib or "cp 690 550" or "cp 690550" or "cp690 550" or cp690550 or HSDB 8311 or xeljanz$2 or UNII-87LA6FU830 or 87LA6FU830 or 477600-75-2 or 540737-29-9).ti,ab,kw. (5449)	5449
156	Ustekinumab/ (8582)	8582
157	(ustekinumab or "cnto 1275" or cnto1275 or stelara$2 or UNII-FU77B4U5Z0 or FU77B4U5Z0 or 15610-63-0).ti,ab,kw. (7078)	7078
158	(vedolizumab or entyvio$2 or "ldp 02" or ldp02 or "mln 0002" or mln0002 or "mln 02" or mln02 or "ldp 02" or UNII-9RV78Q2002 or 9RV78Q2002 or 943609-66-3).ti,ab,kw. (4240)	4240
159	Tumour Necrosis Factor Inhibitors/ (12295)	12295
160	(anti TNF or anti TNFs or antiTNF or antiTNFs or anti tumour necrosis factor? or antitumour necrosis factor?).ti,ab,kw. (43643)	43643
161	((TNF or TNFs or tumour necrosis factor?) adj3 inhibitor?).ti,ab,kw. (21836)	21836
162	((TNF or TNFs or tumour necrosis factor?) adj3 (antagonist* or blocker?)).ti,ab,kw. (10894)	10894
163	Sphingosine 1 Phosphate Receptor Modulators/ (98)	98
164	(sphingosine adj3 (receptor? adj1 modulat*)).ti,ab,kw. (627)	627
165	(sphingosine adj3 receptor affecting agent?).ti,ab,kw. (0)	0
166	((S1P or S1P5 or S1PR) adj3 (immomodulator? or agonist?)).ti,ab,kw. (843)	843
167	((lysosphingolipid? or sphingolipid?) adj3 (receptor? adj1 modulat*)).ti,ab,kw. (9)	9
168	((lysosphingolipid? or sphingolipid?) adj3 receptor affecting agent?).ti,ab,kw. (0)	0
169	((lysosphingolipid? or sphingolipid?) adj3 (immomodulator? or agonist?)).ti,ab,kw. (13)	13
170	Receptors, Lysosphingolipid/ (1936)	1936

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No.	Query	Results
171	or/146-170 [AGENTS OF INTEREST] (174229)	174229
172	145 and 171 [MODERATE OR SEVERE UC - AGENTS OF INTEREST] (6598)	6598
173	limit 172 to yr="2000-current" (6577)	6577
174	(conference abstract or journal conference abstract).pt. (4067580)	4067580
175	173 not 174 [CONFERENCE ABSTRACTS REMOVED] (3627)	3627
176	173 and 174 (2950)	2950
177	limit 176 to yr="2019-current" (695)	695
178	175 or 177 [MOST RECENT 2 YRS CONFERENCE ABSTRACTS RETAINED] (4322)	4322
179	178 use cctr [CENTRAL RECORDS] (492)	492
180	60 or 136 or 179 [ALL DATABASES] (3231)	3231
181	**remove duplicates from 180 (2242) [TOTAL UNIQUE RECORDS]**	**2242**
182	**181 use ppez [MEDLINE RECORDS] (829)**	**829**
183	**181 use oemezd [EMBASE RECORDS] (1172)**	**1172**
184	**181 use cctr [CENTRAL RECORDS] (241)**	**241**

Abbreviations

Notes

Table A-4. Search strategy for reviews

No.	Query	Results
1	Colitis, Ulcerative/	60916
2	((colitis or colorectitis or proctocolitis or procto colitis) adj3 (ulcer* or mucosa* or gravis or idiopathic*)).tw,kf.	105907
3	(((colon or colonic) adj3 ulceration) and chronic*).tw,kf.	126
4	(UC and (ulcer* or colitis*)).tw,kf.	41504
5	or/1-4 [UC]	122201
6	(exp Child/ or exp Infant/) not (Adolescent/ or exp Adult/)	2873615
7	5 not 6 [CHILD-, INFANT-ONLY REMOVED]	118879
8	(ozanimod or rpc 1063 or rpc1063 or HSDB 7852 or OZM or Zeposia$2 or UNII-Z80293URPV or Z80293URPV or 1306760-87-1).tw,kf,rn.	437
9	Adalimumab/	39635
10	(adalimumab or ADA or "abp 501" or abp501 or "abt d2e7" or abtd2e7 or adaly$2 or amgevita$2 or amjevita$2 or "avt 02" or "avt 02" or "bat 1406" or bat1406 or "bax 2923" or bax2923 or "bax 923" or bax923 or "bi 695501" or bi695501 or "chs 1420" or chs1420 or "ct p17" or ctp17 or cyltezo$2 or "da 3113" or da3113 or "dmb 3113" or dmb3113 or exemptia$2 or "fkb 327" or fkb327 or fyzoclad$2 or "gp 2017" or gp2017 or hadlima$2 or halimato$2 or hefiya$2 or "hlx 03" or hlx03 or hulio$2 or humira$2 or hyrimoz$2 or "ibi 303" or ibi303 or imraldi$2 or kromeya$2 or lu 200134 or lu200134 or "m 923" or m923 or mabura$2 or (monoclonal adj3 antibod$ adj3 D2E7) or "msb 11022" or msb11022 or "ons 3010" or ons3010 or "pf 06410293" or "pf 6410293" or pf06410293 or pf6410293 or raheara$2 or "sb 5" or sb5 or solymbic$2 or trudexa$2 or "zrc 3197" or zrc3197 or FYS6T7F842 or 331731-18-1 or 1446410-95-2).tw,kf,rn.	68171
11	(etrasimod or APD334 or UNII-6WH8495MMH or 6WH8495MMH or 1206123-37-6).tw,kf,rn.	78
12	(etrolizumab or pro 145223 or pro145223 or rhumab beta7 or UNII-I2A72G2V3J or I2A72G2V3J or 1044758-60-2).tw,kf,rn.	374

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No.	Query	Results
13	(filgotinib or "g 146034" or "g 146034 101" or g146034 or "g146034 101" or "glpg 0634" or glpg0634 or "gs 6034" or gs6034 or Jyseleca$2).tw,kf,rn.	582
14	(golimumab or CNTO-148 or CNTO148 or Simponi$2 or UNII-91X1KLU43E or 91X1KLU43E or 476181-74-5).tw,kf,rn.	8544
15	Infliximab/	61739
16	(infliximab or CT-P13 or CTP13 or SB2 or "abp 710" or abp710 or avakine$2 or flixabi$2 or "gp 1111" or gp1111 or inflectra$2 or ixifi$2 or "pf 06438179" or "pf 6438179" or pf06438179 or pf6438179 or remicade$2 or remsima$2 or renflexis$2 or revellex$2 or "ta 650" or ta650 or zessly$2).tw,kf,rn.	68390
17	(tofacitinib or "cp 690 550" or "cp 690550" or "cp690 550" or cp690550 or HSDB 8311 or xeljanz$2 or UNII-87LA6FU830 or 87LA6FU830 or 477600-75-2 or 540737-29-9).tw,kf,rn.	6590
18	Ustekinumab/	8398
19	(ustekinumab or "cnto 1275" or cnto1275 or stelara$2 or UNII-FU77B4U5Z0 or FU77B4U5Z0 or 15610-63-0).tw,kf,rn.	9605
20	(vedolizumab or entyvio$2 or "ldp 02" or ldp02 or "mln 0002" or mln0002 or "mln 02" or mln02 or "ldp 02" or UNII-9RV78Q2002 or 9RV78Q2002 or 943609-66-3).tw,kf,rn.	5181
21	Tumour Necrosis Factor Inhibitors/	12259
22	(anti TNF or anti TNFs or antiTNF or antiTNFs or anti tumour necrosis factor? or antitumour necrosis factor?).tw,kf.	40499
23	((TNF or TNFs or tumour necrosis factor?) adj3 inhibitor?).tw,kf.	20335
24	((TNF or TNFs or tumour necrosis factor?) adj3 (antagonist* or blocker?)).tw,kf.	10127
25	Sphingosine 1 Phosphate Receptor Modulators/	95
26	(sphingosine adj3 (receptor? adj1 modulat*)).tw,kf.	553
27	(sphingosine adj3 receptor affecting agent?).tw,kf.	0
28	((S1P or S1P5 or S1PR) adj3 (immomodulator? or agonist?)).tw,kf.	838
29	((lysosphingolipid? or sphingolipid?) adj3 (receptor? adj1 modulat*)).tw,kf.	9
30	((lysosphingolipid? or sphingolipid?) adj3 receptor affecting agent?).tw,kf.	0
31	((lysosphingolipid? or sphingolipid?) adj3 (immomodulator? or agonist?)).tw,kf.	13
32	Receptors, Lysosphingolipid/	1900
33	or/8-32 [AGENTS OF INTEREST]	164775
34	7 and 33 [UC - AGENTS OF INTEREST]	15929
35	systematic review.pt.	137292
36	systematic reviews as topic/	29644
37	meta analysis.pt.	121192
38	exp meta-analysis as topic/	63727
39	(meta-analy* or metanaly* or metaanaly* or met analy* or integrative research or integrative review* or integrative overview* or research integration or research overview* or collaborative review*).tw,kf.	456067
40	(systematic review* or systematic overview* or evidence-based review* or evidence-based overview* or (evidence adj3 (review* or overview*)) or meta-review* or meta-overview* or meta-synthes* or rapid review* or "review of reviews" or umbrella review? or technology assessment* or HTA or HTAs).tw,kf.	556294
41	exp Technology assessment, biomedical/	25899
42	(cochrane or health technology assessment or evidence report or systematic reviews).jw.	48952
43	(network adj (MA or MAs)).tw,kf.	31
44	(NMA or NMAs or MTC or MTCs or MAIC or MAICs).tw,kf.	18482

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No.	Query	Results
45	indirect* compar*.tw,kf.	6137
46	(indirect treatment* adj1 compar*).tw,kf.	982
47	(mixed treatment* adj1 compar*).tw,kf.	1427
48	(multiple treatment* adj1 compar*).tw,kf.	413
49	(multi-treatment* adj1 compar*).tw,kf.	9
50	simultaneous* compar*.tw,kf.	2404
51	mixed comparison?.tw,kf.	77
52	or/35-51 [SRs/NMAs/MAs - FILTER]	928534
53	34 and 52 [UC - AGENTS OF INTEREST - REVIEWS]	913
54	exp Animals/ not Humans/	17360383
55	53 not 54 [ANIMAL-ONLY REMOVED]	580
56	(comment or editorial or newspaper article or news or case reports).pt.	4234662
57	(letter not (letter and randomized controlled trial)).pt.	2245051
58	55 not (56 or 57) [OPINION PIECES REMOVED]	574
59	limit 58 to yr="2000-current" [Limit not valid in DARE; records were retained]	573
60	59 use ppez [MEDLINE RECORDS]	261
61	ulcerative colitis/	108765
62	((colitis or colorectitis or proctocolitis or procto colitis) adj3 (ulcer* or mucosa* or gravis or idiopathic*)).tw,kw.	107163
63	(((colon or colonic) adj3 ulceration) and chronic*).tw,kw.	126
64	(UC and (ulcer* or colitis*)).tw,kw.	41677
65	or/61-64 [UC]	133555
66	exp juvenile/ not exp adult/	2225183
67	65 not 66 [UNDER 18 POPULATION-ONLY REMOVED]	128930
68	ozanimod/	294
69	(ozanimod or rpc 1063 or rpc1063 or HSDB 7852 or OZM or Zeposia$2 or UNII-Z80293URPV or Z80293URPV or 1306760-87-1).tw,kw,rn.	439
70	adalimumab/	39635
71	(adalimumab or ADA or "abp 501" or abp501 or "abt d2e7" or abtd2e7 or adaly$2 or amgevita$2 or amjevita$2 or "avt 02" or "avt 02" or "bat 1406" or bat1406 or "bax 2923" or bax2923 or "bax 923" or bax923 or "bi 695501" or bi695501 or "chs 1420" or chs1420 or "ct p17" or ctp17 or cyltezo$2 or "da 3113" or da3113 or "dmb 3113" or dmb3113 or exemptia$2 or "fkb 327" or fkb327 or fyzoclad$2 or "gp 2017" or gp2017 or hadlima$2 or halimato$2 or hefiya$2 or "hlx 03" or hlx03 or hulio$2 or humira$2 or hyrimoz$2 or "ibi 303" or ibi303 or imraldi$2 or kromeya$2 or lu 200134 or lu200134 or "m 923" or m923 or mabura$2 or (monoclonal adj3 antibod$ adj3 D2E7) or "msb 11022" or msb11022 or "ons 3010" or ons3010 or "pf 06410293" or "pf 6410293" or pf06410293 or pf6410293 or raheara$2 or "sb 5" or sb5 or solymbic$2 or trudexa$2 or "zrc 3197" or zrc3197 or FYS6T7F842 or 331731-18-1 or 1446410-95-2).tw,kw,rn.	68427
72	etrasimod/	64
73	(etrasimod or APD334 or UNII-6WH8495MMH or 6WH8495MMH or 1206123-37-6).tw,kw,rn.	78
74	etrolizumab/	291
75	(etrolizumab or pro 145223 or pro145223 or rhumab beta7 or UNII-I2A72G2V3J or I2A72G2V3J or 1044758-60-2).tw,kw,rn.	376
76	filgotinib/	429

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No.	Query	Results
77	(filgotinib or "g 146034" or "g 146034 101" or g146034 or "g146034 101" or "glpg 0634" or glpg0634 or "gs 6034" or gs6034 or Jyseleca$2).tw,kw,rn.	582
78	golimumab/	7110
79	(golimumab or CNTO-148 or CNTO148 or Simponi$2 or UNII-91X1KLU43E or 91X1KLU43E or 476181-74-5).tw,kw,rn.	8583
80	infliximab/	61739
81	(infliximab or CT-P13 or CTP13 or SB2 or "abp 710" or abp710 or avakine$2 or flixabi$2 or "gp 1111" or gp1111 or inflectra$2 or ixifi$2 or "pf 06438179" or "pf 6438179" or pf06438179 or pf6438179 or remicade$2 or remsima$2 or renflexis$2 or revellex$2 or "ta 650" or ta650 or zessly$2).tw,kw,rn.	68641
82	tofacitinib/	4635
83	(tofacitinib or "cp 690 550" or "cp 690550" or "cp690 550" or cp690550 or HSDB 8311 or xeljanz$2 or UNII-87LA6FU830 or 87LA6FU830 or 477600-75-2 or 540737-29-9).tw,kw,rn.	6633
84	ustekinumab/	8398
85	(ustekinumab or "cnto 1275" or cnto1275 or stelara$2 or UNII-FU77B4U5Z0 or FU77B4U5Z0 or 15610-63-0).tw,kw,rn.	9652
86	vedolizumab/	3896
87	(vedolizumab or entyvio$2 or "ldp 02" or ldp02 or "mln 0002" or mln0002 or "mln 02" or mln02 or "ldp 02" or UNII-9RV78Q2002 or 9RV78Q2002 or 943609-66-3).tw,kw,rn.	5209
88	tumour necrosis factor inhibitor/	14885
89	(anti TNF or anti TNFs or antiTNF or antiTNFs or anti tumour necrosis factor? or antitumour necrosis factor?).tw,kw.	41395
90	((TNF or TNFs or tumour necrosis factor?) adj3 inhibitor?).tw,kw.	20549
91	((TNF or TNFs or tumour necrosis factor?) adj3 (antagonist* or blocker?)).tw,kw.	10329
92	sphingosine 1 phosphate receptor modulator/	95
93	(sphingosine adj3 (receptor? adj1 modulat*)).tw,kw.	561
94	(sphingosine adj3 receptor affecting agent?).tw,kw.	0
95	((S1P or S1P5 or S1PR) adj3 (immomodulator? or agonist?)).tw,kw.	836
96	((lysosphingolipid? or sphingolipid?) adj3 (receptor? adj1 modulat*)).tw,kw.	9
97	((lysosphingolipid? or sphingolipid?) adj3 receptor affecting agent?).tw,kw.	0
98	((lysosphingolipid? or sphingolipid?) adj3 (immomodulator? or agonist?)).tw,kw.	13
99	lysophospholipid receptor affecting agent/	2
100	or/68-99 [AGENTS OF INTEREST]	164203
101	67 and 100 [UC - AGENTS OF INTEREST]	17991
102	"systematic review"/	404705
103	"systematic review (topic)"/	25525
104	exp meta analysis/	321110
105	"meta analysis (topic)"/	43471
106	(meta-analy* or metanaly* or metaanaly* or met analy* or integrative research or integrative review* or integrative overview* or research integration or research overview* or collaborative review*).tw,kw.	459342
107	(systematic review* or systematic overview* or evidence-based review* or evidence-based overview* or (evidence adj3 (review* or overview*)) or meta-review* or meta-overview* or meta-synthes* or rapid review* or "review of reviews" or umbrella review? or technology assessment* or HTA or HTAs).tw,kw.	560339

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No.	Query	Results
108	biomedical technology assessment/	24787
109	(cochrane or health technology assessment or evidence report or systematic reviews).jw.	48952
110	(network adj (MA or MAs)).tw,kw.	31
111	(NMA or NMAs or MTC or MTCs or MAIC or MAICs).tw,kw.	18542
112	indirect* compar*.tw,kw.	6227
113	(indirect treatment* adj1 compar*).tw,kw.	987
114	(mixed treatment* adj1 compar*).tw,kw.	1452
115	(multiple treatment* adj1 compar*).tw,kw.	420
116	(multi-treatment* adj1 compar*).tw,kw.	9
117	simultaneous* compar*.tw,kw.	2404
118	mixed comparison?.tw,kw.	78
119	or/102-118 [SRs/NMAs/MAs - FILTER]	1010433
120	101 and 119 [UC - AGENTS OF INTEREST - REVIEWS]	1280
121	exp animal/ or exp animal experimentation/ or exp animal model/ or exp animal experiment/ or nonhuman/ or exp vertebrate/	51653426
122	exp human/ or exp human experimentation/ or exp human experiment/	40323662
123	121 not 122	11331419
124	120 not 123 [ANIMAL-ONLY REMOVED]	1280
125	editorial.pt.	1215178
126	case report/	4666951
127	letter.pt. not (letter.pt. not randomized controlled trial/)	10752
128	124 not (125 or 126 or 127) [OPINION PIECES REMOVED]	1255
129	limit 128 to yr="2000-current" [Limit not valid in DARE; records were retained]	1252
130	conference abstract.pt.	3890187
131	129 not 130 [CONFERENCE ABSTRACTS REMOVED]	1006
132	129 and 130	246
133	limit 132 to yr="2019-current" [Limit not valid in DARE; records were retained]	72
134	131 or 133 [MOST RECENT 2 YRS CONFERENCE ABSTRACTS RETAINED]	1078
135	134 use oemezd [EMBASE RECORDS]	821
136	((colitis or colorectitis or proctocolitis or procto colitis) adj3 (ulcer* or mucosa* or gravis or idiopathic*)).tw.	103757
137	(((colon or colonic) adj3 ulceration) and chronic*).tw.	126
138	(UC and (ulcer* or colitis*)).tw.	41274
139	or/136-138 [UC]	104653
140	(ozanimod or rpc 1063 or rpc1063 or HSDB 7852 or OZM or Zeposia$2 or UNII-Z80293URPV or Z80293URPV or 1306760-87-1).tw.	324
141	(adalimumab or ADA or "abp 501" or abp501 or "abt d2e7" or abtd2e7 or adaly$2 or amgevita$2 or amjevita$2 or "avt 02" or "avt 02" or "bat 1406" or bat1406 or "bax 2923" or bax2923 or "bax 923" or bax923 or "bi 695501" or bi695501 or "chs 1420" or chs1420 or "ct p17" or ctp17 or cyltezo$2 or "da 3113" or da3113 or "dmb 3113" or dmb3113 or exemptia$2 or "fkb 327" or fkb327 or fyzoclad$2 or "gp 2017" or gp2017 or hadlima$2 or halimato$2 or hefiya$2 or "hlx 03" or hlx03 or hulio$2 or humira$2 or hyrimoz$2 or "ibi 303" or ibi303 or imraldi$2 or kromeya$2 or lu 200134 or lu200134 or "m 923" or m923 or mabura$2 or (monoclonal adj3 antibod$ adj3 D2E7) or "msb 11022" or msb11022 or "ons 3010" or ons3010 or "pf 06410293" or "pf 6410293" or pf06410293 or pf6410293 or raheara$2	52080

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No.	Query	Results
	or "sb 5" or sb5 or solymbic$2 or trudexa$2 or "zrc 3197" or zrc3197 or FYS6T7F842 or 331731-18-1 or 1446410-95-2).tw.	
142	(etrasimod or APD334 or UNII-6WH8495MMH or 6WH8495MMH or 1206123-37-6).tw.	42
143	(etrolizumab or pro 145223 or pro145223 or rhumab beta7 or UNII-I2A72G2V3J or I2A72G2V3J or 1044758-60-2).tw.	226
144	(filgotinib or "g 146034" or "g 146034 101" or g146034 or "g146034 101" or "glpg 0634" or glpg0634 or "gs 6034" or gs6034 or Jyseleca$2).tw.	419
145	(golimumab or CNTO-148 or CNTO148 or Simponi$2 or UNII-91X1KLU43E or 91X1KLU43E or 476181-74-5).tw.	5333
146	(infliximab or CT-P13 or CTP13 or SB2 or "abp 710" or abp710 or avakine$2 or flixabi$2 or "gp 1111" or gp1111 or inflectra$2 or ixifi$2 or "pf 06438179" or "pf 6438179" or pf06438179 or pf6438179 or remicade$2 or remsima$2 or renflexis$2 or revellex$2 or "ta 650" or ta650 or zessly$2).tw.	42809
147	(tofacitinib or "cp 690 550" or "cp 690550" or "cp690 550" or cp690550 or HSDB 8311 or xeljanz$2 or UNII-87LA6FU830 or 87LA6FU830 or 477600-75-2 or 540737-29-9).tw.	4865
148	(ustekinumab or "cnto 1275" or cnto1275 or stelara$2 or UNII-FU77B4U5Z0 or FU77B4U5Z0 or 15610-63-0).tw.	6467
149	(vedolizumab or entyvio$2 or "ldp 02" or ldp02 or "mln 0002" or mln0002 or "mln 02" or mln02 or "ldp 02" or UNII-9RV78Q2002 or 9RV78Q2002 or 943609-66-3).tw.	3939
150	(anti TNF or anti TNFs or antiTNF or antiTNFs or anti tumour necrosis factor? or antitumour necrosis factor?).tw.	39814
151	((TNF or TNFs or tumour necrosis factor?) adj3 inhibitor?).tw.	20067
152	((TNF or TNFs or tumour necrosis factor?) adj3 (antagonist* or blocker?)).tw.	10033
153	(sphingosine adj3 (receptor? adj1 modulat*)).tw.	547
154	(sphingosine adj3 receptor affecting agent?).tw.	0
155	((S1P or S1P5 or S1PR) adj3 (immomodulator? or agonist?)).tw.	824
156	((lysosphingolipid? or sphingolipid?) adj3 (receptor? adj1 modulat*)).tw.	9
157	((lysosphingolipid? or sphingolipid?) adj3 receptor affecting agent?).tw.	0
158	((lysosphingolipid? or sphingolipid?) adj3 (immomodulator? or agonist?)).tw.	13
159	or/140-158 [AGENTS OF INTEREST]	134683
160	139 and 159 [UC - AGENTS OF INTEREST]	12774
161	limit 160 to yr="2000-current" [Limit not valid in DARE; records were retained]	12738
162	161 use dare [DARE RECORDS]	16
163	60 or 135 or 162 [ALL DATABASES]	1098
164	**remove duplicates from 163 [TOTAL UNIQUE RECORDS]**	**846**
165	**164 use ppez [MEDLINE UNIQUE RECORDS]**	**259**
166	**164 use oemezd [EMBASE UNIQUE RECORDS]**	**571**
167	**164 use dare [DARE UNIQUE RECORDS]**	**16**

Appendix A.5 Systematic selection of studies

Details of the study selection process are provided in the PRISMA flow diagram (Figure A-1). The database search conducted on October 21, 2020, identified 3088 citations (1088 from MEDLINE, 1743 from Embase, and 257 from Cochrane CENTRAL).

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There were 1038 citations identified through other sources, including targeted grey literature searches of selected conferences (201 from European Crohn's and Colitis Organisation (ECCO), 324 from Digestive Disease Week (DDW), 77 from American College of Gastroenterology (ACG), 159 from Annual United European Gastroenterology Week (AUEGW), and 13 from Annual Advances in Inflammatory Bowel Diseases (AIBD)), and a search of interventional studies on ClinicalTrials.gov using the search terms "((moderate OR severe OR (moderate to severe) OR moderate-severe) AND ulcerative colitis)" (264 RCTs).

After removing duplicates, 4035 records were screened at the title and abstract stage and, of these, 3364 were excluded. Full texts (published articles and conference abstracts) of the remaining 671 records were obtained and assessed for eligibility. A total of 571 records that did not meet the PICOS criteria were excluded as shown in the PRISMA flow diagram (Figure A-1). Hand searches of the bibliographies of relevant SLRs identified from the database searches and bibliographies of included studies identified 5 additional citations. In total, 105 publications reporting on 27 unique trials met our inclusion criteria. A list of all publications selected for inclusion is provided in Table A-5, and a list of all citations excluded at the full-text stage with reasons for exclusion is provided in Table A-6. The NMA feasibility assessment identified for inclusion 22 RCTs for inclusion. Subsequently, 3 studies, Suzuki et al. (2014)[5], VARSITY [6], and ULTRA 1 [7] that were originally not included in the NMA as not relevant to the clinical setting in Denmark (because they included only biologic-naïve patients treated with adalimumab). However, DMC requested these studies be included in the analysis of SAE and for TT maintenance efficacy analyses, where they allow vedolizumab to be compared with infliximab. Therefore, the total number of included RCTs is 25. Note that the DMC requested that the submission should be aligned with the drugs that in the Danish Medicines Agency's treatment guidelines for ulcerative colitis have been assessed to be equivalent and are placed in the 'Apply' group for bio-naïve and experienced patients (see Figure 2 of the main dossier). Therefore an additional PRISMA item has been included to describe the 17 RCTs that were included in the actual analyses as a result of only including treatments relevant to Denmark, these studies are also included in Table 6 of the main dossier.

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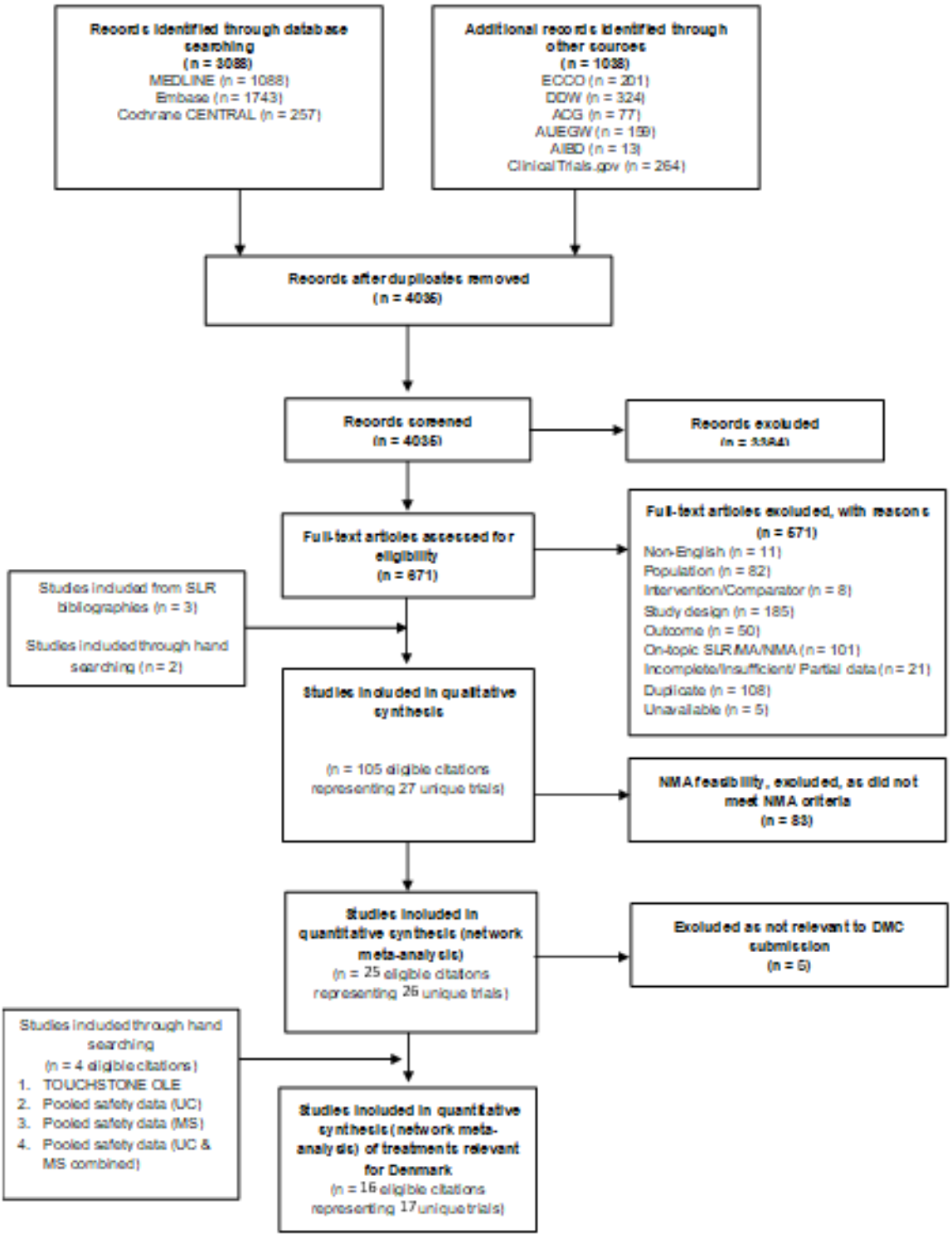
Figure A-1. PRISMA diagram



OLE = open label extension; NMA = network meta-analysis; SLR = systematic literature review.

Table A-5. Studies included in the systematic literature review

Reference
1. Alcala M, Sulleiro S, Hernando T, Garcia I (2020) Efficacy of Ustekinumab at the end of maintenance in Ulcerative Colitis patients receiving 6 mh/kg induction posology. Data from UNIFI trial. United European Gastroenterology Journal 8 (8): 414.
2. Chen J, Hunter S, Kisfalvi K, Lirio R (2020) A Hybrid Approach of Handling Missing Data in Inflammatory Bowel Disease (IBD) Trials: Results from VISIBLE 1 and VARSITY (Su1929). Digestive Disease Week
3. Colombel J, Panes J, D'Haens G, Schreiber S, Panaccione R (2020a) Therapeutic Drug Monitoring Dosing Regimen with Adalimumab in Patients with Moderately to Severely Active Ulcerative Colitis: Results from the SERENE-UC Maintenance Study (P0480). United European Gastroenterology Journal 8 (8): 382-383.
4. Colombel JF, Panes J, D'Haens GR, Schreiber S, Panaccione R et al. (2020b) 945 Higher Versus Standard Adalimumab Maintenance Regimens in Patients with Moderately to Severely Active Ulcerative Colitis: Results from the Serene-Uc Maintenance Study. Gastroenterology 158 (6 Supplement 1) S-192.
5. Colombel JF, Panes J, D'Haens GR, Schreiber S, Panaccione R et al. (2020c) Higher versus standard adalimumab maintenance regimens in patients with moderately to severely active ulcerative colitis: Results from the SERENE-UC maintenance study. Gastroenterology 158 (6): S-192.
6. Colombel JF, Reinisch W, Gibson P, Sandborn WJ, Feagan B et al. (2016) Delayed response to golimumab therapy: UC patient characteristics and long-term clinical outcome-post-hoc analyses from the PURSUIT programme. Journal of Crohn's & colitis 10 S56-S57.
7. Colomel J, Panes J, D'Haens G, Schreiber S, Panaccione R (2020) Therapeutic Drug Monitoring Dosing Regimen With Adalimumab in Patients With Moderately to Severely Active Ulcerative Colitis: Results From the SERENE-UC Maintenance Study (P1686). American College of Gastroenterology Annual Scientific Meeting
8. D'Haens G, Armuzzi A, Su C, Guo X, Modesto I (2020) Association Between Duration of Latest Flare Before Induction Treatment with Tofacitinib and Efficacy Outcomes in Patients with Ulcerative Colitis (P0488). United European Gastroenterology Journal 8 (8): 390-391.
9. Danese S, Feagan B, Hanauer S, Jovanovic I, Ghosh S et al. (2020) P030 Ozanimod Efficacy, Safety, and Histology in Patients with Moderate-to-Severe Ulcerative Colitis During Maintenance in the Phase 3 True North Study. The American Journal of Gastroenterology 115 S8.
10. Danese S, Loftus EV, Colombel JF, Peyrin-Biroulet L, Abhyankar B et al. (2019a) Early clinical response and remission with vedolizumab versus adalimumab in ulcerative colitis: Results from varsity. American Journal of Gastroenterology 114 (Supplement) S421.
11. Danese S, Sands BE, Leong RW, Zhang H, Johanns J et al. (2019b) General health status in patients with moderate to severe ulcerative colitis receiving ustekinumab: Results from the Phase 3 UNIFI induction and maintenance studies. Journal of Crohn's and Colitis 13 (Supplement 1) S311-S312.
12. Danese S, Sands BE, O'Brien CD, Zhang H, Johanns J et al. (2019c) Efficacy and safety of ustekinumab through Week 16 in patients with moderate-to-severe ulcerative colitis randomised to ustekinumab: Results from the UNIFI induction trial. Journal of Crohn's and Colitis 13 (Supplement 1) S061-S062.
13. Danese S, Sands BE, Sandborn WJ, Marano C, O'Brien C et al. (2019d) Efficacy of ustekinumab subcutaneous maintenance treatment by induction-dose subgroup in the unifi study of patients with ulcerative colitis. United European Gastroenterology Journal 7 (10) 1415.
14. Dubinsky M, Hudesman D, Steinwurz F, Kulisek N, Salese L (2020a) C-reactive Protein Levels and Partial Mayo Score as Early Predictors of Clinical and Endoscopic Outcomes in Adult Patients with Moderately to Severely Active Ulcerative Colitis Treated with Tofacitinib: a Post Hoc Analysis of Octave Induction 1&2 (Tu1870). Digestive Disease Week
15. Dubinsky M, Hudesman D, Steinwurz F, Kulisek N, Salese L (2020b) CRP levels and PMS as early predictors of clinical and endoscopic outcomes in adult patients with moderately-to-severely active UC treated with tofacitinib: a post hoc analysis of OCTAVE Induction 1 and 2 (P366). Journal of Crohn's and Colitis 14 (Supplement_1): S346–S347.
16. Dubinsky MC, Bressler B, Armuzzi A, Salese L, DiBonaventura M et al. (2019a) Improvement in patient-reported inflammatory bowel disease questionnaire outcomes, and relationship with disease activity, in tofacitinib treated patients with ulcerative colitis: Data from the OCTAVE clinical trials. Journal of Crohn's and Colitis 13 (Supplement 1) S462-S463.

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Reference

17. Dubinsky MC, Bushmakin AG, Cappelleri JC, Woolcott J, Sharma P et al. (2020c) The concordance of short form-36 health survey scores with mayo scores in the tofacitinib ulcerative colitis clinical program
18. Dubinsky MC, DiBonaventura M, Fan H, Bushmakin AG, Cappelleri JC et al. (2019b) Item-level improvements in inflammatory bowel disease questio nnaire scores in patients with ulcerative colitis treated with to facitinib induction therapy. United European Gastroenterology Journal 7 (8 Supplement) 344-345.
19. Dubinsky MC, DiBonaventura M, Fan H, Bushmakin AG, Cappelleri JC et al. (2020d) Tofacitinib in Patients with Ulcerative Colitis: Inflammatory Bowel Disease Questionnaire Items in Phase 3 Randomized Controlled Induction Studies. Inflammatory Bowel Diseases 14 14.
20. Dubinsky MC, Peyrin-Biroulet L, Melmed GY, Hou JK, Woodworth DA et al. (2017) Efficacy of Tofacitinib in Patients With Ulcerative Colitis by Prior Tumor Necrosis Factor Inhibitor Treatment Status: Results From OCTAVE Induction and Maintenance Studies: 640. Official journal of the American College of Gastroenterology | ACG 112
21. Feagan B, Khanna R, Marana C, Zhang H, Sand sB (2020) Fecal Calprotectin as a Surrogate Marker of Clinical Remission, Clinical Response, Endoscopic Improvement, and Histo-Endoscopic Mucosal Healing: UNIFI Induction Study (P0515). United European Gastroenterology Journal 8 (8): 413-414.
22. Feagan BG, Bhayat F, Khalid M, Blake A, Travis SPL (2018) Respiratory tract infections in patients with inflammatory bowel disease: safety analyses from vedolizumab clinical trials. Journal of Crohn's & colitis 12 (8): 905-919.
23. Feagan BG, Reinisch W, Rutgeerts P, Sandborn WJ, Yan S et al. (2007) The effects of infliximab therapy on health-related quality of life in ulcerative colitis patients. American Journal of Gastroenterology 102 (4): 794-802.
24. Feagan BG, Rubin DT, Danese S, Vermeire S, Abhyankar B et al. (2017) Efficacy of Vedolizumab Induction and Maintenance Therapy in Patients With Ulcerative Colitis, Regardless of Prior Exposure to Tumor Necrosis Factor Antagonists. Clinical Gastroenterology & Hepatology 15 (2): 229-239.e225.
25. Feagan BG, Rutgeerts P, Sands BE, Hanauer S, Colombel J-F et al. (2013) Vedolizumab as Induction and Maintenance Therapy for Ulcerative Colitis. New England Journal of Medicine 369 (8): 699-710.
26. Feagan BG, Sandborn WJ, D'Haens GR, Hanauer SB, Wolf DC et al. (2019a) Clinical remission demonstrated with oral ozanimod in the overall population and across multiple subgroups of patients with moderately to severely active ulcerative colitis in the TOUCHS TONE Trial. United European Gastroenterology Journal 7 (8 Supplement) 358.
27. Feagan BG, Schreiber S, Wolf DC, Axler JL, Kaviya A et al. (2019b) Sustained Clinical Remission with Vedolizumab in Patients with Moderate-to-Severe Ulcerative Colitis. Inflammatory Bowel Diseases 25 (6): 1028-1035.
28. Ghosh S, D'Haens G, Jairath V, Rieder F, Petersen A et al. (2020) P012 Ozanimod Reduced Fecal Calprotectin Levels in Patients with Ulcerative Colitis in the Phase 3 True North Study. The American Journal of Gastroenterology 115 S3.
29. Ghosh S, Sands BE, O'Brien CD, Tikhonov I, Zhou Y et al. (2019) Safety of ustekinumab in inflammatory bowel diseases: Integrated safety analysis of results from phase 2 and 3 studies in crohn's disease and ulcerative colitis. United European Gastroenterology Journal 7 (8 Supplement) 900.
30. Hanauer S, Rubin DT, Gionchetti P, Su C, Woodworth DA et al. (2019) Tofacitinib efficacy in patients with moderate to severe ulcerative colitis: Subgroup analyses of OCTAVE Induction 1 and 2 and OCTAVE sustain by 5-aminosalicylates use. Journal of Crohn's and Colitis 13 (Supplement 1) S477.
31. Hibi T, Imai Y, Senoo A, Ohta K, Ukyo Y (2017) Efficacy and safety of golimumab 52-week maintenance therapy in Japanese patients with moderate to severely active ulcerative colitis: a phase 3, double-blind, randomized, placebo-controlled study-(PURSUIT-J study). Journal of Gastroenterology 52 (10): 1101-1111.
32. Jiang XL, Cui HF, Gao J, Fan H (2015) Low-dose Infliximab for Induction and Maintenance Treatment in Chinese Patients With Moderate to Severe Active Ulcerative Colitis. Journal of Clinical Gastroenterology 49 (7): 582-588.
33. Johansson T, Weinstein C, Meehan A, Tzontcheva A, Xu P et al. (2020) Effect of golimumab induction therapy on histologic disease profile in patients with moderate to severe ulcerative colitis: Results from the randomised, placebo-controlled Phase 3 PURSUIT-SC trial. Journal of Crohn's and Colitis 14 (Supplement_1): S560.

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Reference

34. Kobayashi T, Ito H, Ashida T, Yokoyama T, Nagahori M et al. (2020) Efficacy and safety of a new vedolizumab subcutaneous formulation in Japanese patients with moderately to severely active ulcerative colitis. Intestinal research 18 18.
35. Kobayashi T, Suzuki Y, Motoya S, Hirai F, Ogata H et al. (2016) First trough level of infliximab at week 2 predicts future outcomes of induction therapy in ulcerative colitis-results from a multicenter prospective randomized controlled trial and its post hoc analysis. J Gastroenterol 51 (3): 241-251.
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Table A-6. Studies excluded at the full text level, with reasons

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Appendix A.5.1.1 Selection of studies relevant to Danish submission

The DMC requested that the submission should be aligned with the drugs that in the Danish Medicines Agency's treatment guidelines for ulcerative colitis have been assessed to be equivalent and are placed in the 'Apply' group for bio-naive and experienced patients (Figure 2 in the main dossier). Therefore, an additional PRISMA item has been included. Table A-7 outlines the studies included in the NMA relevant for this submission. Table A-8 outlines the studies excluded from the NMA with reasons.

Table A-7. Studies included in the NMA

Reference
1. Feagan BG, Rutgeerts P, Sands BE, Hanauer S, Colombel J-F et al. (2013) Vedolizumab as Induction and Maintenance Therapy for Ulcerative Colitis. New England Journal of Medicine 369 (8): 699-710.
2. Hibi T, Imai Y, Senoo A, Ohta K, Ukyo Y (2017) Efficacy and safety of golimumab 52-week maintenance therapy in Japanese patients with moderate to severely active ulcerative colitis: a phase 3, double-blind, randomized, placebo-controlled study-(PURSUIT-J study). Journal of Gastroenterology 52 (10): 1101-1111.
3. Jiang XL, Cui HF, Gao J, Fan H (2015) Low-dose Infliximab for Induction and Maintenance Treatment in Chinese Patients With Moderate to Severe Active Ulcerative Colitis. Journal of Clinical Gastroenterology 49 (7): 582-588.
4. Kobayashi T, Suzuki Y, Motoya S, Hirai F, Ogata H et al. (2016) First trough level of infliximab at week 2 predicts future outcomes of induction therapy in ulcerative colitis-results from a multicenter prospective randomized controlled trial and its post hoc analysis. J Gastroenterol 51 (3): 241-251.
5. Motoya S, Watanabe K, Ogata H, Kanai T, Matsui T et al. (2019) Vedolizumab in Japanese patients with ulcerative colitis: A Phase 3, randomized, double-blind, placebo-controlled study. PLoS ONE [Electronic Resource] 14 (2): e0212989.
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9. Sandborn WJ, Feagan BG, Marano C, Zhang H, Strauss R et al. (2014a) Subcutaneous golimumab induces clinical response and remission in patients with moderate-to-severe ulcerative colitis. Gastroenterology 146 (1): 85-95; quiz e14-85.
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11. Sandborn WJ, Feagan BG, Wolf DC, D'Haens G, Vermeire S et al. (2016) Ozanimod Induction and Maintenance Treatment for Ulcerative Colitis. New England Journal of Medicine 374 (18): 1754-1762.
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13. Sands BE, Peyrin-Biroulet L, Loftus EV, Jr D, S C et al. (2019c) Vedolizumab versus Adalimumab for Moderate-to-Severe Ulcerative Colitis. New England Journal of Medicine 381 (13): 1215-1226.
14. Sands BE, Sandborn WJ, Panaccione R, O'Brien CD, Zhang H et al. (2019e) Ustekinumab as Induction and Maintenance Therapy for Ulcerative Colitis. New England Journal of Medicine 381 (13): 1201-1214.
15. Sarl CII (2020, Data on File). Phase 3, multicenter, randomized, double-blind, placebo-controlled trial of oral RPC1063 as induction and maintenance therapy for moderate to severe ulcerative colitis - TRUE NORTH. (CSR)[b]
16. Suzuki Y, Motoya S, Hanai H, Matsumoto T, Hibi T et al. (2014) Efficacy and safety of adalimumab in Japanese patients with moderately to severely active ulcerative colitis. Journal of Gastroenterology 49 (2): 283-294.

[a] Rutgeerts 2005 reported two separate studies ACT1 (NCT00036439)and ACT 2 (NCT00096655) in one publication.

[b] Since the SLR was conducted, results from the TRUE NORTH study have been published in Sandborn WJ, Feagan BG, D'Haens G, Wolf DC, Jovanovic I, Hanauer SB, et al. Ozanimod as induction and maintenance therapy for ulcerative colitis. N Engl J Med. 2021;385(14):1280-91.

Table A-8. Studies excluded from the NMA and reasons why

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Appendix A.6 Quality assessment

The full texts of the 17 randomised trials along with supplementary publications were assessed (Table A-1). All trials provided evidence of appropriate randomisation sequence generation and most reported appropriate allocation concealment (N = 15 trials). For 12 trials, it was not explicitly stated whether care providers, participants, and outcome assessor groups were all blind to treatment allocation. Eleven trials included an intention-to-treat analysis with appropriate methods used to account for missing data.

This SLR report described 14 trials reporting on efficacy and safety results of targeted therapies for the treatment of patients with moderate-to-severe UC. Of the 14 trials, all were placebo-controlled.. Clinical response and clinical remission as per the Mayo Score, as well as endoscopic improvement, were well-reported reported for both induction and maintenance periods of several trials, where applicable. These key outcomes of interest will form the basis of the network meta-analysis presented in the main dossier.

A major strength of this SLR is that it adhered to best practices for the conduct and reporting of systematic reviews.[8] Notably, all the searches were performed and peer-reviewed by experienced information specialists. This SLR also reported detailed search strategies, PRISMA flow diagrams, full included/excluded study lists, and risk of bias assessments using appropriate tools, as per PRISMA guidelines.[2,9] A detailed assessment of patient/study characteristics among identified RCTs was also reported.

A limitation of this SLR is that the included studies were restricted to English language only at the study selection stage. This is likely a minor limitation, given that most of the major RCTs are published in English journals. However, it is noteworthy that this restriction was applied at the study selection phase and did not restrict the search to English-only articles. Therefore, regions which require non-English articles could update this systematic review to capture these studies if deemed relevant for their region.

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Table A-9. Studies included in the systematic literature review

Trial name	Was randomisation carried out appropriately?	Was the concealment of treatment allocation adequate?	Were the groups similar at the outset of the study in terms of prognostic factors?	Were the care providers, participants, and the outcome assessors blind to treatment allocation?	Were there any unexpected imbalances in dropouts between groups?	Is there any evidence to suggest that the authors measured more outcomes than they reported?	Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?
True North Sandborn et al. (2021)[10]	Yes	Yes	Yes	Yes	No	No	Yes
TOUCHSTONE Sandborn et al. (2016)[11]	Yes	Yes	Yes	Unclear	No	No	Yes
ULTRA 1 Reinisch et al. (2011)[7]	Yes	Yes	Yes	Yes	No	No	Yes
ULTRA 2 Sandborn et al. (2012)[12]	Yes	Yes	Yes	Unclear	No	Yes	Yes
Suzuki (2014) Suzuki et al. (2014)[5]	Yes	Yes	Yes	Unclear	No	Yes	Unclear
PURSUIT-SC Sandborn et al. (2014)[13]	Yes	Yes	Yes	Unclear	Unclear	No	Yes
PURSUIT-M Sandborn et al. (2014)[14]	Yes	Yes	Yes	Unclear	Unclear	No	Yes
PURSUIT-J Hibi et al. (2017)[15]	Yes	Unclear	Yes	Unclear	No	No	No
ACT 1 Rutgeerts et al. (2005)[16]	Yes	Yes	Unclear	Unclear	Yes	No	Yes
ACT 2 Rutgeerts et al. (2005)[16]	Yes	Yes	Unclear	Unclear	Yes	No	Yes

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Trial name	Was randomisation carried out appropriately?	Was the concealment of treatment allocation adequate?	Were the groups similar at the outset of the study in terms of prognostic factors?	Were the care providers, participants, and the outcome assessors blind to treatment allocation?	Were there any unexpected imbalances in dropouts between groups?	Is there any evidence to suggest that the authors measured more outcomes than they reported?	Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?
Jiang 2015 Jiang et al. (2015)[17]	Yes	Yes	Yes	Unclear	Yes	Unclear	Yes
Kobayashi 2016 Kobayashi et al. (2016)[18]	Yes	Yes	Yes	Unclear	Unclear	Unclear	No
GEMINI 1 Feagan et al. (2013)[19]	Yes	Yes	Yes	Unclear	No	No	Unclear
VARSITY Sands et al. (2019)[6]	Yes	Yes	Yes	Yes	No	Yes	Yes
VISIBLE 1 Sandborn et al. (2020)[20]	Yes	Yes	Yes	Unclear	No	Yes	Yes
Motoya 2019 Motoya et al. (2019)[21]	Yes	Yes	Unclear	Yes	No	Yes	Yes
UNIFI Sands et al. (2019)[22]	Yes	Unclear	Yes	Unclear	Unclear	Yes	Yes

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Appendix B. Main characteristics of included studies

Appendix B.1 TRUE NORTH

Table B-1. TRUE NORTH

Trial name: TRUE NORTH	NCT number: NCT02435992
Objective	To evaluate the efficacy and safety of ozanimod vs. placebo for induction and maintenance therapy in adults with moderately to severely active UC
Publications – title, author, journal, year	▪ Danese S, Feagan BG, Wolf DC. Ozanimod as maintenance therapy in patients with moderate-to-severe ulcerative colitis: results from the phase 3, randomized, double-blind, placebo-controlled True North study [oral presentation: LB10]. Presented at: United European Gastroenterology (UEG) Week; 11-13 October 2020. Virtual. ▪ Sandborn WJ, D'Haens G, Wolf DC. Ozanimod as induction therapy in moderate-to-severe ulcerative colitis: results from the phase 3, randomized, double-blind, placebo-controlled True North study [oral presentation: LB02]. Presented at: United European Gastroenterology (UEG) Week; 11-13 October 2020. Virtual.
Study type and design	TRUE NORTH (NCT02435992) is a phase 3, multicentre, randomised, double-blind, placebo-controlled 52-week trial. TRUE NORTH was composed of 2 periods: a 10-week induction period followed by a 42-week maintenance period. Patients initiated the trial in 2 separate cohorts through the induction period. Patients with a clinical response at the end of the induction period proceeded on to the maintenance period. Patients were eligible to enter a separate OLE study (RPC01-3102) if they completed the induction period but did not have a clinical response at week 10 (cohort 1 or 2), experienced disease relapse during the maintenance period, or completed the maintenance period. The 10-week induction period was composed of 2 cohorts: ▪ Cohort 1: Patients were randomised (2:1) to receive either – Ozanimod HCl 1 mg (equivalent to ozanimod 0.92 mg) once daily orally in a double-blind manner – Placebo once daily orally in a double-blind manner ▪ Cohort 2: Patients received ozanimod HCl 1 mg once daily orally in an open-label manner Patients in cohort 1 were stratified by corticosteroid use and previous anti-TNF use before randomisation.[23] In cohort 1, 30.2% of patients (195 of 645) had prior anti-TNF use and 43.3% (159 of 367) in cohort 2 had prior anti-TNF use. Patients from cohort 1 or cohort 2 with a clinical response (by either 3- or 4-component Mayo Score) at week 10 of the induction period continued on to the maintenance period. Patients who received ozanimod HCl 1 mg (cohort 1 or cohort 2) and had a clinical response at week 10 of the induction period were rerandomised to receive either ozanimod HCl 1 mg or matching placebo in a 1:1 ratio in a double-blind manner during the maintenance period. Patients who received placebo (cohort 1) and had a clinical response at week 10 of the induction period continued to receive placebo in the maintenance period in a double-blind manner. Patients who were rerandomised in the maintenance period were stratified by clinical remission status at week 10 and corticosteroid use at week 10.
Sample size (n)	1,012
Main inclusion and exclusion criteria	Inclusion criteria ▪ Aged 18-75 years (at screening for cohort 1 and 2) ▪ Male or female adolescent patients aged 12 to < 18 years (at screening) with a body weight ≥ 45 kg ▪ UC confirmed on endoscopy ▪ Moderately to severely active UC (Mayo Score 6-12) ▪ Currently receiving treatment with aminosalicylate, prednisone, or budesonide ▪ Can be receiving azathioprine, mercaptopurine, or methotrexate, but treatment will be stopped prior to randomisation

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Trial name: TRUE NORTH	NCT number: NCT02435992
	Exclusion criteria ▪ Have severe extensive colitis as evidence by – Physician judgement that the patient is likely to require colectomy or ileostomy within 12 weeks of baseline – Current or recent (within 3 months) evidence of fulminant colitis, toxic megacolon, or bowel perforation – Diagnosis of CD, indeterminate colitis, or the presence of fistula consistent with CD; or microscopic colitis, radiation colitis, or ischaemic colitis – Clinically relevant cardiovascular conditions or other relevant diseases that could impact the implementation or interpretation of the trial, or put the patient at risk – History of uveitis or unknown macular oedema – Pregnancy, lactation, or a positive serum β-human chorionic gonadotropin measured during screening
Intervention	▪ Ozanimod 1 mg once daily during induction and maintenance periods ▪ Cohort 1 induction, n = 429 ▪ Cohort 2 induction, n = 367 ▪ Maintenance (rerandomised patients) – Ozanimod/ozanimod, n = 230
Comparator(s)	Placebo once daily during induction and maintenance periods ▪ Cohort 1 induction, n = 216 ▪ Cohort 2 induction, n = not applicable ▪ Maintenance (rerandomised patients) – Ozanimod/placebo, n = 227
Follow-up time	52 weeks
Is the study used in the health economic model?	Yes
Primary, secondary and exploratory endpoints	**Endpoints included in this application:** The primary efficacy endpoint of the induction period was the proportion of patients in clinical remission assessed by Mayo Score (3-component Mayo Score; all subsequent mentions of clinical remission are based on the 3-component Mayo Score unless otherwise specified) at week 10. Hierarchically ranked key secondary efficacy endpoints of the induction period were as follows[24]: ▪ Proportion of patients with a clinical response (3-component Mayo Score; all subsequent mentions of clinical response are based on the 3-component Mayo Score unless otherwise specified) at week 10 ▪ Proportion of patients with endoscopic improvement at week 10 ▪ Proportion of patients with mucosal healing at week 10 Other secondary efficacy endpoints of the induction period for cohort 1 were as follows[24]: ▪ Changes from baseline to week 10 in 3-component Mayo Score, 4-component Mayo Score, and partial Mayo Score ▪ Proportion of patients with histologic remission at week 10 ▪ Proportion of patients in clinical remission (4-component Mayo Score) at week 10 ▪ Proportion of patients with a clinical response (4-component Mayo Score) at week 10 ▪ Proportion of patients with clinical response, clinical remission, or endoscopic improvement at week 10 in patients who previously received anti-TNF therapy ▪ Changes from baseline to week 10 in the SF-36 and the EQ-5D ▪ Work productivity at week 10 The primary efficacy endpoint of the maintenance period was the proportion of patients in clinical remission assessed by Mayo Score (3-component Mayo Score; all subsequent mentions of clinical remission are based on the 3-component Mayo Score unless otherwise specified) at week 52.[25]

Trial name: TRUE NORTH	NCT number: NCT02435992
	Hierarchically ranked key secondary efficacy endpoints of the maintenance period were as follows[24]: ▪ Proportion of patients with a clinical response (3-component Mayo Score; all subsequent mentions of clinical response are based on the 3-component Mayo Score unless otherwise specified) at week 52 ▪ Proportion of patients with endoscopic improvement at week 52 ▪ Proportion of patients with maintenance of remission (clinical remission at week 52 among patients in remission at week 10) ▪ Proportion of patients with corticosteroid-free remission (clinical remission at week 52 after ≥ 12 weeks without corticosteroids) ▪ Proportion of patients with mucosal healing at week 52 ▪ Proportion of patients with durable clinical remission (remission at weeks 10 and 52 among patients entering maintenance phase) Other secondary efficacy endpoints of the maintenance period were as follows[24]: ▪ Changes from baseline to week 52 in 3-component Mayo Score, 4-component Mayo Score, and partial Mayo Score ▪ Proportion of patients with histologic remission at week 52 ▪ Proportion of patients in clinical remission (4-component Mayo Score) at week 52 ▪ Proportion of patients with a clinical response (4-component Mayo Score) at week 52 ▪ Proportion of patients with clinical response, clinical remission, or endoscopic improvement at 52 weeks in patients who previously received anti-TNF therapy ▪ Proportion of patients in clinical remission at 52 weeks while off corticosteroids for any length of time ▪ Changes from baseline to week 52 in the SF-36 and the EQ-5D ▪ Health resource utilisation at weeks 28, 40, and 52 ▪ Work productivity at weeks 28, 40, and 52 ▪ Safety endpoints Safety and tolerability of ozanimod during the induction and maintenance periods (weeks 10 and 52, respectively) were assessed in terms of incidence, severity, and relationship to study drug of TEAEs, serious TEAEs, TEAEs leading to discontinuation of study drug, and TEAEs of special interest.[24]
Method of analysis	Please see Appendix F.
Subgroup analyses	Subgroup analyses were performed for the endpoints of clinical remission and clinical response only using the 3-component Mayo Score based on a 7-day scoring algorithm. The following were the predefined subgroups for the induction period: ▪ Corticosteroid use at screening (yes vs. no) ▪ Prior anti-TNF use (yes vs. no) ▪ Baseline complete Mayo Score (≤ 9 vs. > 9) ▪ Extent of colitis (left-sided vs. extensive) ▪ Sex (female vs. male) ▪ Age at screening (≤ median vs. > median) ▪ Baseline faecal calprotectin (≤ 250 vs. > 250 mg/kg) ▪ Baseline absolute lymphocyte count (≤ 1,500 vs. > 1,500 10^6/L) ▪ Years since initial UC diagnosis (≤ 4 vs. > 4 years) ▪ Region (North America, Eastern Europe, Western Europe, Asia Pacific) ▪ Prior anti-TNF exposure ▪ Baseline partial Mayo Score (≤ median vs. > median) ▪ Baseline partial Mayo Score (≤ 7 vs. > 7) ▪ Baseline endoscopy subscore (2 vs. 3) ▪ Moderate UC status at baseline (4-component Mayo Score 6-10; yes vs. no) The same subgroup analyses performed for the induction period were performed for the maintenance period. Additionally, the following subgroups were added for the maintenance period only:

Trial name: TRUE NORTH	NCT number: NCT02435992
	▪ Clinical remission status at week 10 (yes or no) ▪ Corticosteroids use at week 10 (yes or no)

CD = Crohn's disease; HCl = hydrochloride; NCT = National Clinical Trial Number; OLE = open-label extension; SF-36 = SF-36 Health Survey; TEAE = treatment-emergent adverse event; TNF = tumour necrosis factor; UC = ulcerative colitis.

Appendix B.2 TOUCHSTONE

Table B-2. TOUCHSTONE

Trial name: TOUCHSTONE	NCT number: NCT01647516
Objective	To evaluate the efficacy and safety of ozanimod in adults with moderately to severely active UC.
Publications – title, author, journal, year	▪ Sandborn WJ, Feagan BG, Wolf DC, D'Haens G, Vermeire S, Hanauer SB, et al. Ozanimod induction and maintenance treatment for ulcerative colitis. N Engl J Med. 2016 May 5;374(18):1754-62. doi:http://dx.doi.org/10.1056/NEJMoa1513248. ▪ Sandborn W, Feagan B, Hanauer SB, et al. Long-term safety and efficacy of ozanimod in patients with moderate-to-severe ulcerative colitis: results from the TOUCHSTONE open-label extension [oral presentation: OP087]. Presented at: United European Gastroenterology (UEG) Week; 11-13 October 2020. Virtual.
Study type and design	TOUCHSTONE (NCT01647516) is a phase 2, multicentre, randomised, double-blind, placebo-controlled 32-week trial. Patients were eligible to enter the TOUCHSTONE OLP if they completed the induction period but did not have a clinical response at week 8, experienced disease relapse during the maintenance period, or completed the maintenance period. The TOUCHSTONE OLP was ended in 2019 and all active patients who consented to the RPC01-3102 phase 3 study were rolled over to that OLE. **TOUCHSTONE main study** Patients were randomized (1:1:1) to 1 of the following study treatments for 32 weeks[11]: ▪ Ozanimod HCl 0.5 mg (equivalent to ozanimod 0.46 mg) once daily orally ▪ Ozanimod 1 HCl mg (equivalent to ozanimod 0.92 mg) once daily orally ▪ Placebo once daily orally Randomisation was performed centrally using a computerised system. Patients were stratified before randomisation by previous exposure to an anti-TNF. Patients with a clinical response (defined as a reduction in 4-component Mayo Score of ≥ 3 points and ≥ 30% from baseline, with a decrease in the RBS of ≥ 1 point or a subscore of ≤ 1) at week 8 continued their blinded treatment regimen during the maintenance period. Patients who did not have a clinical response at week 8 could cross over to optional open-label treatment. **TOUCHSTONE OLP** Patients received ozanimod HCl 1 mg once daily orally.
Sample size (n)	197
Main inclusion and exclusion criteria	▪ Inclusion criteria – UC confirmed on endoscopy – Moderately to severely active UC (Mayo Score 6-12) ▪ Exclusion criteria – Current use of anti-TNF agents
Intervention	▪ Ozanimod 0.5 mg (n = 65) ▪ Ozanimod 1 mg (n = 67)
Comparator(s)	Placebo (n = 65)
Follow-up time	32 weeks
Is the study used in the health economic model?	No

Trial name: TOUCHSTONE	NCT number: NCT01647516
Primary, secondary and exploratory endpoints	**Endpoints included in this application:** The primary efficacy endpoint was the proportion of patients in clinical remission (defined as 4-component Mayo Score ≤ 2, with no subscore > 1) at week 8.[11] Hierarchically ranked secondary efficacy endpoints were[11]: ▪ Proportion of patients with a clinical response (defined as a reduction in 4-component Mayo Score of ≥ 3 points and ≥ 30% from baseline, with a decrease in the RBS of ≥ 1 point or a subscore of ≤ 1) at week 8 ▪ Change from baseline to week 8 in the 4-component Mayo Score ▪ Proportion of patients with mucosal healing (Endoscopic subscore of ≤ 1) at week 8 Exploratory efficacy endpoints included the proportion of patients with clinical response, clinical remission, mucosal healing, and change in the 4-component Mayo Score at week 32, and the proportion of patients with histologic remission (Geboes Score < 2, on a scale from 0-5) at weeks 8 and 32. Pharmacodynamic endpoints included changes from baseline in the following biomarkers: absolute lymphocyte count and the concentrations of CRP, faecal calprotectin, and faecal lactoferrin. Safety was assessed in terms of incidence and types of AEs, SAEs, and AEs leading to discontinuation of study.
Method of analysis	Please see Appendix G.
Subgroup analyses	Prespecified subgroup analyses were performed for clinical remission at week 8 by previous use of anti-TNF therapy (yes or no), age (less than the median or at least as old as the median), sex, colonic area involved (left side or extensive), and baseline 4-component Mayo Score (≤ 8 or > 8).
Other relevant information	None

AE = adverse event; CRP = C-reactive protein; HCl = hydrochloride; NCT = National Clinical Trial Number; OLE = open-label extension; OLP = open-label period; RBS = rectal bleeding score; SAE = serious adverse event; TNF = tumour necrosis factor; UC = ulcerative colitis.

Appendix B.3 TOUCHSTONE open-label extension

Table B-3. TOUCHSTONE open-label extension

Trial name: TOUCHSTONE OLE	NCT number: NCT02531126
Objective	To examine the long-term safety and efficacy of ozanimod in patients with moderately to severely active ulcerative colitis
Publications – title, author, journal, year	Sandborn WJ, Feagan BG, Hanauer S, Vermeire S, Ghosh S, Liu WJ, et al. Long-term efficacy and safety of ozanimod in moderately to severely active ulcerative colitis: results from the open-label extension of the randomized, phase 2 TOUCHSTONE study. J Crohns Colitis. 2021 Jul 5;15(7):1120-9. doi:http://dx.doi.org/10.1093/ecco-jcc/jjab012.
Study type and design	OLE to the TOUCHSTONE [NCT01647516] randomised, double-blind, placebo-controlled phase 2 trial.
Sample size (n)	N = 170 (n = 81, non-responders at the end of the 9-week induction period; n = 7 lost their response during maintenance period; n = 82 completed the 24-week maintenance period) of which 71 completed OLE to week 200.
Main inclusion and exclusion criteria	Patients were eligible to enter this OLE if they: ▪ Were non-responders at the end of the 9-week TOUCHSTONE induction period, or ▪ Lost their response during the 24-week TOUCHSTONE maintenance period, or ▪ Completed the 24-week TOUCHSTONE maintenance period, or ▪ Were active patients in the TOUCHSTONE trial when it ended in 2019 (after all active patients had completed at least 200 weeks of follow-up).

Trial name: TOUCHSTONE OLE	NCT number: NCT02531126
Intervention	Ozanimod HCl 1 mg orally once daily
Comparator(s)	None
Follow-up time	On entry to this OLE, participants had previously completed up to 32 weeks of treatment. Participants were then followed up for 200 weeks in the OLE.
Is the study used in the health economic model?	No
Primary, secondary and exploratory endpoints	▪ Efficacy measures: pMS derived from patient self-report of stool frequency and bleeding, combined with PGA severity scores; total Mayo Score derived from pMS combined with endoscopy findings. ▪ Biomarkers: CRP and faecal calprotectin. ▪ Safety: treatment-emergent adverse events, vital signs, Holter monitoring, electrocardiograms, pulmonary function tests, optical coherence tomography, blood chemistry and haematology panels, coagulation panels, urinalysis, absolute lymphocyte count.
Method of analysis	▪ Partial Mayo clinical remission/response, and endoscopic endpoints were summarised descriptively using observed cases and non-responder imputation analyses. ▪ Change from baseline in Mayo Score, stool frequency scores, rectal bleeding scores, and CRP biomarker levels were calculated using observed cases. ▪ Safety endpoints were summarised descriptively.
Subgroup analyses	None
Other relevant information	None

CRP = C-reactive protein; HCl = hydrochloride; NCT = National Clinical Trial Number; OLE = open-label extension; PGA = Physician's Global Assessment; pMS = partial Mayo Score.

Appendix B.4 Pooled ulcerative colitis safety data

Table B-4. Pooled ulcerative colitis safety data

Trial name: UC Pooled Safety Data	NCT number: not applicable
Objective	To evaluate the safety profile of ozanimod HCl 1 mg across controlled and uncontrolled studies in patients with UC
Publications – title, author, journal, year	D'Haens G, Colombel J, Lichtenstein GR, Charles L, Petersen A, Ather S, et al. Safety of ozanimod in patients with moderately to severely active ulcerative colitis over time: pooled analysis from phase 2, phase 3, and open-label extension trials. Presented at: Digestive Disease Week (DDW); 21-23 May 2021. Virtual.
Study type and design	Pooled safety analysis from 32-week TOUCHSTONE trial (phase 2), 52-week TRUE NORTH study (phase 3), and the respective OLE trials
Sample size (n)	N = 1,666 (all patients in TOUCHSTONE, TRUE NORTH, and/or the OLE)
Main inclusion and exclusion criteria	▪ Aged 18-75 years ▪ Moderately to severely active UC (total Mayo Score 6–12, endoscopic subscore 2 or 3) ▪ TRUE NORTH: rectal bleeding subscore ≥ 1, stool frequency subscore ≥ 1[a] ▪ Currently receiving treatment with stable oral aminosalicylates, prednisone (≤ 30 mg/day in TOUCHSTONE; ≤ 20 mg/day in TRUE NORTH), or budesonide[b] (TRUE NORTH only)
Intervention	Ozanimod HCl 1 mg
Comparator(s)	None – all patients received the intervention treatment
Follow-up time	1,922 patient-years of exposure
Is the study used in the health economic model?	No

Trial name: UC Pooled Safety Data	NCT number: not applicable
Primary, secondary and exploratory endpoints	Treatment-emergent adverse events; serious adverse events
Method of analysis	The pooled safety analysis included 2 analyses: the induction period for TOUCHSTONE and TRUE NORTH (controlled UC induction population) and all patients from TOUCHSTONE, TRUE NORTH, and/or the OLE (all-UC population).
Subgroup analyses	None
Other relevant information	None

HCl = hydrochloride; NCT = National Clinical Trial Number; OLE = open-label extension; UC = ulcerative colitis.

[a] Each category was rated 0-3, which was summed to give a total Mayo Score between 0 and 12; higher scores indicate greater activity.

[b] In TRUE NORTH, corticosteroids had to be tapered upon entering the maintenance period.

Appendix B.5 Pooled relapsing multiple sclerosis safety data

Table B-5. Pooled relapsing multiple sclerosis safety data

Trial name:	NCT number: not applicable
Objective	To provide a broad overview of the safety of ozanimod 0.92 mg in a large RMS population.
Publications – title, author, journal, year	Selmaj KW, Cohen JA, Comi G, Bar-Or A, Arnold DL, Steinman L, et al. Ozanimod in relapsing multiple sclerosis: pooled safety results from the clinical development program. Mult Scler Relat Disord. 2021 Jun;51:102844. doi:http://dx.doi.org/10.1016/j.msard.2021.102844.
Study type and design	Pooled safety analysis from a 12-week unpublished phase 1 pharmacokinetic/pharmacodynamic study, 24-week RADIANCE (phase 2), 24-month RADIANCE (phase 3), ≥ 12 month SUNBEAM (phase 3), and DAYBREAK, an ongoing OLE study which, upon completion of any of the previously named trials, participants were eligible to enrol.
Sample size (n)	2,631
Main inclusion and exclusion criteria	See Appendix G
Intervention	Ozanimod 0.92 mg (N = 2,631)
Comparator(s)	Phase 3 population: ozanimod 0.92 mg (N = 882)
Follow-up time	For the intervention arm, the mean exposure to ozanimod 0.92 mg was 32.0 months with 7,058.5 PYs on study, maximum exposure was approximately 75 months. For the phase 3 comparator patients, exposure to ozanimod 0.92 mg (n = 882) was 18.1 months with 1,345.4 PYs on study.
Is the study used in the health economic model?	No
Primary, secondary and exploratory endpoints	The authors did not report primary and secondary endpoints. TEAE were reported. The safety assessment schedule is available in Appendix G.
Method of analysis	Safety results among those exposed to at least 1 dose of ozanimod 0.92 mg were included in the pooled population from all RRMS trials. For safety outcomes with low event rates and/or longer time to onset, calculated incidences and incident rates for all participants exposed to either dose of ozanimod (0.46 or 0.92 mg) are presented. TEAE rates are reported throughout the duration of ozanimod exposure up to the cutoff date. However, absolute lymphocyte count and blood pressure over time are reported up to month 42, the last timepoint for which approximately 40% of participants have data available. All outcomes were analysed descriptively.
Subgroup analyses	None
Other relevant information	None

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NCT = National Clinical Trial Number; OLE = open-label extension; PY = person-year; RRMS relapsing-remitting multiple sclerosis; TEAE = treatment-emergent adverse event.

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Appendix C. Baseline characteristics of patients in studies used for the comparative analysis of efficacy and safety

Appendix C.1 Comparability of patients across studies

Appendix C.1.1 Induction period characteristics

Patients in the induction period were broadly similar in terms of mean age (range, 34.1-44.8 years), and mean Mayo Score (range, 8.0-9.1). Differences were noted between trials with respect to the percentage of male participants (range, 42%-100%), mean C-reactive protein (CRP) level at baseline (range, 7.0-35.8 mg/L), years since ulcerative colitis (UC) diagnosis (range, 3.8-14.6 years), extent of disease (left-sided [range, 15%-63%] vs. extensive [range, 6.6%-80.8%] vs. other [range, 0.0%-63.4%]), and use of concomitant steroids (range, 25.0%-100.0%).[26]

Trials differed in their eligibility criteria regarding prior anti–tumour necrosis factor (TNF) biologics. Nine trials required patients to be naïve to anti-TNF biologics at study entry. Among studies that allowed but did not require prior therapy with anti-TNF biologics, there was variation in the percentage of patients who did have prior therapy with these agents (range, 15.0%-58.0%).[26]

Full details on patient baseline characteristics in the induction period can be found in Table C-1.

Appendix C.1.2 Maintenance period characteristics

Baseline characteristics in the maintenance period were only reported for the rerandomised arms of rerandomised trials. Patients in maintenance period trials were mostly similar in terms of age (range of mean age, 38.6-43.4 years) and sex (range of percentage male, 48.1%-61.1%). Mean Mayo Score was similar for most trials (range, 7.9-8.9), with the exception of the OCTAVE SUSTAIN trial, which showed lower mean Mayo Scores. Where reported, there were differences among trials in terms of mean CRP level at baseline (range, 0.7-9.6 mg/L), years since UC diagnosis (range, 5.4-8.7 years), extent of disease (left-sided [range, 30.6%-69.2%] versus extensive [range, 11.2%-68.3%] versus other [range, 10.6%-52.8%]) and use of concomitant steroids (range, 28%-58%). Full details on patient baseline characteristics in the maintenance period can be found in Table C-2.[26]

A full discussion on the heterogeneity regarding patient baseline characteristics in the induction and maintenance periods can be found in Appendix C.1.3.

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Table C-1. Induction baseline patient characteristics of trials identified in the systematic literature review

Trial name	Treatment	N	Age (mean)	Male (%)	CRP (mg/L)	Years since UC diagnosis (mean)	Mayo Score (mean)	Extent of disease (%)			Exposure and/or failure to prior therapies (%)		Prior Anti-TNF biologic failure (%)[a,c]	Concomitant corticosteroids (%)
								Left-sided	Exten-sive	Other	Biologics (anti-TNF)[a]	Biologics (non-anti-TNF)[b]		
TRUE NORTH[27,28]	PBO	216	41.9	66.2	11.1	6.8	8.9	62.0	38.0	NA	30.1	20.4	NR	30.4
	OZA 1 mg	429	41.4	57.1	8.0	6.9	8.9	62.5	37.5	NA	30.3	18.6	NR	34.8
TOUCHSTONE[11]	PBO	65	41.9	54.0	4.9[d]	6.1	8.6	63	37	NR	15	NR	NR	37
	OZA 0.5 mg	65	38.8	49.0	3.9[d]	5.9	8.3	63	37	NR	20	NR	NR	34
	OZA 1 mg	67	41.8	72.0	4.3[d]	6.7	8.5	61	39	NR	19	NR	NR	40
OASIS[29]	PBO	54	44.8	59.3	79.3[e]	NR	8.7	NR	NR	NR	33.3	22.2	NR	29.6
	ETRA 1 mg	52	43.2	57.7	142.98[e]	NR	8.8	NR	NR	NR	28.8	7.7	NR	25.0
	ETRA 2 mg	50	40.4	54.0	92.39[e]	NR	8.9	NR	NR	NR	34.0	14.0	NR	36.0
ULTRA 1[7]	PBO	130	37[d]	63.1	3.2[d]	5.4[d]	8.7	32.3	56.2	11.5	*NA*	*NA*	*NA*	*67.6*
	ADA 80/40 mg	130	40[d]	60.0	6.4[d]	6.9[d]	9.0	36.9	53.8	9.2	*NA*	*NA*	*NA*	*56.9*
	ADA 160/80/40 mg	130	36.5[d]	63.8	3.3[d]	6.1[d]	8.8	46.9	46.2	6.9	*NA*	*NA*	*NA*	*54.6*
ULTRA 2[12]	PBO	246	41.3	61.8	13.1	8.5	8.9	39.0	48.8	12.2	41.1	*NA*[f]	41.1	56.9
	ADA 160/80/40 mg	248	39.6	57.3	14.5	8.1	8.9	38.7	48.4	12.9	39.1	*NA*[f]	39.1	60.5
SERENE-UC[30]	ADA 160/40 mg	573	40.5	58.3	NR	NR	8.87 n = 570	NR	NR	NR	NR	NR	NR	NR
	ADA 160/80/40 mg	379	40.2	56.2	NR	NR	8.69	NR	NR	NR	NR	NR	NR	NR
Suzuki et al. (2014)[5]	PBO	96	41.3	72.9	3.4[d]	7.8	8.5	36.5	61.5	2.1	NA	NA	NA	60.4
	ADA 80/40 mg	87	44.4	57.5	3.1[d]	8.3	8.5	36.8	62.1	1.1	NA	NA	NA	72.4
	ADA 160/80/40 mg	90	42.5	67.8	2.2[d]	7.8	8.6	30.0	70.0	0.0	NA	NA	NA	63.3

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Trial name	Treatment	N	Age (mean)	Male (%)	CRP (mg/L)	Years since UC diagnosis (mean)	Mayo Score (mean)	Extent of disease (%)			Exposure and/or failure to prior therapies (%)		Prior Anti-TNF biologic failure (%)[a,c]	Concomitant corticosteroids (%)
								Left-sided	Exten-sive	Other	Biologics (anti-TNF)[a]	Biologics (non-anti-TNF)[b]		
PURSUIT SC[13]	PBO	331	39.0	52.9	10.7 n = 321	6.0	8.3	57.0 n = 330	43.0 n = 330	NR	NA	NA	NA	*42.9*
	GOL 100/50 mg	72	40.9	55.6	8.2 n = 69	6.6	8.2	59.7	40.3	NR	NA	NA	NA	*51.4*
	GOL 200/100 mg	331	40.0	54.4	11.3 n = 324	6.4	8.6	58.3	41.7	NR	NA	NA	NA	*44.7*
	GOL 400/200 mg	331	40.7	60.7	13.2 n = 328	6.4	8.5	57.7	42.3	NR	NA	NA	NA	*46.5*
ACT 1[16]	PBO	121	41.4	59.5	*17* n = 119	6.2	8.4	55.0 n = 120	45.0 n = 120	NR	NA	*NA*[f]	NA	65.3
	IFX 5 mg/kg	121	42.4	64.5	*14* n = 120	5.9	8.5	52.9 n = 119	47.1 n = 119	NR	NA	*NA*[f]	NA	57.9
	IFX 10 mg/kg	122	41.8	59.0	*16* n = 121	8.4	8.4	55.4 n = 121	44.6 n = 121	NR	NA	*NA*[f]	NA	59.8
ACT 2[16]	PBO	123	39.3	57.7	*16* n = 121	6.5	8.5	58.3 n = 120	41.7 n = 120	NR	NA	*NA*[f]	NA	48.8
	IFX 5 mg/kg	121	40.5	62.8	*13* n = 120	6.7	8.3	59.3 n = 118	40.7 n = 118	NR	NA	*NA*[f]	NA	49.6
	IFX 10 mg/kg	120	40.3	56.7	*14* n = 119	6.5	8.3	62.5	37.5	NR	NA	*NA*[f]	NA	55.0
UC-SUCCESS[31]	AZA 2.5 mg/kg	79	40.7	*42*	NR	6.6	8.5	NR	NR	NR	NA	*NA*[f]	NA	34.2
	IFX 5 mg/kg	78	38.5	*54*	NR	6.3	8.1	NR	NR	NR	NA	*NA*[f]	NA	39.7
	AZA 2.5 mg/kg + IFX 5 mg/kg	80	38.0	*60*	NR	5.2	8.6	NR	NR	NR	NA	*NA*[f]	NA	47.5

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								Left-sided	Exten-sive	Other	Biologics (anti-TNF)[a]	Biologics (non-anti-TNF)[b]		
Jiang et al. (2015)[17]	PBO	41	34.5	60.9	35.1	4.4	NR	41.5	NR	58.5	NA	*NA*[f]	NA	51.2
	IFX 3.5 mg/kg	41	34.1	58.5	35.7	4.3	NR	36.6	NR	63.4	NA	*NA*[f]	NA	53.7
	IFX 5 mg/kg	41	34.3	63.4	35.8	4.4	NR	39.1	NR	60.9	NA	*NA*[f]	NA	53.7
Kobayashi et al. (2016)[18]	PBO	104	37.8	64.4	*7*	7.1	8.5	19.2	80.8	NR	NA	*NA*[f]	NA	66.3
	IFX 5 mg/kg	104	40	63.5	*10*	8.1	8.6	20.2	79.8	NR	NA	*NA*[f]	NA	65.4
Probert et al. (2003)[32]	PBO	20	40[d]	NR	12	NR	NR	15	65	20	NA	NA	NA	NR
	IFX 5 mg/kg	23	41[d]	NR	9	NR	NR	22	61	17	NA	NA	NA	NR
Sands et al. (2001)[33]	PBO	3	40.3	66.7	NR	4.0	NR	NR	NR	NR	NR	NR	NR	100
	IFX 5 mg/kg	3	43.7	66.7	NR	14.6	NR	NR	NR	NR	NR	NR	NR	100
	IFX 10 mg/kg	3	35.0	66.7	NR	3.8	NR	NR	NR	NR	NR	NR	NR	100
	IFX 20 mg/kg	2	NR	100.0	NR	NR	NR	NR	NR	NR	NR	NR	NR	100
GEMINI 1[19]	PBO	149	41.2	61.7	NR	7.1	8.6	39.6	33.6	*26.9*	49.0	*NA*[f]	42.3	*56.3*
	Cohort 1 VEDO 300 mg	225	40.1	58.7	NR	6.1	8.5	40.9	36.9	*22.2*	42.2	*NA*[f]	36.4	*56.0*
	Cohort 2 VEDO 300 mg	521	40.1	57.8	NR	7.2	8.6	36.1	38.0	*25.9*	50.5	*NA*[f]	42.6	*52.0*
	Total VEDO 300 mg	746	40.1	58.0	NR	6.8	8.6	37.5	37.7	*24.8*	48.0	*NA*[f]	40.8	*53.2*
VARSITY[6]	VEDO 300 mg	385	40.8	60.8	NR	7.3	8.7	NR	NR	NR	20.8	NA	18.7	36.1
	ADA 160/80/40 mg	386	40.5	56.0	NR	6.4	8.7	NR	NR	NR	21.0	NA	20.5	36.3

Trial name	Treatment	N	Age (mean)	Male (%)	CRP (mg/L)	Years since UC diagnosis (mean)	Mayo Score (mean)	Extent of disease (%)			Exposure and/or failure to prior therapies (%)		Prior Anti-TNF biologic failure (%)[a,c]	Concomitant corticosteroids (%)
								Left-sided	Exten-sive	Other	Biologics (anti-TNF)[a]	Biologics (non-anti-TNF)[b]		
VISIBLE 1[20]	PBO	56	39.4	60.7	NR	7.4	9.0[d]	42.9	7.1	*50.0*	35.7	NA	NR	42.9
	VEDO 108 mg Q2W	106	38.1	61.3	NR	8.0	9.0[d]	43.4	6.6	*49.1*	37.7	NA	NR	42.5
	VEDO 300 mg Q8W	54	41.6	57.4	NR	8.2	9.0[d]	38.9	13.0	*48.2*	44.4	NA	NR	38.9
Motoya et al. (2019)[21]	PBO	82	44.0	67.1	NR	8.6	8.1	37.8	62.2	NR	50.0	NA	50.0	*30.5*
	VEDO 300 mg	164	42.3	60.4	NR	7.2	8.3	38.4	61.6	NR	51.8	NA	51.2	*31.7*
UNIFI[22]	PBO	319	41.2	61.8	4.7[d] n = 316	8.0	8.9	52.8 n = 316	NR	NR	NR	NR	49.8	49.2
	UST 130 mg	320	42.2	59.4	4.5[d] n = 315	8.1	8.9	57.5 n = 318	NR	NR	NR	NR	50.6	54.1
	UST 6 mg/kg	322	41.7	60.6	4.8[d] n = 320	8.2	8.9	52.5 n = 320	NR	NR	NR	NR	50.9	52.2
Study A3921063[34]	PBO	48	42.5	48	9.7	8.8	8.2	26	43	30	31	*NA*[f]	NR	27
	TOF 0.5 mg	31	43.8	55	18.8	8.8	8.6	27	30	43	29	*NA*[f]	NR	35
	TOF 3 mg	33	42.5	58	12.6	8.9	8.3	34	38	28	30	*NA*[f]	NR	30
	TOF 10 mg	33	43.2	64	11.3	10.9	8.0	35	42	23	30	*NA*[f]	NR	58
	TOF 15 mg	49	41.2	53	17.1	7.6	8.0	24	37	39	31	*NA*[f]	NR	27
OCTAVE 1[35]	PBO	122	41.8	63.1	4.7[d]	6.0[d]	9.1	30.3 n = 475	54.1 n = 475	15.6 n = 475	53.3	NR	52.5	47.5
	TOF 10 mg	476	41.3	58.2	4.4[d]	6.5[d]	9.0	33.3 n = 475	53.1 n = 475	13.7 n = 475	53.4	NR	51.1	45.0

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Trial name	Treatment	N	Age (mean)	Male (%)	CRP (mg/L)	Years since UC diagnosis (mean)	Mayo Score (mean)	Extent of disease (%)			Exposure and/or failure to prior therapies (%)		Prior Anti-TNF biologic failure (%)[a,c]	Concomitant corticosteroids (%)
								Left-sided	Exten-sive	Other	Biologics (anti-TNF)[a]	Biologics (non-anti-TNF)[b]		
OCTAVE 2[35]	PBO	112	40.4	49.1	5.0[d]	6.2[d]	8.9	35.1 n = 111	50.5 n = 111	14.4 n = 111	58.0	NR	53.6	49.1
	TOF 10 mg	429	41.1	60.4	4.6[d]	6.0[d]	9.0	34.8 n = 428	49.3 n = 428	15.7 n = 428	54.5	NR	51.7	46.2

ADA = adalimumab; AZA = azathioprine; CRP = C-reactive protein; ETRA = etrasimod; GOL = golimumab; IFX = infliximab; LD = loading dose; NA = not applicable; NR = not reported; OZA = ozanimod; PBO = placebo; Q2W = every 2 weeks; Q8W = every 8 weeks; TOF = tofacitinib; TNF = tumour necrosis factor; UC = ulcerative colitis; UST = ustekinumab; VEDO = vedolizumab.

Note: Italicised values are based on calculations or assumptions using data reported in the articles.

[a] Golimumab, infliximab, or adalimumab.

[b] Vedolizumab or ustekinumab.

[c] Inadequate response, loss of response, or intolerance to a prior anti-TNF therapy.

[d] Median value reported instead of mean.

[e] Reported in nmol/L.

[f] Study took place prior to approval of vedolizumab and ustekinumab.

Source: BMS Celgene data on file (2021)[26]

Table C-2. Maintenance baseline patient characteristics of trials identified in the systematic literature review

Trial name	Treatment	N	Age (mean)	Male (%)	CRP (mg/L)	Years since UC diagnosis (mean)	Mayo Score (mean)	Extent of disease (%)			Exposure and/or failure to prior therapies (%)		Prior Anti-TNF biologic failure (%)[a,c]	Concomitant cortico-steroids (%)
								Left-sided	Exten-sive	Other	Biologics (anti-TNF)[a]	Biologics (non-anti-TNF)[b]		
TRUE NORTH[27,28]	PBO	227	43.0	53.7	6.8	7.2	8.6	69.2	30.8	NA	30.4	14.5	NR	28.2
	OZA 1 mg	230	42.4	50.9	6.8	8.4	8.9	66.1	33.9	NA	33.0	18.3	NR	30.9
TOUCHSTONE[11]	PBO	65	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	OZA 0.5 mg	65	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	OZA 1 mg	67	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
ULTRA 2[12]	PBO	246	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	ADA 160/80/40 mg	248	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
SERENE-UC[30]	ADA 40 mg EOW	175	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	ADA 40 mg EOW	163	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Suzuki et al. (2014)[5]	PBO	96	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	ADA 80/40 mg	87	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	ADA 160/80/40 mg	90	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
PURSUIT M[14]	PBO	156	40.2	48.1	9.6 n = 150	6.9	8.3	NR	NR	NR	NA	NA	NA	*56.4*
	GOL 50 mg	154	41.4	50.0	8.5 n = 149	6.8	8.1	NR	NR	NR	NA	NA	NA	*53.9*
	GOL 100 mg	154	39.1	57.8	8.9 n = 152	7.2	8.5	NR	NR	NR	NA	NA	NA	*53.9*
PURSUIT J[15]	PBO	31	42.9	61.0	4.1	5.7[d]	8.0[d]	61	39	NR	NA	NA	NA	*29*

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Trial name	Treatment	N	Age (mean)	Male (%)	CRP (mg/L)	Years since UC diagnosis (mean)	Mayo Score (mean)	Extent of disease (%)			Exposure and/or failure to prior therapies (%)		Prior Anti-TNF biologic failure (%)[a,c]	Concomitant cortico-steroids (%)
								Left-sided	Exten-sive	Other	Biologics (anti-TNF)[a]	Biologics (non-anti-TNF)[b]		
	GOL 100 mg	32	39.3	59.0	5.3	5.4[d]	8.0[d]	63	38	NR	NA	NA	NA	*28*
ACT 1[16]	PBO	121	NR	NR	NR	NR	NR	NR	NR	NR	NA	*NA*[e]	NA	NR
	IFX 5 mg/kg	121	NR	NR	NR	NR	NR	NR	NR	NR	NA	*NA*[e]	NA	NR
	IFX 10 mg/kg	122	NR	NR	NR	NR	NR	NR	NR	NR	NA	*NA*[e]	NA	NR
ACT 2[16]	PBO	123	NR	NR	NR	NR	NR	NR	NR	NR	NA	*NA*[e]	NA	NR
	IFX 5 mg/kg	121	NR	NR	NR	NR	NR	NR	NR	NR	NA	*NA*[e]	NA	NR
	IFX 10 mg/kg	120	NR	NR	NR	NR	NR	NR	NR	NR	NA	*NA*[e]	NA	NR
Jiang et al. (2015)[17]	PBO	41	NR	NR	NR	NR	NR	NR	NR	NR	NA	*NA*[e]	NA	NR
	IFX 3.5 mg/kg	41	NR	NR	NR	NR	NR	NR	NR	NR	NA	*NA*[e]	NA	NR
	IFX 5 mg/kg	41	NR	NR	NR	NR	NR	NR	NR	NR	NA	*NA*[e]	NA	NR
Kobayashi et al. (2016)[18]	PBO	104	NR	NR	NR	NR	NR	NR	NR	NR	NA	*NA*[e]	NA	NR
	IFX 5 mg/kg	104	NR	NR	NR	NR	NR	NR	NR	NR	NA	*NA*[e]	NA	NR
GEMINI 1[19]	PBO	126	40.3	54.8	NR	7.8	8.4	42.1	13.5	*44.4*	37	*NA*[e]	30.2	*57*
	VEDO 300 mg Q8W	122	41	57.4	NR	6.2	8.4	41.8	11.5	*46.7*	41	*NA*[e]	35.2	*57*
	VEDO 300 mg Q4W	125	38.6	54.4	NR	7.6	8.3	36.0	11.2	*52.8*	42	*NA*[e]	32.0	*58*
VARSITY[6]	VEDO 300 mg	385	NR	NR	NR	NR	NR	NR	NR	NR	NR	NA	NR	NR
	ADA 160/80/40 mg	386	NR	NR	NR	NR	NR	NR	NR	NR	NR	NA	NR	NR
VISIBLE 1[20]	PBO	56	NR	NR	NR	NR	4.0[d]	NR	NR	NR	NR	NA	NR	NR
	VEDO 108 mg Q2W	106	NR	NR	NR	NR	3.5[d]	NR	NR	NR	NR	NA	NR	NR

Trial name	Treatment	N	Age (mean)	Male (%)	CRP (mg/L)	Years since UC diagnosis (mean)	Mayo Score (mean)	Extent of disease (%)			Exposure and/or failure to prior therapies (%)		Prior Anti-TNF biologic failure (%)[a,c]	Concomitant cortico-steroids (%)
								Left-sided	Exten-sive	Other	Biologics (anti-TNF)[a]	Biologics (non-anti-TNF)[b]		
	VEDO 300 mg Q8W	54	NR	NR	NR	NR	4.0[d]	NR	NR	NR	NR	NA	NR	NR
Motoya et al. (2019)[21]	PBO	42	42.6	54.8	NR	8.7	7.9	45.2	54.8	NR	33.3	NA	33.3	*35.7*
	VEDO 300 mg	41	43.0	51.2	NR	8.6	8.1	31.7	68.3	NR	41.5	NA	39.0	*31.8*
UNIFI[22]	PBO	175	42.0	61.1	3.4[e] n = 174	7.5	8.7	50.9	NR	NR	NR	NR	49.7	54.3
	UST 90 mg Q12W	172	40.7	55.8	3.3[e] n = 170	8.6	8.9	53.5	NR	NR	NR	NR	40.7	48.3
	UST 90 mg Q8W	176	39.5	53.4	4.0[e] n = 174	8.1	8.9 n = 174	54.3 n = 174	NR	NR	NR	NR	51.1	54.0
OCTAVE SUSTAIN[35]	PBO	198	43.4	58.6	1.0[e]	7.2[e]	3.3	34.3	54.5	10.6	46.5	NR	44.9	50.5
	TOF 5 mg	198	41.9	52.0	0.7[e]	6.5[e]	3.3	33.7 n = 196	52.0 n = 196	14.3 n = 196	45.5	NR	41.9	51.0
	TOF 10 mg	197	42.9	55.8	0.9[e]	6.8[e]	3.4	30.6 n = 196	52.6 n = 196	16.8 n = 196	51.3	NR	47.2	44.2

ADA = adalimumab; CRP = C-reactive protein; EOW = every other week; GOL = golimumab; IFX = infliximab; NR = not reported; OZA = ozanimod; PBO = placebo; Q2W = every 2 weeks; Q4W = every 4 weeks; Q8W = every 8 weeks; Q12W = every 12 weeks; TOF = tofacitinib; TNF = tumour necrosis factor; UC = ulcerative colitis; UST = ustekinumab; VEDO = vedolizumab.

Note: Italicised values are based on calculations or assumptions using data reported in the articles.

[a] Golimumab, infliximab, or adalimumab.

[b] Vedolizumab or ustekinumab.

[c] Inadequate response, loss of response, or intolerance to a prior anti-TNF therapy.

[d] Median value reported instead of mean.

[e] Study took place prior to approval of vedolizumab and ustekinumab.

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Source: BMS Celgene data on file (2021)[26]

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Appendix C.1.3 Treatment effect modifier assessment

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Appendix C.2 Comparability of the study populations with Danish patients eligible for treatment

The peak age for clinical presentation of UC is from 15 to 35 years, with a second smaller peak from 55 to 65 years.[36,37] The mean age across all studies included in the indirect treatment comparison (ITC) ranged from 34.1 to 44.8 years. However, the mean years since UC diagnosis ranged from 3.8 to 14.6 years suggesting that the population in the ITC was reflective of the general UC population.

Appendix C.3 Baseline characteristics of studies assessing ozanimod not included in network meta-analysis

Table C-3. TOUCHSTONE OLE baseline characteristics

Characteristic	Ozanimod (n = 170)
Sex, n (%)	
Female	72 (42.4)
Male	98 (57.6)
Age (years), mean (SD)	40.4 (11.76)
Race, n (%)	
White	157 (92.4)
Black	3 (1.8)
Other	10 (5.9)
BMI [kg/m^2], mean (SD)	25.0 (4.96)
Years since UC diagnosis, mean (SD)	5.9 (5.29)
Prior anti-TNF treatment, n (%)	
Yes	31 (18.2)
No	139 (81.8)
Partial Mayo Score at OLE baseline, median (range)	6.0 (3-9)
Total Mayo Score at OLE baseline, median (range)	8.0 (5-12)

BMI = body mass index; OLE = open-label extension; SD = standard deviation; TNF = tumour necrosis factor; UC = ulcerative colitis.

Source: Sandborn et al. (2021)[38]

Table C-4. Pooled safety analysis in ulcerative colitis baseline characteristics

	Controlled UC induction period		All UC studies	
Characteristic	Ozanimod 1 mg (n = 496)	Placebo (n = 281)	Ozanimod 1 mg (n = 1,158)	Placebo (n = 508)
Male, n (%)	293 (59.1)	178 (63.3)	688 (59.4)	300 (59.1)
Age (years), mean (SD)	41.4 (13.2)	41.9 (13.3)	41.6 (13.3)	42.4 (13.5)
Race, n (%)[a]				
White	432 (87.1)	253 (90.0)	1,036 (89.5)	455 (89.6)
Black	15 (3.0)	6 (2.1)	31 (2.7)	15 (3.0)
Asian	39 (7.9)	19 (6.8)	68 (5.9)	31 (6.1)

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Characteristic	Controlled UC induction period		All UC studies	
	Ozanimod 1 mg (n = 496)	Placebo (n = 281)	Ozanimod 1 mg (n = 1,158)	Placebo (n = 508)
Other	10 (2.0)	3 (1.1)	22 (1.9)	7 (1.4)
Use of ≥ 1 concomitant medication, n (%)[b]	495 (99.8)	281 (100)	1,076 (92.9)	480 (94.5)
Corticosteroids (systemic), n (%)	146 (29.4)	92 (32.7)	415 (35.8)	142 (28.0)

SD = standard deviation; UC = ulcerative colitis.

[a] One participant in the ozanimod group is missing data for race.

[b] The most common classes of concomitant medications (used by ≥ 20% of ozanimod-treated participants): anti-diarrheals, intestinal anti-inflammatory/anti-infective agents (primarily mesalazine), treatments for constipation, systemic corticosteroids (primarily prednisone), medications used for endoscopy procedures (anaesthetics, psycholeptics), and analgesics (primarily paracetamol).

Source: D'Haens et al. (2021)[39]

Table C-5. Pooled safety analysis in relapsing multiple sclerosis baseline characteristics

Characteristic	Phase 3 study population	Overall RMS population	
	Ozanimod 0.92 mg (n = 882)	Ozanimod 0.92 mg (n = 2,631)	Any ozanimod (n = 2,787)[a]
Age (years), mean (SD)	35.4 (9.1)	36.0 (9.2)	35.9 (9.1)
Sex, n (%)			
Female	576 (65.3)	1,765 (67.1)	1,868 (67.0)
Male	306 (34.7)	866 (32.9)	919 (33.0)
Race, n (%)[a]			
White	876 (99.3)	2,608 (99.1)	2,758 (99.0)
Black	5 (0.6)	16 (0.6)	21 (0.8)
Asian	1 (0.1)	4 (0.2)	4 (0.1)
Other	0	3 (0.1)	4 (0.1)
Hispanic ethnicity, n (%)	16 (1.8)	29 (1.1)	32 (1.1)
Region, n (%)	790 (89.6)	2,365 (89.9)	2,490 (89.3)
Eastern Europe	92 (10.4)	266 (10.1)	297 (10.7)
Rest of world	24.3 (4.8)	24.3 (4.8)	24.3 (4.8)
BMI, mean (SD), kg/m^2	6.9 (6.3)	6.8 (6.2)	6.8 (6.1)
Time since MS symptom onset, mean (SD), years	3.8 (4.7)	3.7 (4.6)	3.7 (4.6)
Time since MS diagnosis, mean (SD), years	2.6 (1.2)	2.6 (1.2)	2.6 (1.2)
EDSS score, mean (SD)	1.7 (3.6)	1.6 (3.3)	1.7 (3.3)
Number of GdE lesions, mean (SD)	1.7 (3.6)	1.6 (3.3)	1.7 (3.3)
Number of T2 lesions, mean (SD)	51.3 (36.3)	51.4 (36.2)	51.2 (36.1)
Prior exposure to any MS disease-modifying therapy, n (%)	252 (28.6)	753 (28.6)	801 (28.7)[b]

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BMI = body mass index; EDSS = Expanded Disability Status Scale; GdE = gadolinium-enhancing; MS = multiple sclerosis; RMS = relapsing multiple sclerosis; SD = standard deviation.

[a] Includes participants who received only ozanimod 0.92 mg as well as those who received ozanimod 0.46 mg alone (if they did not enrol in the OLE study) or followed by ozanimod 0.92 mg in the OLE study.

[b] Previous disease-modifying therapies used by the "any ozanimod" group included glatiramer acetate (n = 317 [11.4%]), interferon beta-1a (n = 288 [10.3%]), interferon beta-1b (n = 229 [8.2%]), peginterferon beta-1a (n = 35 [1.3%]), teriflunomide (n = 33 [1.2%]), daclizumab (n = 12 [0.4%]), dimethyl fumarate (n = 9 [0.3%]), interferon (unspecified, n = 8 [0.3%]), and mitoxantrone (n = 2 [0.07%]).

Source: Selmaj et al. (2021)[40]

Figure C-5. Pooled safety data in ulcerative colitis and remitting multiple sclerosis baseline characteristics

	UC studies	MS study
Characteristic	**Ozanimod 0.92 mg (N = 1,158)**	**Ozanimod 0.92 mg (N = 2,494)**
Male, n (%)	688 (59.4)	826 (33.1)
Age (years), mean (SD)	41.6 (13.3)	37.7 (9.2)
Race, n (%)		
White	1,036 (89.5)	2,474 (99.2)
Black	31 (2.7)	14 (0.6)
Other	90 (7.8)	6 (0.2)

MS = multiple sclerosis; SD = standard deviation; UC = ulcerative colitis.

Source: Danese et al. (2021)[41]

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Appendix D. Efficacy and safety results per study

Appendix D.1 Definition, validity, and clinical relevance of included outcome measures in the NMA

Outcome definitions across trials are summarised below for the key outcomes of clinical response, clinical remission, and endoscopic improvement explored in the network meta-analyses (NMAs). The use of local versus central endoscopy readings is also discussed. Note that for many decades, mucosal healing equated endoscopic healing; the definition today also includes histological healing, and the term used is endoscopic improvement. Outcome definitions for safety outcomes are only briefly discussed for studies included in the NMA because they were often implicitly or poorly defined in comparator trials.[26]

Appendix D.1.1 4-Component and 3-component Mayo Score

In the TRUE NORTH trial, the 3 main efficacy outcomes (clinical response, clinical remission, and endoscopic improvement) were based on Mayo Score components that include stool frequency, rectal bleeding, findings on endoscopy, and physician's global assessment. The primary outcomes of TRUE NORTH measured clinical response and clinical remission using the 3-component Mayo Score that excludes the physician's global assessment subscore.[27] To align with other trials that reported outcomes based on the 4-component Mayo Score, a post hoc analysis of the TRUE NORTH data was conducted, and these data was leveraged in the base-case NMAs, with a separate sensitivity analysis exploring the influence of 3-component TRUE NORTH data on NMA findings. Comparison of the outcomes in the TRUE NORTH trial based on the 3-component Mayo Score versus the 4-component Mayo Score is provided in Table D-4 and Table D-5.[26]

Appendix D.1.2 Central versus local endoscopy readings

Most trials defined endoscopy subscores on local readings in contrast to the recent TRUE NORTH, TOUCHSTONE, VISIBLE 1, SERENE-UC, and the 3 OCTAVE trials, which read the scores centrally. Central endoscopy scores represent a more robust, but laborious, assessment of the extent of disease that has recently become a requirement in clinical trial endpoints to better capture disease severity.[26]

Locally read efficacy outcomes also were presented for the overall treatment populations in the OCTAVE trials in NICE TA547 but were not available in the biologic subgroups. To preserve consistency of the overall NMA outcomes with those evaluated in the biologic subgroups, the centrally read outcomes from the OCTAVE trials were included in NMAs. Within the OCTAVE trials, local readings led to higher clinical remission scores when compared with the centrally read scores. Therefore, use of the published efficacy data based on central readings may lead to bias against tofacitinib in the clinical remission analyses for the overall population, a source of heterogeneity that has been highlighted in previous NMAs in ulcerative colitis (UC).[42-44] It is possible that centralised readings used in the TRUE NORTH, TOUCHSTONE, and VISIBLE 1 trials could similarly introduce some bias.[26]

In addition, the Motoya 2019 and UNIFI trials used a combination of local and central readings. Following the local read, an assessment by a Clinical Endpoint Committee was conducted in the Motoya 2019 trial and the video endoscopy was reviewed centrally in the UNIFI trial. The final score was based on consensus between the 2 reviewers.[26]

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Appendix D.1.3 Clinical remission

Definitions of clinical remission were generally consistent across trials and aligned with the 4-component definition of clinical remission from TRUE NORTH with the exception of Probert 2003, which based clinical remission on the UC symptom score rather than the Mayo Score (Table D-1). To avoid introducing heterogeneity attributable to using an entirely different scale to assess outcomes, combined with heterogeneity due to the patient population recruited, this trial was excluded from analyses of clinical remission. The 3 OCTAVE trials required patients to have a rectal bleeding score of 0 in addition to meeting the criteria used in the other trials, but only 1 patient in the tofacitinib 10 mg arms of OCTAVE 2 and OCTAVE SUSTAIN was excluded from the analysis because of this restriction.[26]

Appendix D.1.4 Clinical response

All trials except for VARSITY, UC-SUCCESS, and Sands 2001 aligned with TRUE NORTH's 4-component definition of clinical response (Table D-1). The Sands 2001 trial used a modified Truelove and Witts Severity Index score instead of the Mayo Score when measuring clinical response. As with Probert 2003, use of an outcome defined by a scale other than the Mayo Score represented a reason for exclusion in the NMAs to avoid the heterogeneity that may be introduced in analyses. In addition, the VARSITY trial defined clinical response based on a partial Mayo Score, which may overestimate effect sizes relative to complete Mayo Scores. Although not substantially different from TRUE NORTH's definition of clinical response, the definition used in the UC-SUCCESS trial further supported the exclusion of UC-SUCCESS from the base-case analyses.[26]

Appendix D.1.5 Endoscopic improvement

All trials that reported endoscopic improvement data aligned with the definition from TRUE NORTH (Table D-1). The definition used in the trials is the Mayo endoscopic subscore of 0-1. Although the outcome was often referred to as *mucosal healing* within the relevant trials[26], note that for many decades, mucosal healing equated endoscopic healing; the definition of mucosal healing today also includes histological healing, and the term used in this analysis is endoscopic improvement.

Appendix D.1.6 Safety outcomes

Most trials did not provide explicit definitions for the safety outcomes of interest. In TRUE NORTH, treatment-emergent adverse events were defined as any adverse event with date of first onset or date of worsening in severity on or after the date of first induction period or maintenance period dose. Adverse events were classified using the Medical Dictionary for Regulatory Activities (MedDRA). Eight other trials also reported using MedDRA classifications (Table D-1).[26]

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Table D-1. Definition, validity, and clinical relevance of included outcome measures

Outcome measure	Definition	Trials using definition in NMAs
Clinical remission	Complete Mayo Score of ≤ 2 points with no individual subscore > 1 point	TRUE NORTH, TOUCHSTONE, ULTRA 1, ULTRA 2, SERENE-UC, Suzuki 2014, PURSUIT-SC, PURSUIT-M, PURSUIT-J, ACT 1, ACT 2, Jiang 2015, Kobayashi 2016, GEMINI 1, VARSITY, VISIBLE 1, Motoya 2019, UNIFI, Study A3921063
	Complete Mayo Score of ≤ 2 points with no individual subscore > 1 point and an RBS of 0	OCTAVE 1, OCTAVE 2, OCTAVE SUSTAIN
	RBS = 0, stool frequency subscore ≤ 1 (and a decrease of ≥ 1 point from the baseline stool frequency subscore), and endoscopy subscore ≤ 1	TRUE NORTH (sensitivity analysis)
	UC symptom score ≤ 2	Probert 2003[a]
Clinical response	Decrease of ≥ 3 points and ≥ 30% in the complete Mayo Score	UC-SUCCESS[b]
	Decrease of ≥ 3 points and ≥ 30% in the complete Mayo Score and either an absolute RBS of ≤ 1 point or a ≥ 1-point decrease in RBS	TRUE NORTH, TOUCHSTONE, ULTRA 1, ULTRA 2, SERENE-UC, Suzuki 2014, PURSUIT-SC, PURSUIT-M, PURSUIT-J, ACT 1, ACT 2, Jiang 2015, Kobayashi 2016, GEMINI 1, VISIBLE 1, Motoya 2019, UNIFI, Study A3921063, OCTAVE 1, OCTAVE 2, OCTAVE SUSTAIN
	Decrease of ≥ 2 points and ≥ 25% in the partial Mayo Score (excludes endoscopy subscore) and either an absolute RBS of ≤ 1 or a ≥ 1-point decrease in RBS	VARSITY
	Decrease of ≥ 2 points and ≥ 35% in the 9-point Mayo Score and either an absolute RBS of ≤ 1 point or a ≥ 1-point decrease in RBS	TRUE NORTH
	Modified Truelove and Witts Severity Index score of < 10 and a 5-point reduction compared with baseline	Sands 2001[b]
Endoscopic improvement	Endoscopy subscore of ≤ 1 point (previously referred to as mucosal healing)	TRUE NORTH, TOUCHSTONE, ULTRA 1, ULTRA 2, SERENE-UC, Suzuki 2014, PURSUIT-SC, PURSUIT-M, PURSUIT-J, ACT 1, ACT 2, UC-SUCCESS, Jiang 2015, Kobayashi 2016, GEMINI 1, VARSITY, VISIBLE 1, Motoya 2019, UNIFI, Study A3921063, OCTAVE 1, OCTAVE 2, OCTAVE SUSTAIN
Adverse events	Based on the Medical Dictionary for Regulatory Activities (MedDRA)	TRUE NORTH, GEMINI 1, VARSITY, VISIBLE 1, Motoya 2019, UNIFI, OCTAVE 1, OCTAVE 2, OCTAVE SUSTAIN

Outcome measure	Definition	Trials using definition in NMAs
Discontinuations due to adverse events	Discontinuation due to treatment-emergent adverse event	TRUE NORTH
	Discontinuation due to adverse event	TOUCHSTONE, ULTRA 1, ULTRA 2, Suzuki 2014, PURSUIT-SC, PURSUIT-M, ACT 1, ACT 2, UC-SUCCESS, Jiang 2015, Kobayashi 2016, Sands 2001, VARSITY, VISIBLE 1, Motoya 2019, UNIFI, Study A3921063
	Discontinuation due to adverse event or worsening UC	OCTAVE 1, OCTAVE 2, OCTAVE SUSTAIN
	Discontinuations	SERENE-UC[c]

NMA = network meta-analysis; RBS = rectal bleeding score; UC = ulcerative colitis.

[a] Trial was excluded from NMAs of clinical remission.

[b] Trial was excluded from NMAs of clinical response.

[c] Trial was excluded from NMAs of adverse events leading to discontinuation.

Table D-2. Outcome definition alignment with TRUE NORTH

UC therapy	Trial name	Endoscopy reading	Clinical response		Clinical remission		Endoscopic improvement	
			Induction	Maintenance	Induction	Maintenance	Induction	Maintenance
Ozanimod	TRUE NORTH[27]	Central	Decrease of ≥ 3 points and ≥ 30% in the complete Mayo Score and either an absolute RBS of ≤ 1 point or a ≥ 1-point decrease in RBS		Complete Mayo Score of ≤ 2 points with no individual subscore > 1 point		Endoscopy subscore of ≤ 1 point	
	TOUCHSTONE[11]							
Adalimumab	ULTRA 1[7]	Local						
	ULTRA 2[12]	Local						
	SERENE-UC[30]							
	Suzuki et al. (2014)[5]	Local						
Golimumab	PURSUIT-SC[13]	Local						
	PURSUIT-M[14]	Local						
	PURSUIT-J[15]	Local						

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UC therapy	Trial name	Endoscopy reading	Clinical response		Clinical remission		Endoscopic improvement	
			Induction	Maintenance	Induction	Maintenance	Induction	Maintenance
Infliximab	ACT 1[16]	Local						
	ACT 2[16]	Local						
	UC-SUCCESS[31]		No RBS component					
	Jiang et al. (2015)[17]	Local						
	Kobayashi et al. (2016)[18]	Local						
	Probert et al. (2003)[32]	Local			UC symptom score			
	Sands et al. (2001)[33]	Local	Truelove and Witts Severity Index					
Vedolizumab	GEMINI 1[19]	Local						
	VARSITY[6]		Partial Mayo Score					
	VISIBLE 1[20]							
	Motoya et al. (2019)[21]	Local and central						
Ustekinumab	UNIFI[22]	Local and central						

RBS = rectal bleeding score; UC = ulcerative colitis.

Colour legend: green = aligns with TRUE NORTH definition; orange = used a different definition than TRUE NORTH; grey = not applicable or outcome not reported.

Source: BMS Celgene data on file (2021)[26]

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Appendix D.1.7 Outcome definition summary

Most trials used similar outcome definitions as the TRUE NORTH trial. Notable exceptions are the Probert 2003 and Sands 2001 trials, which used different scoring systems for clinical remission and clinical response, respectively. The efficacy outcomes from these 2 trials are not comparable to those based on Mayo Scores and therefore were excluded from the analysis. It should also be noted that 3 of the adalimumab trials—ULTRA 1, ULTRA 2, and Suzuki 2014— also may have underestimated the effect size by using the worst patient-recorded score from the 3 days before each study visit as opposed to the average when calculating the stool frequency and rectal bleeding scores. The inclusion of the adalimumab trials and the exclusion of the Probert 2003 and Sands 2001 trials is consistent with previous NMAs in UC.[26]

Appendix D.2 Definition, validity, and clinical relevance of included outcome measures in True North, TOUCHSTONE and TOUCHSTONE OLE

Table D-3. Definition of included outcome measures used in True North and TOUCHSTONE

Outcome measure	Definition	Trials using definition
Clinical remission	Complete Mayo Score of ≤ 2 points with no individual subscore > 1 point	TRUE NORTH and TOUCHSTONE,
	Partial Mayo Score of ≤ 2 points with no individual subscore of > 1 point[a]	TOUCHSTONE OLE
	4-component Mayo: Complete Mayo Score of ≤ 2 points with no individual subscore of > 1 point[b] or 3-component Mayo: rectal bleeding score of 0 and SFS ≤ 1 and a decrease of ≥ 1 point from the baseline stool frequency score, and endoscopy subscore ≤ 1[b]	
Clinical response	Decrease of ≥ 3 points and ≥ 30% in the complete Mayo Score and either an absolute RBS of ≤ 1 point or a ≥ 1 point decrease in RBS	TRUE NORTH and TOUCHSTONE
	A reduction from baseline in Partial Mayo Score of ≥ 2 points and ≥ 30% and either a reduction in rectal bleeding score [RBS] of ≥ 1 point or an absolute RBS of ≤ 1 point[a]	TOUCHSTONE OLE
	4-component Mayo: Reduction from baseline in Complete Mayo Score of ≥ 3 points and reduction from baseline in Complete Mayo Score of ≥ 30%, and reduction in rectal bleeding of ≥ 1 point or a rectal bleeding of ≤ 1 point[b] or 3-component Mayo: Reduction from baseline in the 9-point Mayo Score of ≥ 2 points and reduction from baseline in the 9-point Mayo Score ≥ 35%, and reduction from baseline in the rectal bleeding of ≥ 1 point or an rectal bleeding of ≤ 1 point[b]	
Endoscopic improvement	Endoscopy subscore of ≤ 1 point	TRUE NORTH, TOUCHSTONE and TOUCHSTONE OLE
Histologic remission	Geboes score < 2.0 on a scale from 0 to 5.4	TRUE NORTH, TOUCHSTONE and TOUCHSTONE OLE
Mucosal healing	Endoscopy subscore of ≤ 1 point without friability and a Geboes index score < 2.0	TRUE NORTH
	Endoscopy subscore of ≤ 1	TOUCHSTONE
	Endoscopy subscore of 0 and a Geboes index score < 2.0	TOUCHSTONE OLE
Durable remission[c]	Clinical remission at Week 10 and at 52 weeks in all subjects who entered the Maintenance Period	TRUE NORTH
Maintenance of remission[c]	Clinical remission at 52 weeks in the subset of subjects who are in remission at Week 10	TRUE NORTH
Steroid-free remission[c]	Clinical remission at 52 weeks while off corticosteroids for ≥ 12 weeks	TRUE NORTH

Outcome measure	Definition	Trials using definition
Adverse events[d]	Based on the Medical Dictionary for Regulatory Activities (MedDRA)	TRUE NORTH,
	A serious adverse event was defined as any untoward medical occurrence that resulted in death, was life-threatening (was associated with an immediate risk of death), required admission to a hospital or prolongation of existing hospitalisation, resulted in persistent or clinically significant disability or incapacity, or resulted in a congenital anomaly or birth defect	TOUCHSTONE
Discontinuations due to adverse events[d]	Discontinuation due to treatment-emergent adverse event	TRUE NORTH
	Discontinuation due to adverse event	TOUCHSTONE
SF-36[c]	An improvement in score of ≥ 5 points was defined as the minimum clinically important difference	TRUE NORTH

[a] Efficacy measures with assessments up to OLE week 200

[b] Efficacy measures with limited data after OLE week 104. Endoscopy assessments beyond week 104 were limited based on protocol requirements; therefore, the parameters that are associated with endoscopy were reported based on assessments at OLE week 56 using non-responder imputation analyses, and at OLE weeks 56 and 104 in observed cases only

[c] Outcome not included in TOUCHSTONE and TOUCHSTONE OLE

[d] Not defined in TOUCHSTONE OLE

Sources: Sandborn et al. (2016)[11], Sandborn et al. (2021)[38]; Sandborn et al. (2021)[10]

Appendix D.3 TRUE NORTH: additional clinical endpoints

Appendix D.3.1 TRUE NORTH: all efficacy endpoints–induction period

Table D-4. Results of TRUE NORTH (NCT02435992): induction (intention-to-treat population)

				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome[a]	Study arm	N	Result	Difference[b]	95% CI	*P* value	Difference	95% CI	*P* value		
Patients in clinical remission at week 10, n (%)	Ozanimod 1 mg	429	79 (18.4)	12.4	7.5-17.2	NR	OR, 3.586	1.938-6.636	< 0.0001[c]	Analyses used NRI for proportion-based endpoints and	BMS data on file (2020)[24]
	Placebo	216	13 (6.0)								
Patients in clinical remission at week 10, n (%): 4-component Mayo analysis	Ozanimod 1 mg	429	50 (11.7)	7.0	2.9-11.1	NR	OR, 2.718	1.351-5.467	0.0037		
	Placebo	216	10 (4.6)								

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Outcome [a]	Study arm	N	Result	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
				Difference [b]	95% CI	*P* value	Difference	95% CI	*P* value		
Patients with a clinical response at week 10, n (%)	Ozanimod 1 mg	429	205 (47.8)	21.9	14.4-29.3	NR	OR, 2.670	1.858-3.836	< 0.0001 [c]	observed values for changes from baseline	
	Placebo	216	56 (25.9)								
Patients with a clinical response at week 10, n (%): 4-component Mayo analysis	Ozanimod 1 mg	429	222 (51.7)	26.3	18.9-33.7	NR	OR, 3.213	2.232-4.626	< 0.0001		
	Placebo	216	55 (25.5)								
Patients with endoscopic improvement at week 10, n (%)	Ozanimod 1 mg	429	117 (27.3)	15.7	9.7-21.7	NR	OR, 2.876	1.802-4.591	< 0.0001 [c]		
	Placebo	216	26 (12.0)								
Patients with mucosal healing at week 10, n (%)	Ozanimod 1 mg	429	54 (12.6)	8.9	4.9-12.9	NR	OR, 3.767	1.759-8.068	< 0.0001 [c]		
	Placebo	216	8 (3.7)								
Change in partial Mayo Score from baseline to week 10, LS mean (SE)	Ozanimod 1 mg	429	−2.7 (0.12)	−1.1	−1.5 to −0.8	NR	NA	NA	< 0.0001		
	Placebo	216	−1.5 (0.17)								
Change in Mayo Score from baseline to week 10, LS mean (SE): 4-component Mayo analysis	Ozanimod 1 mg	429	−3.2 (0.15)	−1.5	−1.9 to −1.0	NR	NA	NA	< 0.001		
	Placebo	216	−1.7 (0.21)								
Patients with histologic remission at week 10, n (%)	Ozanimod 1 mg	429	78 (18.2)	10.8	5.8-15.8	NR	OR, 2.803	1.593-4.934	< 0.0001		
	Placebo	216	16 (7.4)								
Patients in clinical remission, at week 10, n/N (%): No previous anti-TNF therapy	Ozanimod 1 mg	299	66 (22.1)	15.4	9.2-21.5	NR	OR, 4.03	2.00-8.12	< 0.0001		
	Placebo	151	10 (6.6)								
Patients in clinical remission, at week 10, n/N (%): Previous anti-TNF therapy	Ozanimod 1 mg	130	13 (10.0)	5.4	−1.8 to 12.6	NR	OR, 2.32	0.63-8.49	0.1947		
	Placebo	65	3 (4.6)								
Patients in clinical remission, at week 10, n/N (%): No previous anti-TNF therapy, 4-component Mayo analysis	Ozanimod 1 mg	299	42 (14.0)	9.4	4.2-14.5	NR	OR, 3.347	1.467-7.638	0.0026		
	Placebo	151	7 (4.6)								
	Ozanimod 1 mg	130	8 (6.2)	1.6	−5.0 to 8.1	NR	OR, 1.364	0.348-5.345	0.6564		

Outcome [a]	Study arm	N	Result	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
				Difference [b]	95% CI	*P* value	Difference	95% CI	*P* value		
Patients in clinical remission, at week 10, n/N (%): Previous anti-TNF therapy, 4-component Mayo analysis	Placebo	65	3 (4.6)								
Patients with a clinical response, at week 10, n/N (%): No previous anti-TNF therapy	Ozanimod 1 mg	299	157 (52.5)	23.3	14.1-32.5	NR	OR, 2.69	1.77-4.08	< 0.0001		
	Placebo	151	44 (29.1)								
Patients with a clinical response, at week 10, n/N (%): Previous anti-TNF therapy	Ozanimod 1 mg	130	48 (36.9)	18.5	6.0-31.0	NR	OR, 2.62	1.27-5.41	0.0084		
	Placebo	65	12 (18.5)								
Patients with a clinical response, at week 10, n/N (%): No previous anti-TNF therapy, 4-component Mayo analysis	Ozanimod 1 mg	299	165 (55.2)	25.3	16.1-34.5	NR	OR, 2.899	1.911-4.399	< 0.0001		
	Placebo	151	45 (29.8)								
Patients with a clinical response, at week 10, n/N (%): Previous anti-TNF therapy, 4-component Mayo analysis	Ozanimod 1 mg	130	57 (43.8)	28.5	16.3-40.7	NR	OR, 4.354	2.033-9.325	< 0.0001		
	Placebo	65	10 (15.4)								
Patients with endoscopic improvement at week 10, n/N (%): No previous anti-TNF therapy	Ozanimod 1 mg	299	97 (32.4)	19.8	12.3-27.0	NR	OR, 3.33	1.94-5.70	< 0.001		
	Placebo	151	19 (12.6)								
Patients with endoscopic improvement at week 10, n/N (%): Previous anti-TNF therapy	Ozanimod 1 mg	130	20 (15.4)	4.6	−5.1 to 14.4	NR	OR, 1.51	0.60-3.79	0.378		
	Placebo	65	7 (10.8)								
Patients with mucosal healing at week 10, n/N (%): No previous anti-TNF therapy	Ozanimod 1 mg	299	47 (15.7)	11.7	6.5-16.9	NR	OR, 4.49	1.87-10.74	< 0.001		
	Placebo	151	6 (4.0)								
Patients with mucosal healing at week 10, n/N (%): Previous anti-TNF therapy	Ozanimod 1 mg	130	7 (5.4)	2.3	−3.4 to 8.0	NR	OR, 1.81	0.36-9.08	0.465		
	Placebo	65	2 (3.1)								

CI = confidence interval; ITT = intention-to-treat; LS = least squares; NA = not applicable; NR = not reported; NRI = non-responder imputation; OR = odds ratio; SE = standard error; TNF = tumour necrosis factor.

[a] Clinical remission and clinical response are based on the 3-component Mayo Score unless otherwise specified.

[b] Treatment differences are in terms of the difference in proportions (percentage points) for proportion-based endpoints and in terms of LS mean difference for changes from baseline.

[c] Statistically significant according to the closed, hierarchical testing procedure used to control the overall type I error rate.

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Appendix D.3.2 TRUE NORTH: all efficacy endpoints–maintenance period

Table D-5. Results of TRUE NORTH (NCT02435992): maintenance period (intention-to-treat population)

Outcome[a]	Study arm	N	Result	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
				Difference[b]	95% CI	*P* value	Difference	95% CI	*P* value		
Patients in clinical remission at week 52, n (%)	Ozanimod 1 mg/ Placebo	227	42 (18.5)	18.6	10.8-26.4	NR	OR, 2.755	1.767-4.294	< 0.0001[c]	Analyses used NRI for proportion-based endpoints and observed values for changes from baseline	BMS data on file (2020)[24]
	Ozanimod 1 mg/ Ozanimod 1 mg	230	85 (37.0)								
Patients in clinical remission at week 52, n (%): 4-component Mayo analysis	Ozanimod 1 mg/ Placebo	227	42 (18.5)	19.9	12.0-27.8	NR	OR, 2.876	1.854-4.461	< 0.0001		
	Ozanimod 1 mg/ Ozanimod 1 mg	230	88 (38.3)								
Patients with a clinical response at week 52, n (%)	Ozanimod 1 mg/ Placebo	227	93 (41.0)	19.2	10.4-28.0	NR	OR, 2.266	1.542-3.331	< 0.0001[c]		
	Ozanimod 1 mg/ Ozanimod 1 mg	230	138 (60.0)								
Patients with a clinical response at week 52, n (%): 4-component Mayo analysis	Ozanimod 1 mg/ Placebo	227	97 (42.7)	20.5	11.6-29.3	NR	OR, 2.370	1.615-3.477	< 0.0001		
	Ozanimod 1 mg/ Ozanimod 1 mg	230	145 (63.0)								
Patients with endoscopic improvement at week 52, n (%)	Ozanimod 1 mg/ Placebo	227	60 (26.4)	19.4	11.0-27.7	NR	OR, 2.476	1.650-3.716	< 0.0001[c]		
	Ozanimod 1 mg/ Ozanimod 1 mg	230	105 (45.7)								
Patients with maintenance of remission at week 52 in the subset of patients in remission at week 10, n/N (%)	Ozanimod 1 mg/ Placebo	75	22 (29.3)	23.9	9.1-38.6	NR	OR, 2.881	1.447-5.738	0.0025[c]		
	Ozanimod 1 mg/ Ozanimod 1 mg	79	41 (51.9)								

Outcome [a]	Study arm	N	Result	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
				Difference [b]	95% CI	*P* value	Difference	95% CI	*P* value		
Patients with corticosteroid-free remission at week 52, n (%)	Ozanimod 1 mg/ Placebo	227	38 (16.7)	15.2	7.8-22.6	NR	OR, 2.557	1.598-4.093	< 0.0001 [c]		
	Ozanimod 1 mg/ Ozanimod 1 mg	230	73 (31.7)								
Patients with mucosal healing at week 52, n (%)	Ozanimod 1 mg/ Placebo	227	32 (14.1)	15.6	8.2-22.9	NR	OR, 2.643	1.642-4.256	< 0.0001 [c]		
	Ozanimod 1 mg/ Ozanimod 1 mg	230	68 (29.6)								
Patients with durable clinical remission, n (%)	Ozanimod 1 mg/ Placebo	227	22 (9.7)	8.2	2.8-13.6	NR	OR, 2.646	1.384-5.061	0.003 [c]		
	Ozanimod 1 mg/ Ozanimod 1 mg	230	41 (17.8)								
Patients with durable clinical remission, n (%): 4-component Mayo analysis	Ozanimod 1 mg/ Placebo	227	13 (5.7)	10.4	5.3-15.5	NR	OR, 4.381	2.078-9.235	< 0.0001		
	Ozanimod 1 mg/ Ozanimod 1 mg	230	37 (16.1)								
Change in partial Mayo Score from baseline to week 52, LS mean (SE)	Ozanimod 1 mg/ Placebo	227	−4.3 (0.18)	−0.4	−0.9 to 0.0	NR	NA	NA	0.032		
	Ozanimod 1 mg/ Ozanimod 1 mg	230	−4.7 (0.15)								
Change in partial Mayo Score from baseline to week 52, LS mean (SE): 4-component Mayo analysis	Ozanimod 1 mg/ Placebo	227	−5.3 (0.25)	−0.8	−1.3 to −0.2	NR	NA	NA	0.008		
	Ozanimod 1 mg/ Ozanimod 1 mg	230	−6.1 (0.21)								
Patients with histologic remission at week 52, n (%)	Ozanimod 1 mg/ Placebo	227	37 (16.3)	17.3	9.6-24.9	NR	OR, 2.684	1.703-4.229	< 0.001		
	Ozanimod 1 mg/ Ozanimod 1 mg	230	77 (33.5)								

Outcome [a]	Study arm	N	Result	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
				Difference [b]	95% CI	*P* value	Difference	95% CI	*P* value		
Patients in clinical remission at 52 weeks while off corticosteroids for any length of time, n (%)	Ozanimod 1 mg/Placebo	227	38 (16.7)	15.2	7.8-22.6	NR	OR, 2.557	1.598-4.093	< 0.0001		
	Ozanimod 1 mg/ Ozanimod 1 mg	230	73 (31.7)								
Patients in clinical remission, at week 52, n/N (%): No previous anti-TNF therapy	Ozanimod 1 mg/ Placebo	158	35 (22.2)	18.5	8.6-28.3	NR	OR, 2.54	1.52-4.24	0.0003		
	Ozanimod 1 mg/ Ozanimod 1 mg	154	63 (40.9)								
Patients in clinical remission, at week 52, n/N (%): Previous anti-TNF therapy	Ozanimod 1 mg/ Placebo	69	7 (10.1)	18.4	6.2-30.6	NR	OR, 3.74	1.44-9.71	0.0053		
	Ozanimod 1 mg/ Ozanimod 1 mg	76	22 (28.9)								
Patients in clinical remission, at week 52, n/N (%): No previous anti-TNF therapy, 4-component Mayo analysis	Ozanimod 1 mg/ Placebo	158	34 (21.5)	19.3	9.4-29.1	NR	OR, 2.601	1.565-4.322	0.0002		
	Ozanimod 1 mg/ Ozanimod 1 mg	154	63 (40.9)								
Patients in clinical remission, at week 52, n/N (%): Previous anti-TNF therapy, 4-component Mayo analysis	Ozanimod 1 mg/ Placebo	69	8 (11.6)	20.7	8.0-33.3	NR	OR, 3.927	1.580-9.762	0.0025		
	Ozanimod 1 mg/ Ozanimod 1 mg	76	25 (32.9)								
Patients with a clinical response, at week 52, n/N (%): No previous anti-TNF therapy	Ozanimod 1 mg/ Placebo	158	76 (48.1)	14.0	3.3-24.8	NR	OR, 1.80	1.14-2.85	0.0119		
	Ozanimod 1 mg/ Ozanimod 1 mg	154	96 (62.3)								
Patients with a clinical response, at week 52, n/N (%): Previous anti-TNF therapy	Ozanimod 1 mg/ Placebo	69	17 (24.6)	30.4	15.8-45.1	NR	OR, 4.15	1.96-8.78	0.0002		
	Ozanimod 1 mg/ Ozanimod 1 mg	76	42 (55.3)								

Outcome [a]	Study arm	N	Result	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
				Difference [b]	95% CI	*P* value	Difference	95% CI	*P* value		
Patients with a clinical response, at week 52, n/N (%): No previous anti-TNF therapy, 4-component Mayo analysis	Ozanimod 1 mg/ Placebo	158	79 (50.0)	14.1	3.4-24.9	NR	OR, 1.810	1.144-2.864	0.0112		
	Ozanimod 1 mg/ Ozanimod 1 mg	154	99 (64.3)								
Patients with a clinical response, at week 52, n/N (%): Previous anti-TNF therapy, 4-component Mayo analysis	Ozanimod 1 mg/ Placebo	69	18(26.1)	34.3	19.4-49.1	NR	OR, 4.594	2.209-9.551	< 0.001		
	Ozanimod 1 mg/ Ozanimod 1 mg	76	46 (60.5)								
Patients with endoscopic improvement at week 52, n/N (%): No previous anti-TNF therapy	Ozanimod 1 mg/ Placebo	158	48 (30.4)	19.4	8.9-29.8	NR	OR, 2.35	1.46-3.77	< 0.001		
	Ozanimod 1 mg/ Ozanimod 1 mg	154	77/154 (50.0)								
Patients with endoscopic improvement at week 52, n/N (%): Previous anti-TNF therapy	Ozanimod 1 mg/ Placebo	69	12/69 (17.4)	18.9	5.3-32.4	NR	OR, 2.93	1.30-6.61	0.009		
	Ozanimod 1 mg/ Ozanimod 1 mg	76	28/76 (36.8)								
Patients with mucosal healing at week 52, n/N (%): No previous anti-TNF therapy	Ozanimod 1 mg/ Placebo	158	28/158 (17.7)	15.3	5.8-24.7	NR	OR, 2.32	1.36-3.96	0.002		
	Ozanimod 1 mg/ Ozanimod 1 mg	154	51/154 (33.1)								
Patients with mucosal healing at week 52, n/N (%): Previous anti-TNF therapy	Ozanimod 1 mg/ Placebo	69	4/69 (5.8)	16.2	5.5-27.0	NR	OR, 4.78	1.48-15.44	0.005		
	Ozanimod 1 mg/ Ozanimod 1 mg	76	17/76 (22.4)								
Patients with durable clinical remission, n (%): No previous anti-TNF therapy, 4-component Mayo analysis	Ozanimod 1 mg/ Placebo	158	11 (7.0)	11.7	5.0-18.4	NR	OR, 4.055	1.792-9.178	< 0.001		
	Ozanimod 1 mg/ Ozanimod 1 mg	154	29 (18.8)								

Outcome [a]	Study arm	N	Result	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
				Difference [b]	95% CI	*P* value	Difference	95% CI	*P* value		
Patients with durable clinical remission, n (%): Previous anti-TNF therapy, 4-component Mayo analysis	Ozanimod 1 mg/ Placebo	69	2 (2.9)	7.2	1.0-14.3	NR	OR, 5.674	0.869-37.038	0.057		
	Ozanimod 1 mg/ Ozanimod 1 mg	76	8 (10.5)								

CI = confidence interval; ITT = intention-to-treat; LS = least squares; NA = not applicable; NR = not reported; NRI = non-responder imputation; OR = odds ratio; SE = standard error; TNF = tumour necrosis factor.

[a] Clinical remission and clinical response are based on the 3-component Mayo Score unless otherwise specified.

[b] Treatment differences are in terms of the difference in proportions (percentage points) for proportion-based endpoints and in terms of LS mean difference for changes from baseline.

[c] Statistically significant according to the closed, hierarchical testing procedure used to control the overall type I error rate.

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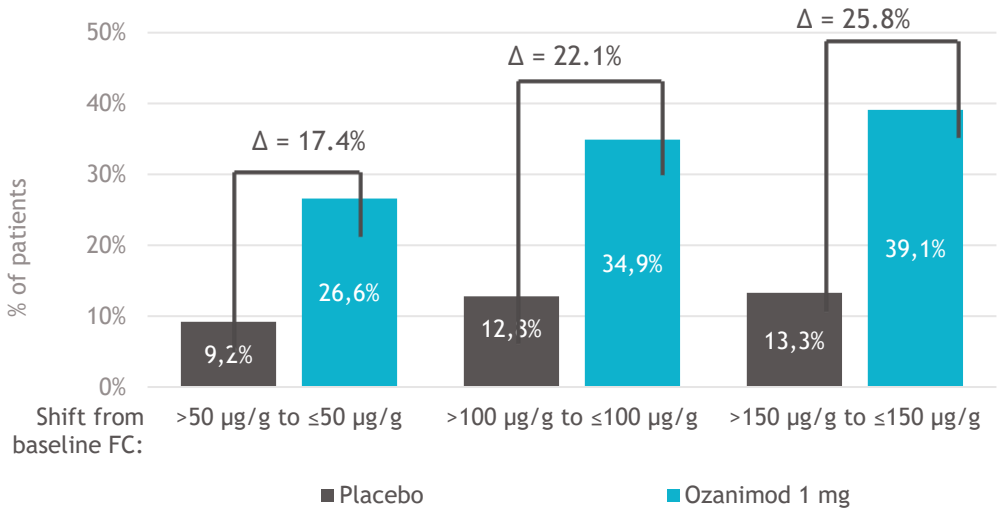
Appendix D.3.3 Biomarker analysis

Faecal calprotectin is a biomarker useful in monitoring UC disease activity within a range of 0 to > 1,000 µg/g, wherein < 50 to < 250 µg/g is a threshold for remission.[45] The change in faecal calprotectin from baseline to week 10 was significantly greater with ozanimod 1 mg than it was with placebo (−470.2 µg/g vs. 21.1 µg/g; *P* = 0.002 (Figure D-12); this change was also significant at week 52 (−1,575.1 µg/g vs. −463.3 µg/g; *P* = 0.019) (Figure D-13).[24]

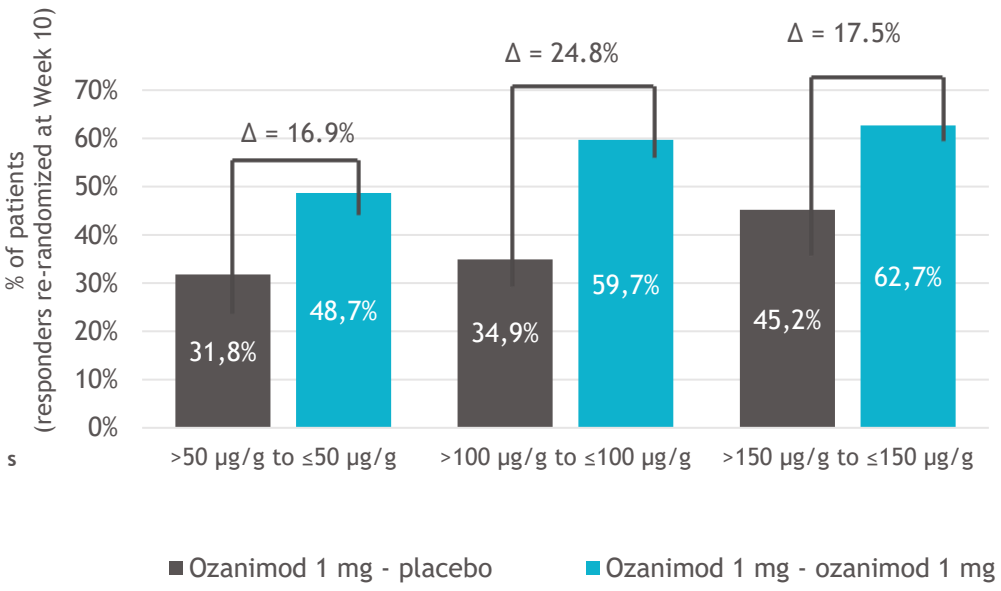
Figure D-12. TRUE NORTH: change from baseline faecal calprotectin to week 10



FC = faecal calprotectin.

Source: BMS data on file (2020)[24]

Figure D-13. **TRUE NORTH: change from baseline faecal calprotectin to week 52**

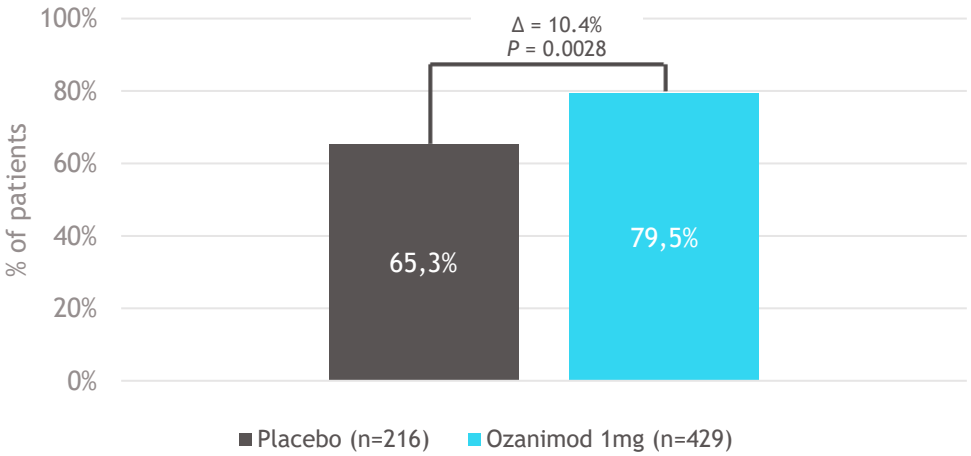


FC = faecal calprotectin.

Source: BMS data on file (2020)[24]

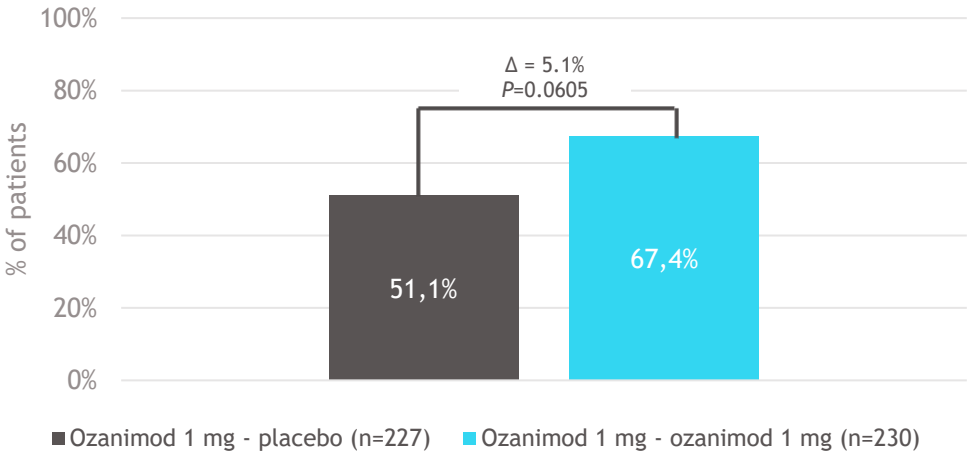
C-reactive protein (CRP) is also a biomarker used in monitoring UC disease activity within a range of 0 to > 200 mg/L, wherein ≤ 5 mg/L is a threshold for remission.[45] A reduction in plasma CRP has been correlated with treatment response, and CRP weakly correlates with endoscopic disease activity.[45] The percentage of patients with a CRP < 10 mg/L during induction at week 10 was significantly greater with ozanimod 1 mg than it was with placebo (79.5% vs. 65.3%; *P* = 0.0028) (Figure D-14). The proportion of patients with a CRP < 10 mg/L at week 52 was not statistically significantly different for those in the ozanimod/ozanimod arm versus those in the ozanimod/placebo arm (67.4% vs. 51.1%; *P* = 0.0605) (Figure D-15).[24]

Figure D-14. **TRUE NORTH: percentage of patients with C-reactive protein < 10 mg/L at week 10**



Source: BMS data on file (2020)[46]

Figure D-15. TRUE NORTH: percentage of patients with C-reactive protein < 10 mg/L at week 52

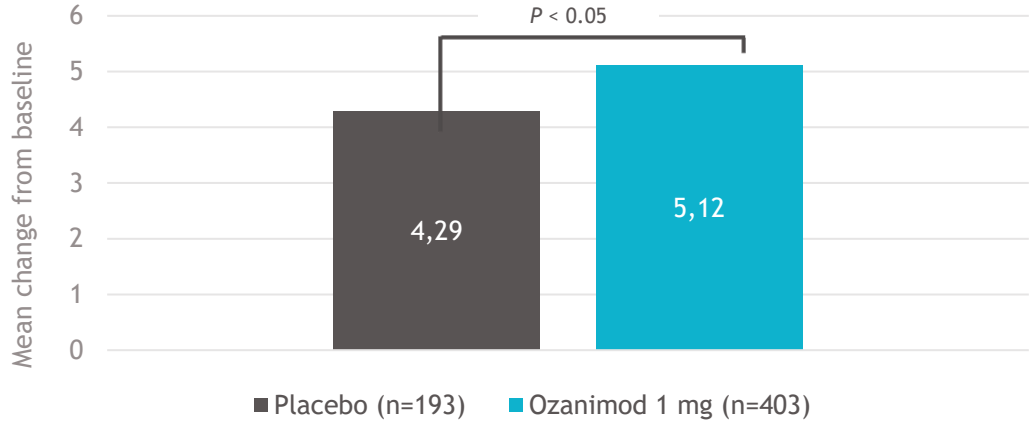


Source: BMS data on file (2020)[46]

Appendix D.3.4 TRUE NORTH: health-related quality of life

The SF-36 MCS is composed of scales measuring vitality, social functioning, role-emotional, and emotional well-being. There was no significant difference in the mean change from baseline in the SF-36 MCS scores for patients receiving ozanimod and those who received placebo during the induction period (Figure D-16).

Figure D-16. TRUE NORTH: mean change from baseline in SF-36 Mental Component Summary score at week 10



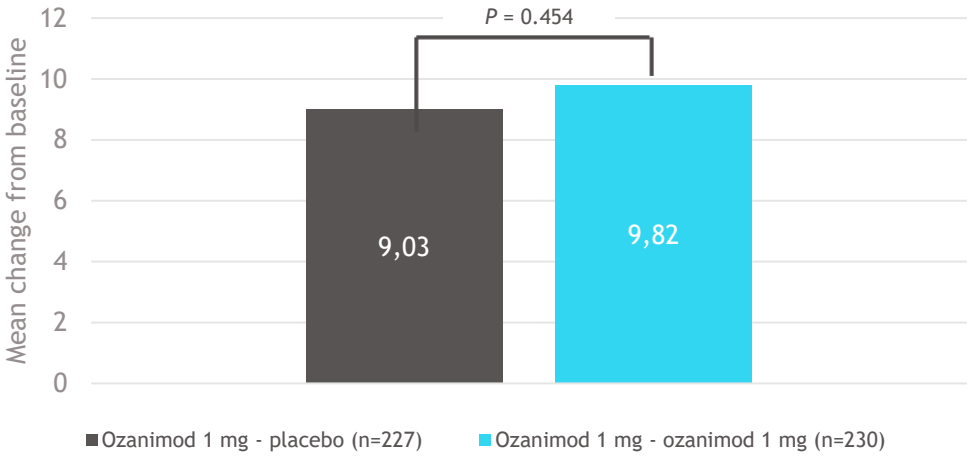
SF-36 = SF-36 Health Survey.

Source: BMS data on file (2020)[47]

Although the change from baseline in the SF-36 MCS score for ozanimod 1 mg was numerically higher than placebo ($P < 0.05$), there was no difference in the proportion of patients with a ≥ 5-point improvement in SF-36 MCS score from baseline (nominal $P = 0.105$) relative to patients in the placebo arm.

At week 52, there was no significant difference in SF-36 MCS scores between patients in the ozanimod/ozanimod arm and the ozanimod/placebo arm (nominal $P = 0.454$) (Figure D-17). There was no difference between the treatment arms in the proportion of patients who achieved an minimum clinically important difference in the SF-36 MCS.[24,46]

Figure D-17. TRUE NORTH: mean change from baseline in SF-36 Mental Component Summary score at week 52



SF-36 = SF-36 Health Survey.

Source: BMS data on file (2020)[46]

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Appendix E. Safety data for intervention and comparator(s)

Appendix E.1 TRUE NORTH

Appendix E.1.1 TRUE NORTH: treatment-emergent adverse events during the induction period

Analysis of treatment-emergent adverse events (TEAEs) by system organ class during the induction period identified some of the most frequently occurring TEAEs as those involving infections and infestations, gastrointestinal disorders, and general disorders and administration site conditions (Table E-1). In the induction period, analysis of TEAEs by preferred term identified some of the most common TEAEs as anaemia, nasopharyngitis, and headache (Table E-2). During the induction period, adverse events of special interest (AESIs) most commonly included alanine aminotransferase (ALT) increased, hepatic enzyme increased, and aspartate aminotransferase increased (Table E-3). Although rarely necessary, extended cardiac monitoring results are likewise illustrated from the induction period (Table E-4). The mean heart rate over time in the first 6 hours after dose 1 is shown in Figure E-1.

Table E-1. TRUE NORTH: treatment-emergent adverse events by system organ class reported by ≥ 5% of patients in any treatment group—induction period

	Cohort 1		Cohort 2
System organ class, n (%)	Placebo (n = 216)	Ozanimod 1 mg (n = 429)	Ozanimod 1 mg (n = 367)
Patients with ≥ 1 TEAE	82 (38.0)	172 (40.1)	146 (39.8)
Infections and infestations	25 (11.6)	46 (10.7)	46 (12.5)
Gastrointestinal disorders	20 (9.3)	41 (9.6)	38 (10.4)
General disorders and administration site conditions	10 (4.6)	32 (7.5)	9 (2.5)
Nervous system disorders	11 (5.1)	30 (7.0)	16 (4.4)
Investigations	7 (3.2)	25 (5.8)	21 (5.7)
Musculoskeletal and connective tissue disorders	11 (5.1)	25 (5.8)	11 (3.0)
Blood and lymphatic system disorders	13 (6.0)	22 (5.1)	17 (4.6)

TEAE = treatment-emergent adverse event.

Note: Safety population.

Source: BMS data on file (2020)[24]

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Table E-2. TRUE NORTH: treatment-emergent adverse events by preferred term reported by ≥ 2% of patients in any treatment group—induction period

	Cohort 1		Cohort 2
Preferred term, n (%)	Placebo (n = 216)	Ozanimod 1 mg (n = 429)	Ozanimod 1 mg (n = 367)
Patients with ≥ 1 TEAE	82 (38.0)	172 (40.1)	146 (39.8)
Anaemia	12 (5.6)	18 (4.2)	16 (4.4)
Nasopharyngitis	3 (1.4)	15 (3.5)	10 (2.7)
Headache	4 (1.9)	14 (3.3)	10 (2.7)
Nausea	3 (1.4)	12 (2.8)	3 (0.8)
ALT increased	0	11 (2.6)	6 (1.6)
Pyrexia	3 (1.4)	11 (2.6)	2 (0.5)
Arthralgia	3 (1.4)	10 (2.3)	5 (1.4)
Colitis ulcerative	5 (2.3)	6 (1.4)	9 (2.5)
Upper respiratory tract infection	1 (0.5)	5 (1.2)	8 (2.2)

ALT = alanine aminotransferase; MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event.

Note: Safety population. TEAEs were coded using MedDRA version 22.1.

Source: BMS data on file (2020)[24]

Table E-3. TRUE NORTH: adverse events of special interest—induction period

	Cohort 1		Cohort 2
AESI category[a] Preferred term, n (%)	Placebo (n = 216)	Ozanimod 1 mg (n = 429)	Ozanimod 1 mg (n = 367)
Any AESI (investigator-coded or sponsor-identified)	1 (0.5)	14 (3.3)	16 (4.4)
Hepatic effects			
ALT increased	0	2 (0.5)	1 (0.3)
Hepatic enzyme increased	0	2 (0.5)	0
AST increased	0	1 (0.2)	0
LFT increased	0	1 (0.2)	0
Transaminases increased*	0	1 (0.2)	0
Infection			
Herpes zoster	0	2 (0.5)	1 (0.3)
Appendicitis*	0	1 (0.2)	2 (0.5)
Nasopharyngitis*	0	1 (0.2)	0
Otitis externa*	0	1 (0.2)	0
Pyelonephritis*	0	1 (0.2)	0
Vestibular neuronitis*	0	1 (0.2)	0
Bronchitis*	1 (0.5)	0	0
Gastroenteritis*	0	0	1 (0.3)
Pneumonia influenzal*	0	0	1 (0.3)
Respiratory syncytial virus text positive*	0	0	1 (0.3)
Urinary tract infection*	0	0	1 (0.3)

AESI category[a] Preferred term, n (%)	Cohort 1 Placebo (n = 216)	Cohort 1 Ozanimod 1 mg (n = 429)	Cohort 2 Ozanimod 1 mg (n = 367)
Macular oedema	0	1 (0.2)	1 (0.3)
Pulmonary			
Dyspnoea	0	1 (0.2)	0
Chronic obstructive pulmonary disease	0	0	1 (0.3)
Forced expiratory volume decreased	0	0	1 (0.3)
Cardiac			
Bradycardia	0	0	3 (0.8)
Sinus bradycardia	0	0	1 (0.3)
Malignancy			
Basal cell carcinoma	0	0	1 (0.3)
Cervix carcinoma stage	0	0	1 (0.3)

* Asterisk denotes AESI identified by sponsor review of TEAE reports.

AE = adverse event; AESI = adverse events of special interest; ALT = alanine aminotransferase; AST = aspartate aminotransferase; AV = atrioventricular; CRF = case report form; IP = induction period; LFT = liver function test; MP = maintenance period; TEAE = treatment-emergent adverse event.

Note: Safety population. A TEAE is defined as any AE with date of first onset or date of worsening in severity on or after the date of first IP dose, excluding those with onset on or after the date of first MP dose. Subjects with multiple events reported for the same summary level will be counted only once. Percentages are based upon the number of subjects in the safety population. AESI categories are sorted by decreasing frequency in the cohort 1 ozanimod 1 mg group.

[a] AESIs include bradycardia, heart conduction abnormalities (second-degree and higher AV block), macular oedema, malignancy, serious or opportunistic infection, pulmonary effects, and hepatic effects and have been adjudicated by the safety review team per the safety management plan. Sponsor designated AESIs from AESI-Disposition CRF not categorised by the investigator will show up as "Additional Event of Interest Defined by Sponsor."

Source: BMS data on file (2020)[24]

Table E-4. TRUE NORTH: extended cardiac monitoring summary—induction period

Parameter[a], n (%)	Cohort 1 Placebo (n = 216)	Cohort 1 Ozanimod 1 mg (n = 429)	Cohort 2 Ozanimod 1 mg (n = 367)
Patient received protocol-mandated extended monitoring after 6 hours	3 (1.4)	15 (3.5)	11 (3.0)
Primary reason for extended monitoring			
HR < 45 bpm at hour 6	0	0	0
HR lowest value at hour 6 (and below baseline)	2 (0.9)	9 (2.1)	7 (1.9)
New onset of AV block (second-degree or higher)	0	0	0
Prolonged QTcF interval (> 450 msec males, > 470 msec females)	1 (0.5)	2 (0.5)	2 (0.5)
Symptomatic bradycardia	0	0	0
Other[b]	0	4 (0.9)	2 (0.5)
Patient required overnight monitoring	0	0	1 (0.3)
Discharged but returned for monitoring on day 2	1 (0.5)	1 (0.2)	0

AV = atrioventricular; HR = heart rate; QTcF = QT corrected by Fridericia's formula.

Note: Safety population.

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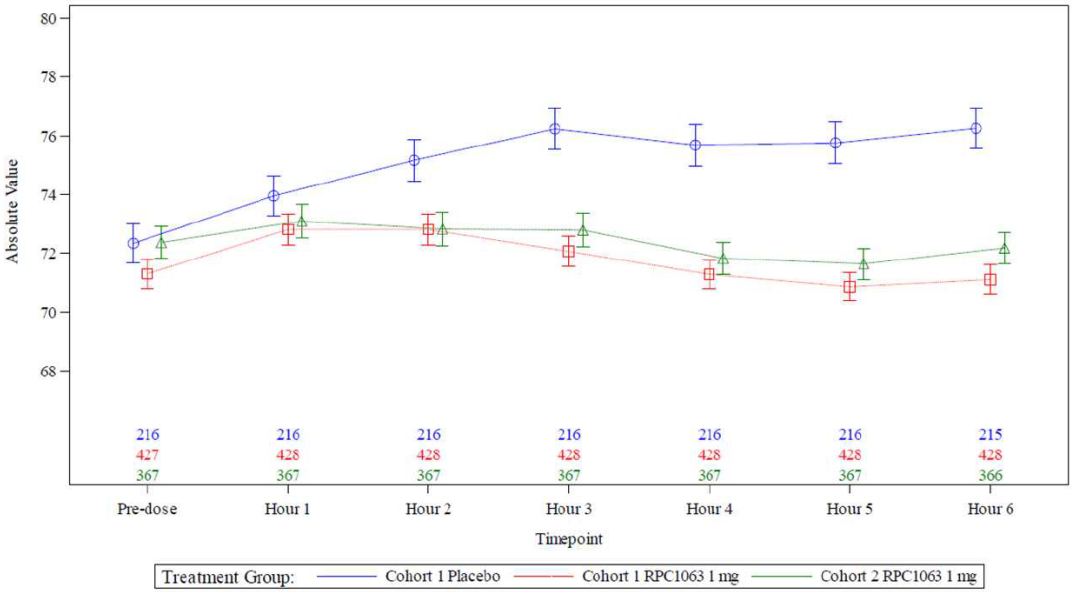
[a] All parameters are based on monitoring procedures in accordance with the protocol.

[b] Other reasons for extended monitoring were primarily investigator decision not due to adverse effect.

Source: BMS data on file (2020)[24]

Figure E-1. TRUE NORTH: mean heart rate during 6 hours after first dose—induction period



Notes: Safety population.

Error bars denote standard error.

Key: circle = cohort 1 placebo; square = cohort 1 ozanimod 1 mg; RPC-1063 = ozanimod; triangle = cohort 2 ozanimod 1 mg.

Source: BMS data on file (2020)[24]

Appendix E.1.2 TRUE NORTH: treatment-emergent adverse events during the maintenance period

During the maintenance period, identification TEAEs by system organ class during the maintenance period labelled some of the most common TEAEs as those involving infections and infestations, investigations, and gastrointestinal disorders (Table E-5). Descriptions of TEAEs by preferred term during the maintenance period identified some of the most common as ALT increased, headache, and arthralgia (Table E-6). A description of AESIs during the maintenance period found some of the most frequently occurring categorised as infections, hepatic effects, and malignancies (Table E-7). The mean heart rate through week 52 is shown in Figure E-2.

Table E-5. TRUE NORTH: incidence of treatment-emergent adverse events by system organ class reported for ≥ 5% of patients in any treatment group—maintenance period

		Rerandomised patients	
System organ class, n (%)	Placebo (n = 69)	Ozanimod 1 mg/ placebo (n = 227)	Ozanimod 1 mg/ ozanimod 1 mg (n = 230)
Patients with ≥ 1 TEAE	27 (39.1)	83 (36.6)	113 (49.1)
Infections and infestations	12 (17.4)	27 (11.9)	53 (23.0)
Investigations	4 (5.8)	9 (4.0)	26 (11.3)
Gastrointestinal disorders	9 (13.0)	25 (11.0)	27 (11.7)

System organ class, n (%)	Placebo (n = 69)	Rerandomised patients: Ozanimod 1 mg/ placebo (n = 227)	Rerandomised patients: Ozanimod 1 mg/ ozanimod 1 mg (n = 230)
General disorders and administration site conditions	1 (1.4)	4 (1.8)	16 (7.0)
Musculoskeletal and connective tissue disorders	3 (4.3)	15 (6.6)	14 (6.1)
Nervous system disorders	0	5 (2.2)	14 (6.1)
Skin and subcutaneous tissue disorders	3 (4.3)	11 (4.8)	13 (5.7)

TEAE = treatment-emergent adverse event.

Note: Safety population.

Source: BMS data on file (2020)[24]

Table E-6. TRUE NORTH: incidence of treatment-emergent adverse events by preferred term reported for ≥ 2% of patients in any treatment group—maintenance period

Preferred term, n (%)	Placebo (n = 69)	Rerandomised patients: Ozanimod 1 mg/ placebo (n = 227)	Rerandomised patients: Ozanimod 1 mg/ ozanimod 1 mg (n = 230)
Patients with ≥ 1 TEAE	27 (39.1)	83 (36.6)	113 (49.1)
ALT increased	0	1 (0.4)	11 (4.8)
Headache	0	1 (0.4)	8 (3.5)
Arthralgia	2 (2.9)	6 (2.6)	7 (3.0)
Gamma-glutamyltransferase increased	0	1 (0.4)	7 (3.0)
Nasopharyngitis	3 (4.3)	4 (1.8)	7 (3.0)
Oedema peripheral	0	0	6 (2.6)
Herpes zoster	0	1 (0.4)	5 (2.2)
Upper respiratory tract infection	3 (4.3)	4 (1.8)	2 (0.9)
Vomiting	2 (2.9)	2 (0.9)	2 (0.9)
Abdominal pain	2 (2.9)	1 (0.4)	1 (0.4)
Colitis ulcerative	1 (1.4)	10 (4.4)	1 (0.4)
Constipation	3 (4.3)	1 (0.4)	1 (0.4)

* Asterisk denotes AESI identified by sponsor review of TEAE reports

AESI = adverse events of special interest; ALT = alanine aminotransferase; MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event.

Note: Safety population. TEAEs were coded using MedDRA version 22.1. Preferred terms are listed in order of decreasing frequency in the ozanimod 1 mg – ozanimod 1 mg treatment group.

Source: BMS data on file (2020)[24]

Table E-7. TRUE NORTH: adverse events of special interest—maintenance period

AESI category[a] Preferred term, n (%)	Placebo (n = 69)	Rerandomised patients: Ozanimod 1 mg/ placebo (n = 227)	Rerandomised patients: Ozanimod 1 mg/ ozanimod 1 mg (n = 230)
Any AESI (Investigator-coded or sponsor-identified)	1 (1.4)	7 (3.1)	11 (4.8)

AESI category[a] Preferred term, n (%)	Placebo (n = 69)	Rerandomised patients Ozanimod 1 mg/ placebo (n = 227)	Rerandomised patients Ozanimod 1 mg/ ozanimod 1 mg (n = 230)
Infection			
Herpes zoster	0	0	4 (1.7)
Clostridium difficile infection	0	0	1 (0.4)
Complicated appendicitis	0	1 (0.4)	0
Gastroenteritis norovirus*	0	0	1 (0.4)
Appendicitis*	0	1 (0.4)	0
Complicated appendicitis*	0	1 (0.4)	0
Herpes Zoster*	0	1 (0.4)	0
Large intestine infection*	1 (1.4)	0	0
Measles*	0	1 (0.4)	0
Yersinia infection*	0	1 (0.4)	0
Hepatic effects			
ALT increased	0	0	1 (0.4)
LFT increased	0	0	1 (0.4)
Hepatitis	0	1 (0.4)	0
Blood bilirubin increased*	0	1 (0.4)	0
Malignancy			
Basal cell carcinoma	0	0	1 (0.4)
Rectal adenocarcinoma	0	0	1 (0.4)
Adenocarcinoma of colon	0	1 (0.4)	0
Breast cancer	0	1 (0.4)	0
Macular oedema	**0**	**0**	**1 (0.4)**
Pulmonary			
Asthma	0	0	1 (0.4)

* Asterisk denotes AESI identified by sponsor review of TEAE reports.

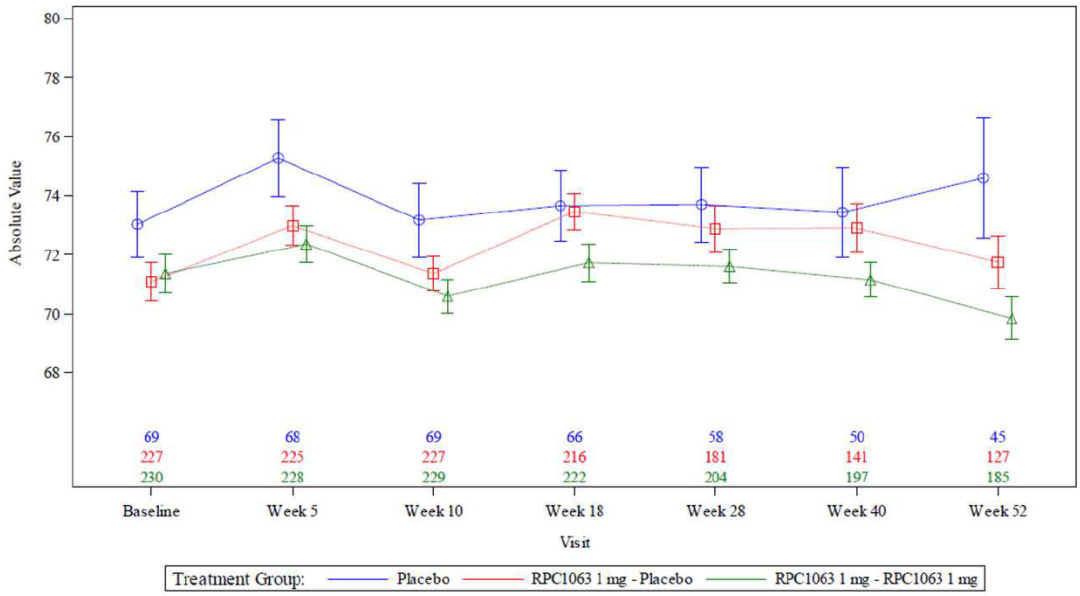
AE = adverse event; AESI = adverse events of special interest; ALT = alanine aminotransferase; AV = atrioventricular; CRF = case report form; LFT = liver function test; MP = maintenance phase; TEAE = treatment-emergent adverse event.

Note: Safety population. TEAEs were coded using MedDRA version 22.1. A TEAE is defined as any AE with date of first onset or date of worsening in severity on or after the date of first MP dose, excluding those with onset after the 90-day safety follow-up visit. Subjects with multiple events reported for the same summary level will be counted only once. Percentages are based upon the number of subjects in the safety population.

[a] AESIs include bradycardia, heart conduction abnormalities (second-degree and higher AV block), macular oedema, malignancy, serious or opportunistic infection, pulmonary effects, and hepatic effects and have been adjudicated by the safety review team per the safety management plan. Sponsor designated AESIs from AESI-Disposition CRF not categorised by the investigator will show up as "Additional Event of Interest Defined by Sponsor."

Source: BMS data on file (2020)[24]

Figure E-2. TRUE NORTH: mean heart rate by visit—maintenance period



Notes: Safety population.

Error bars denote standard error.

Key: circle = placebo; RPC-1063 = ozanimod; square = ozanimod 1 mg/placebo; triangle = ozanimod 1 mg/ozanimod 1 mg.

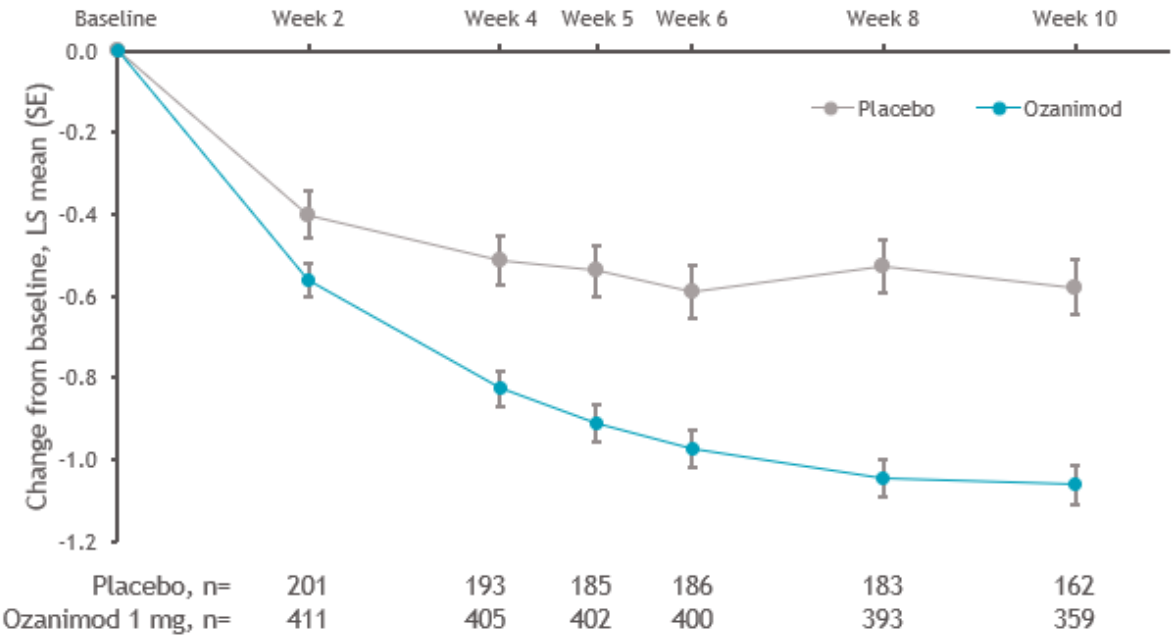
Source: BMS data on file (2020)[24]

During the maintenance period, there were no clinically significant changes in mean PR, QRS, or QT intervals across treatment groups, and there were also no notable differences in the proportions of patients with electrocardiogram outliers across treatment groups.[24]

Appendix E.1.3 TRUE NORTH: post hoc analyses (induction)

Post hoc analyses were conducted to investigate the timing during which the onset of action for ozanimod occurs. Rectal bleeding score reductions from baseline were statistically significantly greater in the ozanimod 1 mg arm versus the placebo arm starting at week 2, with increasing separation of ozanimod from placebo through week 10. From week 2 onwards, the ozanimod 1 mg arm had further reductions in the rectal bleeding score than the placebo arm, which generally held steady (Figure E-3).[23]

Figure E-3. TRUE NORTH: change in rectal bleeding score from baseline through week 10 (induction)



LS = least square; SE = standard error.

Note: Intention-to-treat population. Observed data.

Source: Sandborn et al. (2020)[23]

Appendix E.2 TOUCHSTONE

Appendix E.2.1 TOUCHSTONE: safety in main study

No important differences were observed between the treatment arms in terms of the percentages of adverse events (AEs) reported during the trial; moreover, the ozanimod treatment arms had fewer serious AEs and AEs leading to discontinuation than the placebo arm (Table E-8). Overall, the most common AEs were ulcerative colitis (UC) flare, anaemia, and headache.[11]

Table E-8. TOUCHSTONE main study: safety summary in induction and maintenance phases

Event	Placebo (n = 65)	Ozanimod 0.5 mg (n = 65)	Ozanimod 1 mg (n = 67)
Number of AEs	59	45	51
AEs, n (%)	26 (40)	26 (40)	26 (39)
SAEs, n (%)[a]	6 (9)	1 (2)	3 (4)
AEs leading to treatment discontinuation, n (%)	4 (6)	3 (5)	1 (1)
Cardiac AEs, n (%)	2 (3)	1 (2)	0
AEs occurring in ≥ 2 patients receiving ozanimod, n (%)			
UC flare	5 (8)	2 (3)	3 (4)
Anaemia	4 (6)	3 (5)	0
Headache	3 (5)	0	2 (3)
Nausea	2 (3)	1 (2)	2 (3)
Pyrexia	0	1 (2)	3 (4)

Event	Placebo (n = 65)	Ozanimod 0.5 mg (n = 65)	Ozanimod 1 mg (n = 67)
Arthralgia	1 (2)	1 (2)	2 (3)
ALT increased	0	1 (2)	3 (4)
Back pain	1 (2)	1 (2)	1 (1)
Rash	0	1 (2)	2 (3)
Abdominal pain	1 (2)	1 (2)	1 (1)
Vomiting	0	0	2 (3)
Orthostatic hypotension	0	2 (3)	0
AST increased	0	1 (2)	1 (1)
Hyperbilirubinemia	0	1 (2)	1 (1)
Insomnia	0	1 (2)	1 (1)
Nasopharyngitis	0	2 (3)	0
Proctalgia	0	1 (2)	1 (1)

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; SAE = serious adverse event; UC = ulcerative colitis.

[a] An SAE was defined as any untoward medical occurrence that resulted in death, was life-threatening (was associated with an immediate risk of death), required admission to a hospital or prolongation of existing hospitalisation, resulted in persistent or clinically significant disability or incapacity, or resulted in a congenital anomaly or birth defect. Events occurring in the placebo arm included worsening UC (n = 3), iron-deficiency anaemia (n = 1), herpes zoster infection and autoimmune haemolytic anaemia (n = 1), and jaundice (n = 1). In the ozanimod 0.5 mg arm, there was an event of hyperpyrexia (n = 1). In the ozanimod 1 mg arm, events included worsening UC (n = 2) and adenoma of the colon (n = 1).

Source: Sandborn et al. (2016)[11]

An increase in the ALT level to more than 3 times the upper limit of normal range occurred during treatment with ozanimod in 4 patients (0.5-mg dose, n = 1; 1-mg dose, n = 3). In addition, squamous cell carcinoma of the skin developed after treatment with ozanimod 1 mg in a patient who was previously treated with mercaptopurine for over 2 years.[11]

Appendix E.2.2 TOUCHSTONE: safety in open-label period

The mean (standard deviation) duration of exposure to ozanimod was 2.8 (1.85) patient-years. The most common TEAEs were UC, hypertension, upper respiratory tract infection, and gamma-glutamyl transferase increased (Table E-9). Serious TEAEs occurring in ≥ 2 patients were UC, anaemia, and ischaemic stroke (Table E-9).[48]

Table E-9. TOUCHSTONE OLP: safety summary

Event, n (%)	Ozanimod 1 mg (n = 170)
Any TEAEs	102 (60.0)
Patients experiencing ≥ 1 serious TEAE, n (%)	5 (9.1)
TEAEs leading to treatment discontinuation	17 (10.0)
TEAEs in ≥ 5% of patients in any group, n (%)	
UC	11 (6.5)
Hypertension	10 (5.9)
URTI	10 (5.9)

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Event, n (%)	Ozanimod 1 mg (n = 170)
Gamma-glutamyl transferase increased	9 (5.3)
Serious TEAEs occurring in ≥ 1 patients	
UC	6 (3.5)
Anaemia	2 (1.2)
Ischaemic stroke	2 (1.2)

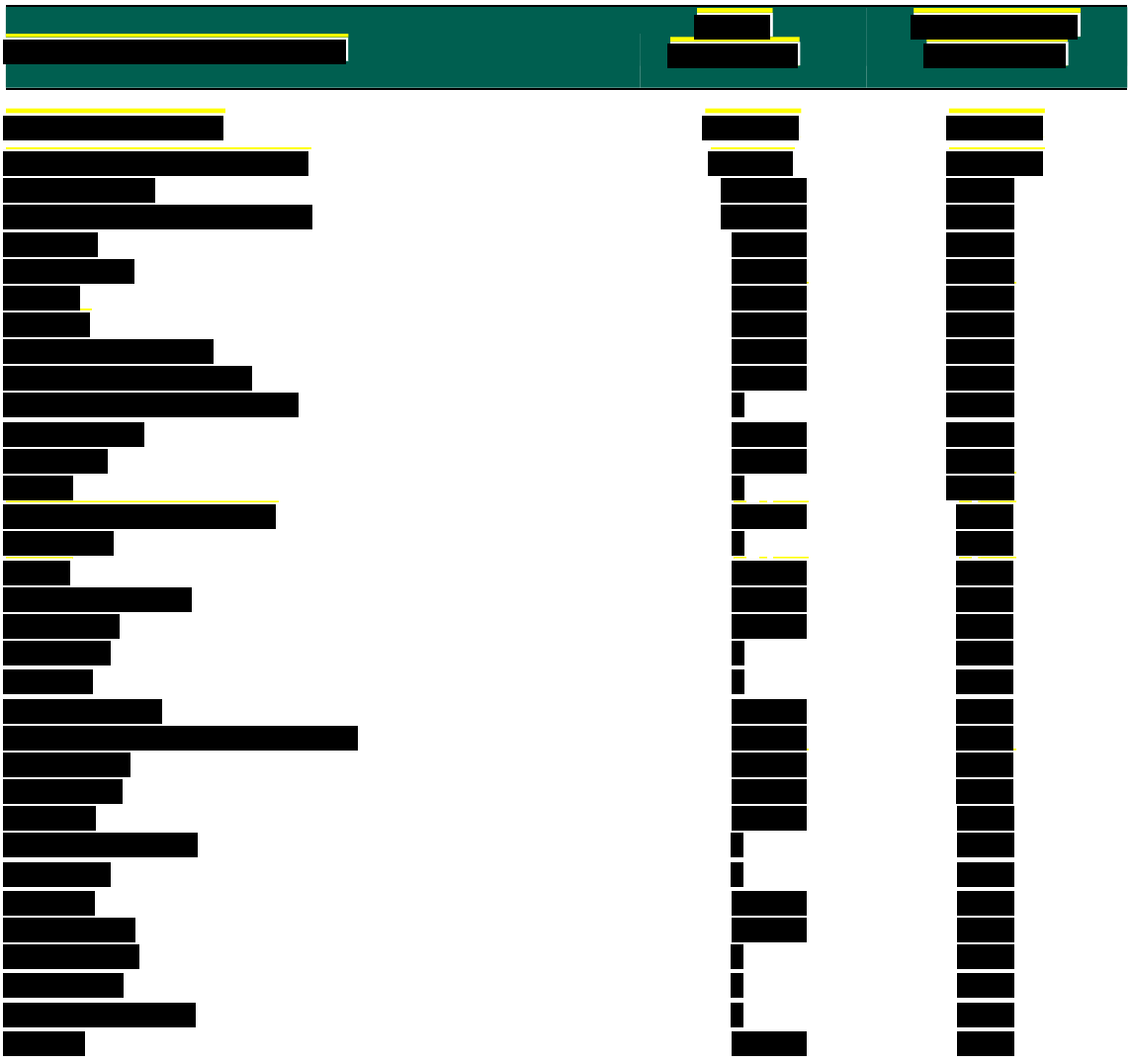
OLP = open-label treatment period; TEAE = treatment-emergent adverse event; UC = ulcerative colitis; URTI = upper respiratory tract infection.

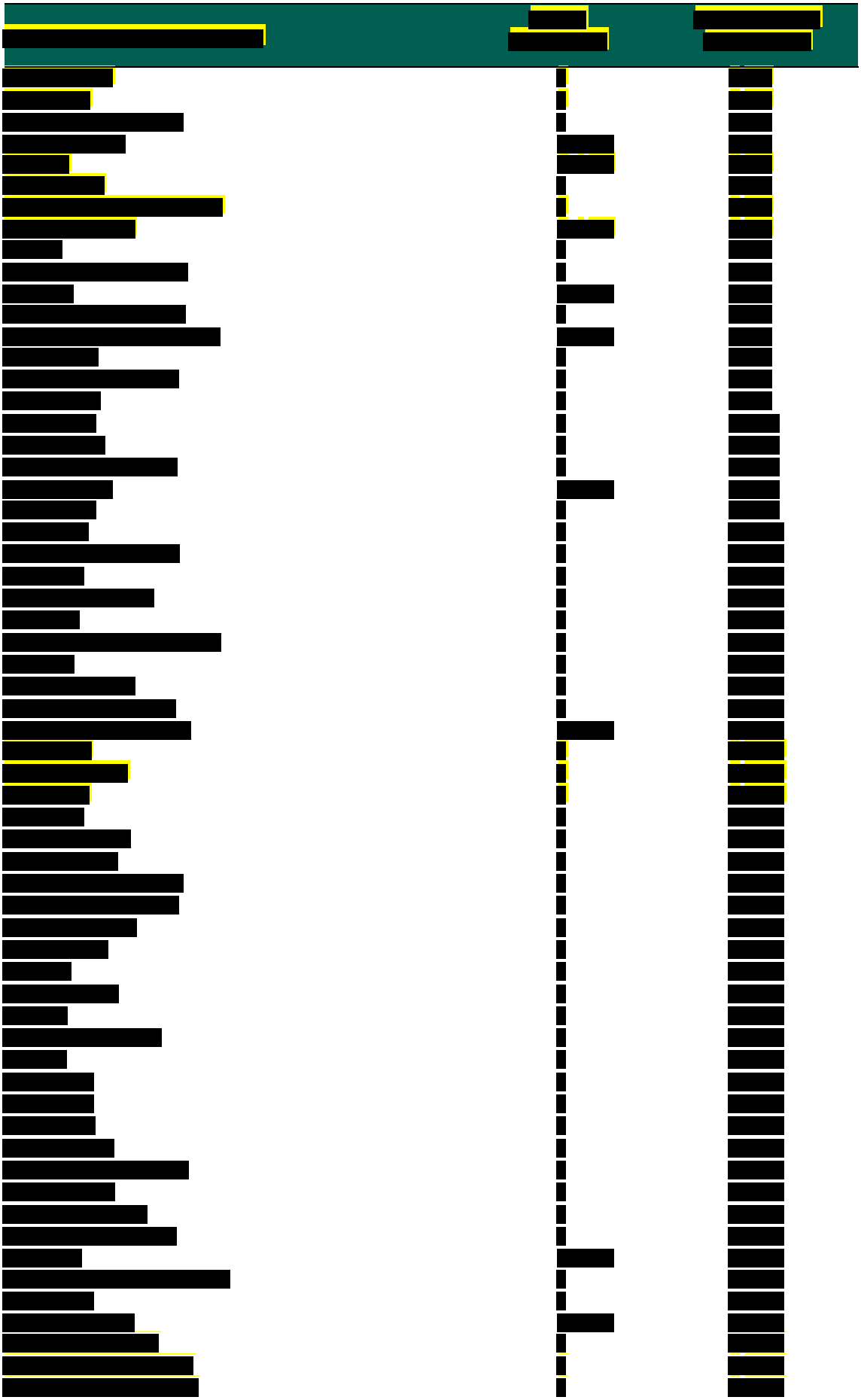
Source: Sandborn et al. (2020)[48]

Appendix E.3 Safety data for all phases of TRUE NORTH and TOUCHSTONE studies combined

All TEAEs that occurred in at least one patient in any phase of either of the clinical trilas are presented in Table E-10. An event was considered treatment-emergent (TEAEs) if the AE start date was on or after the date of the first dose of study drug or the start date was before Study Day 1 but the event worsened in severity on or after Study Day 1.

Table E-10. Incidence of TEAEs by system organ class and preferred term across all phases of the TRUE NORTH and TOUCHSTONE studies.





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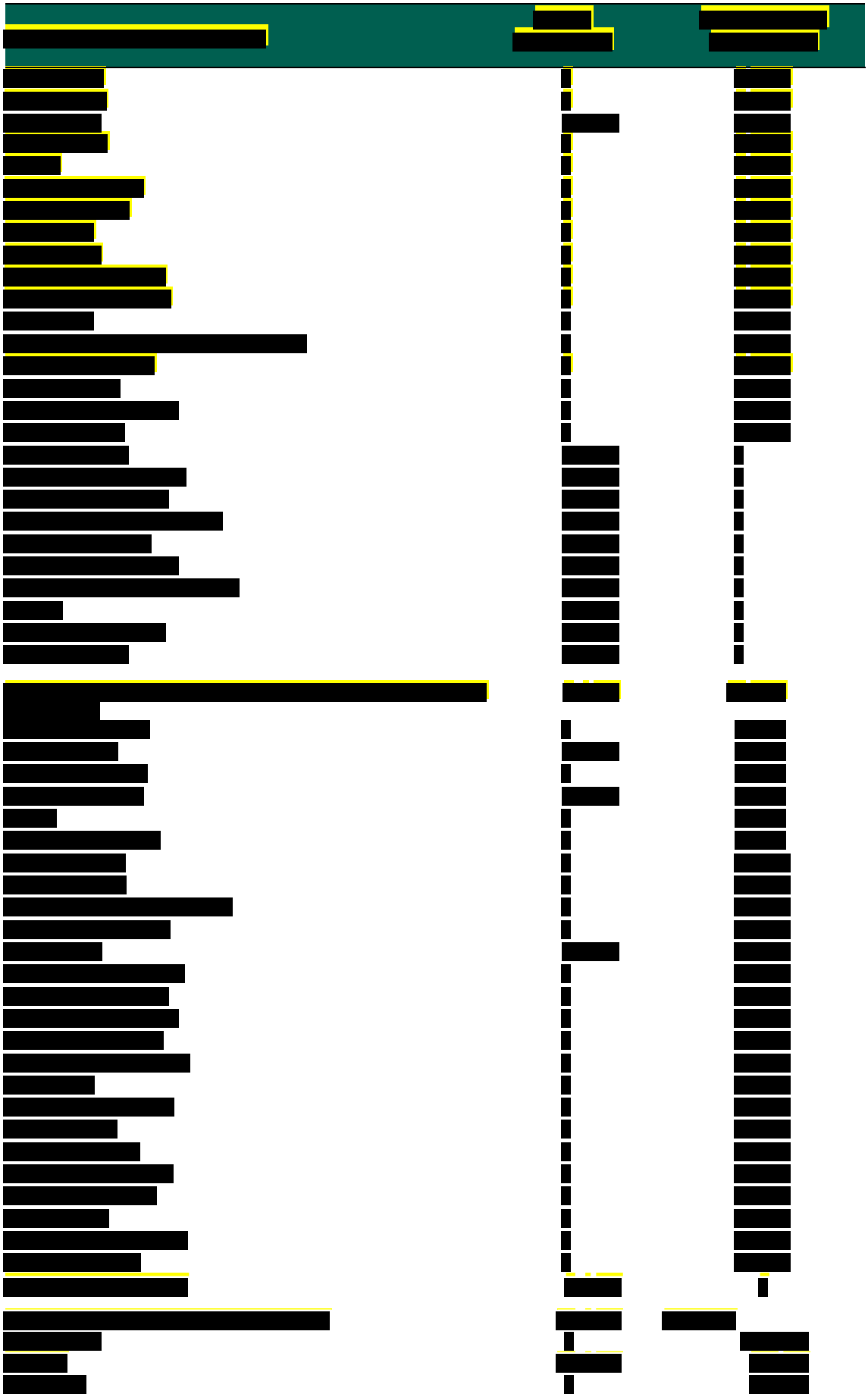

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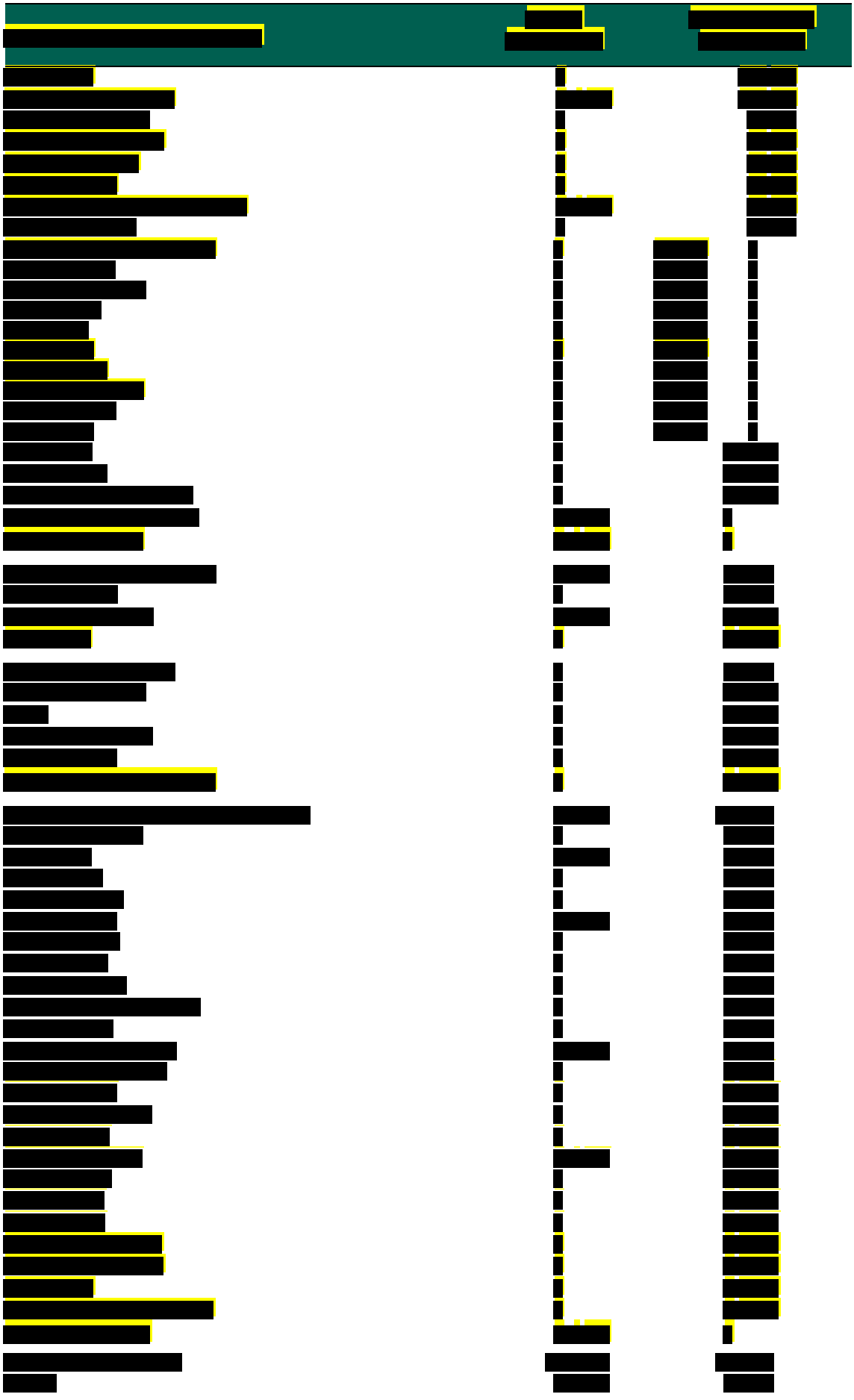

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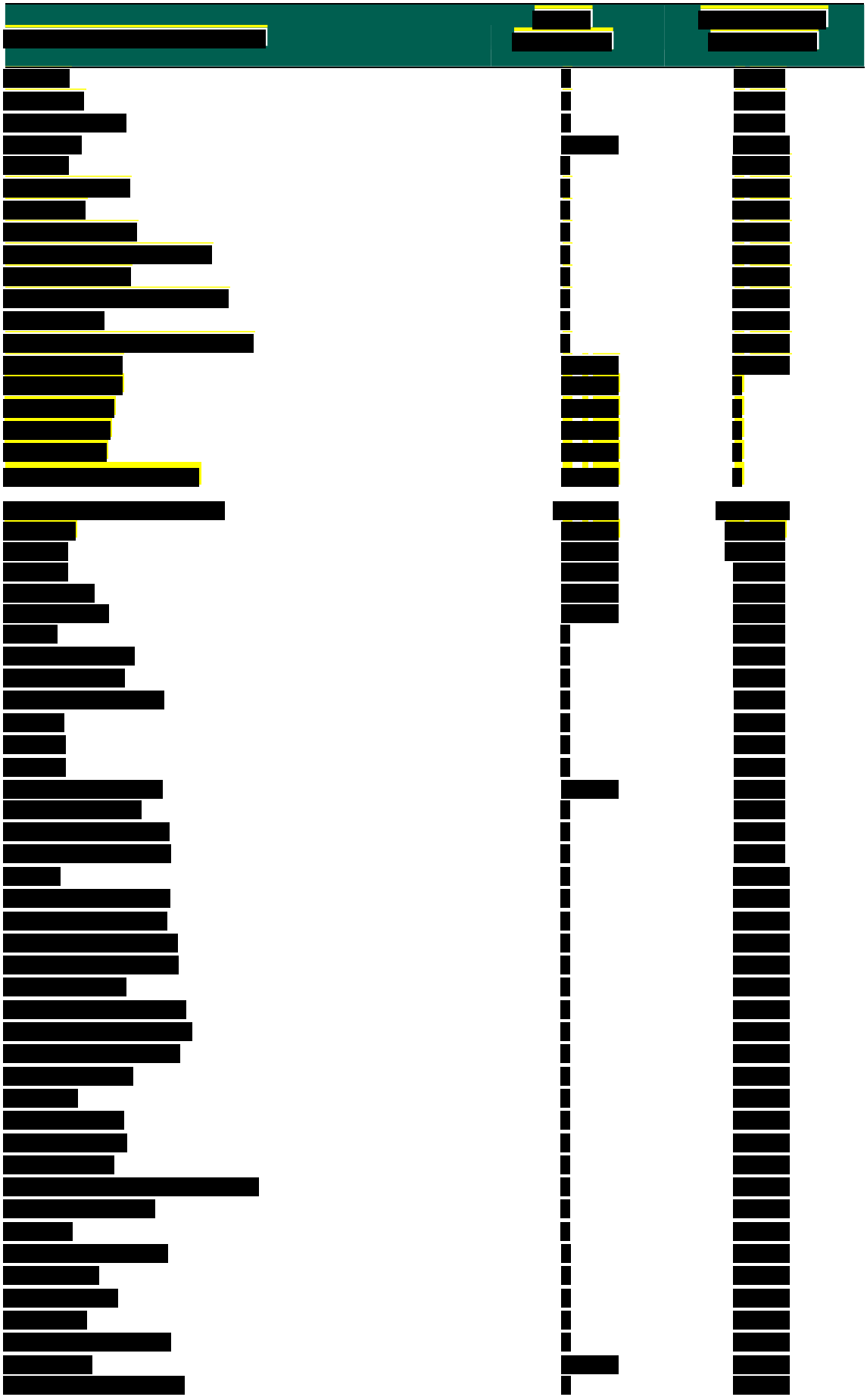

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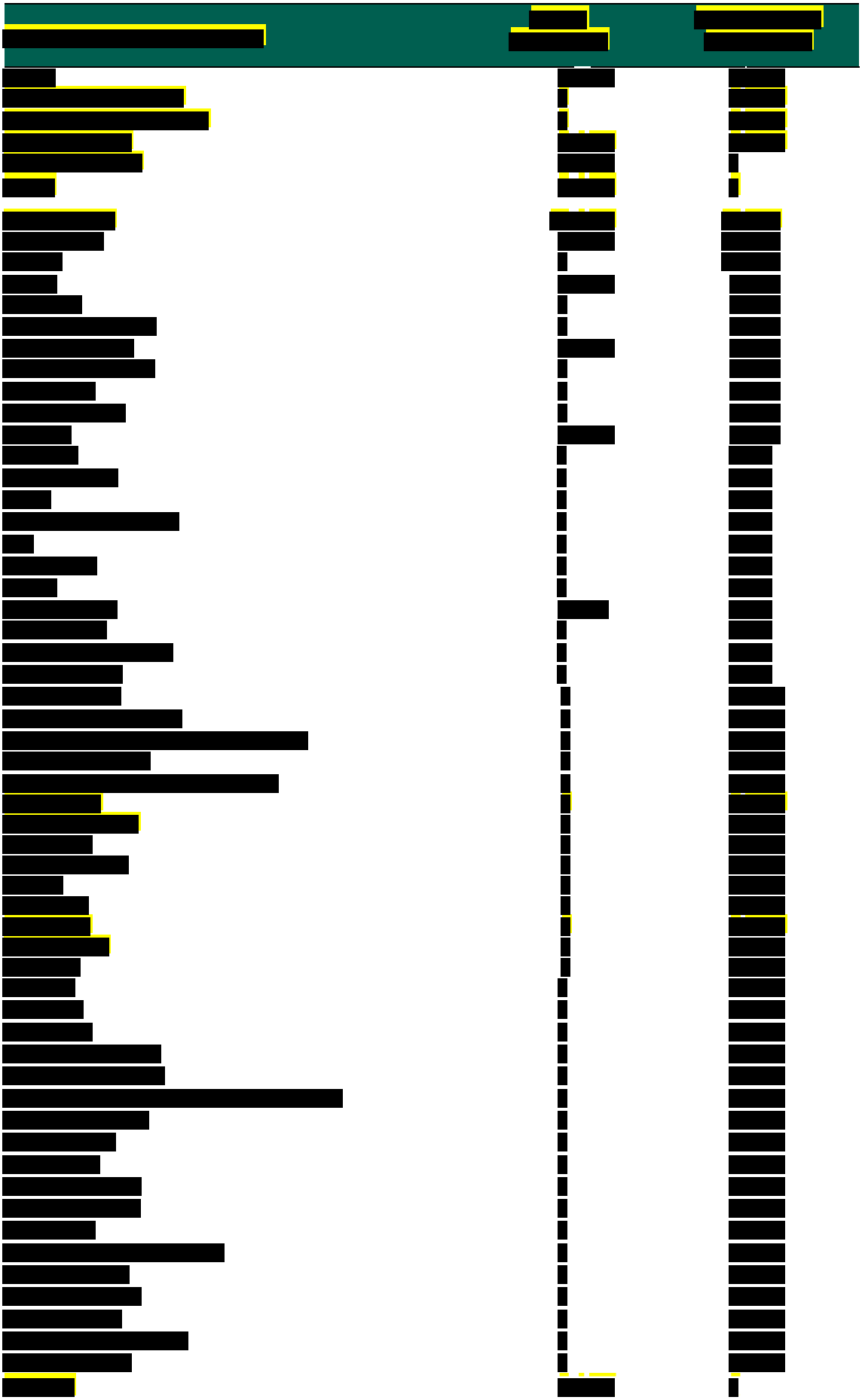

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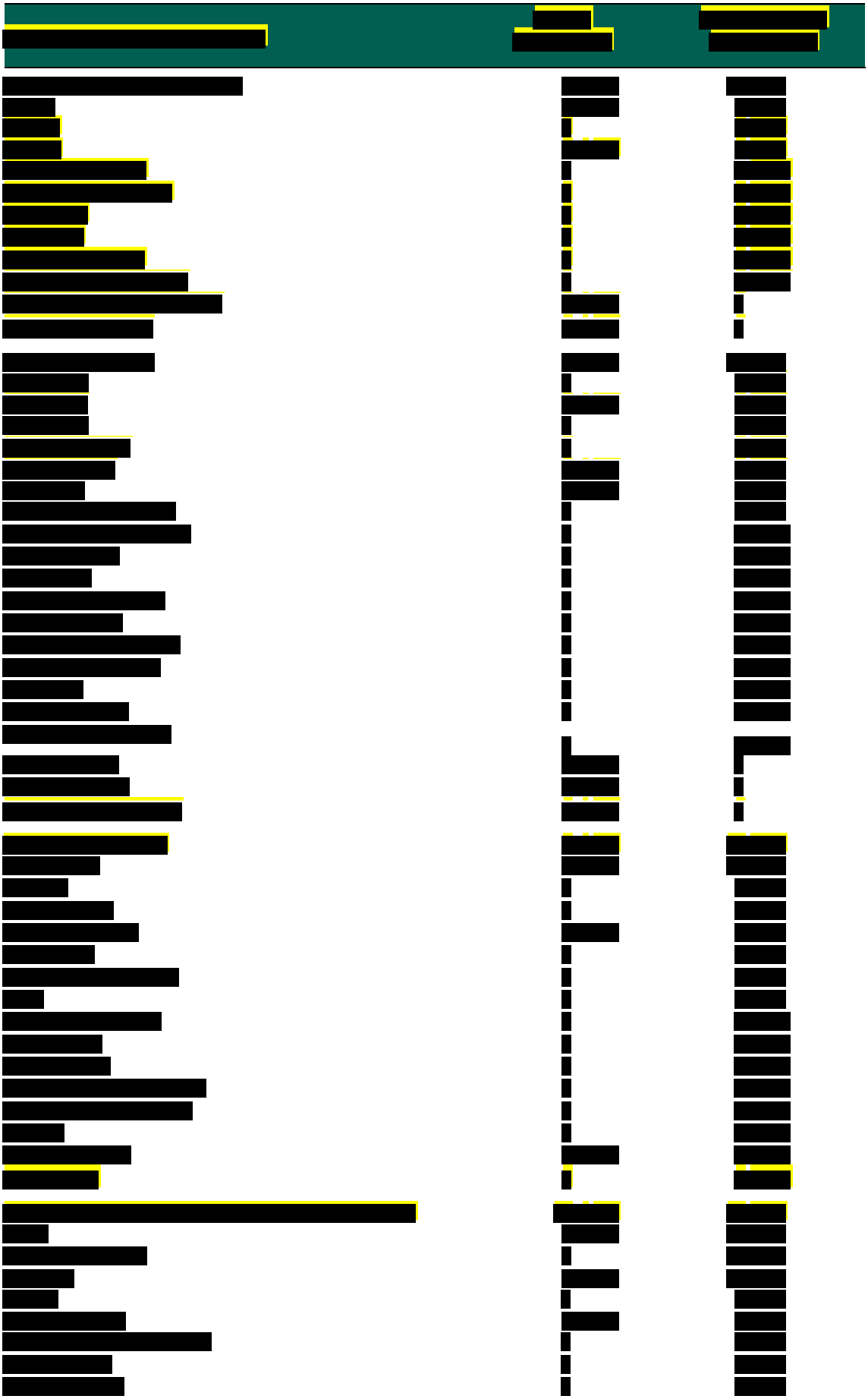

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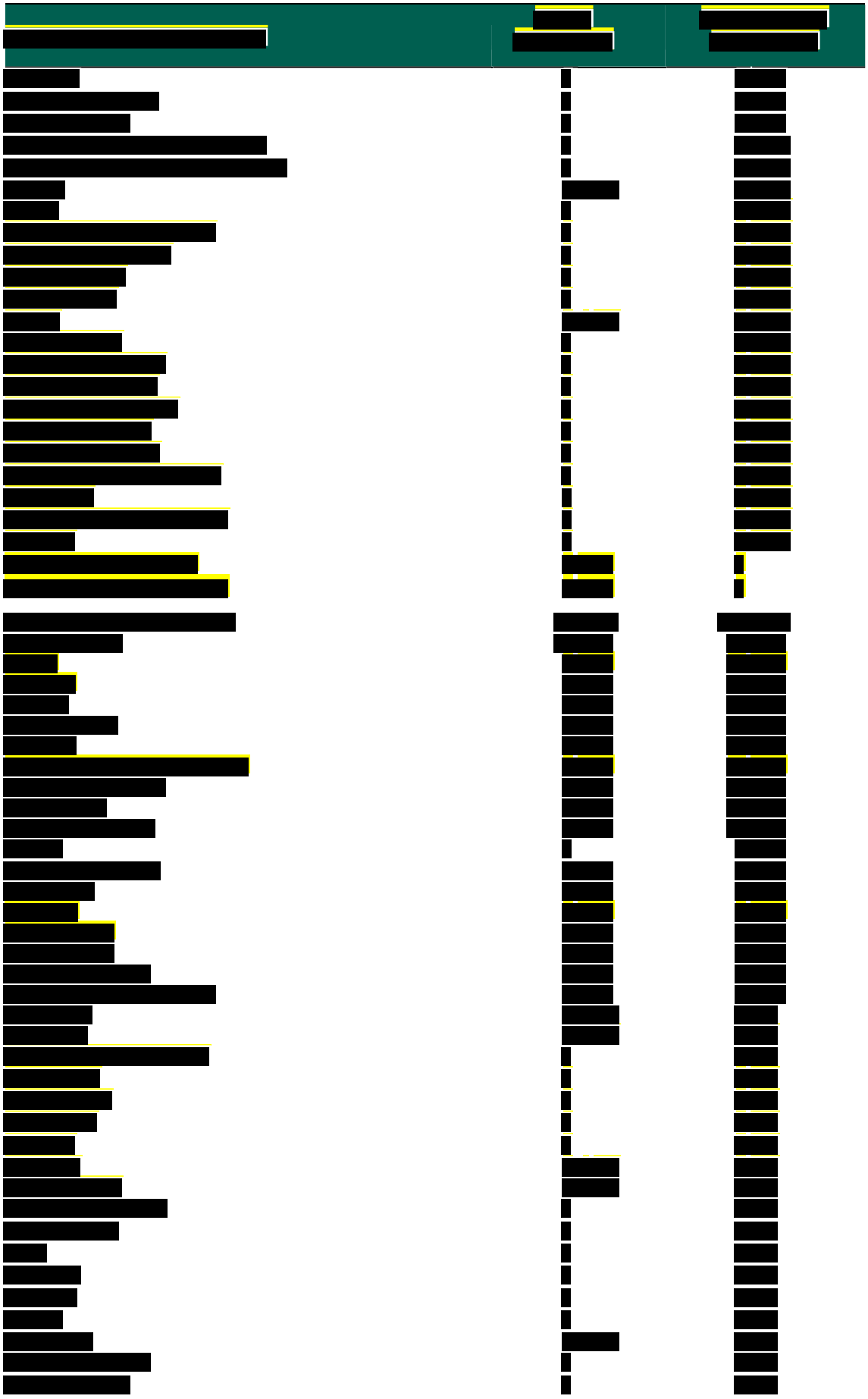

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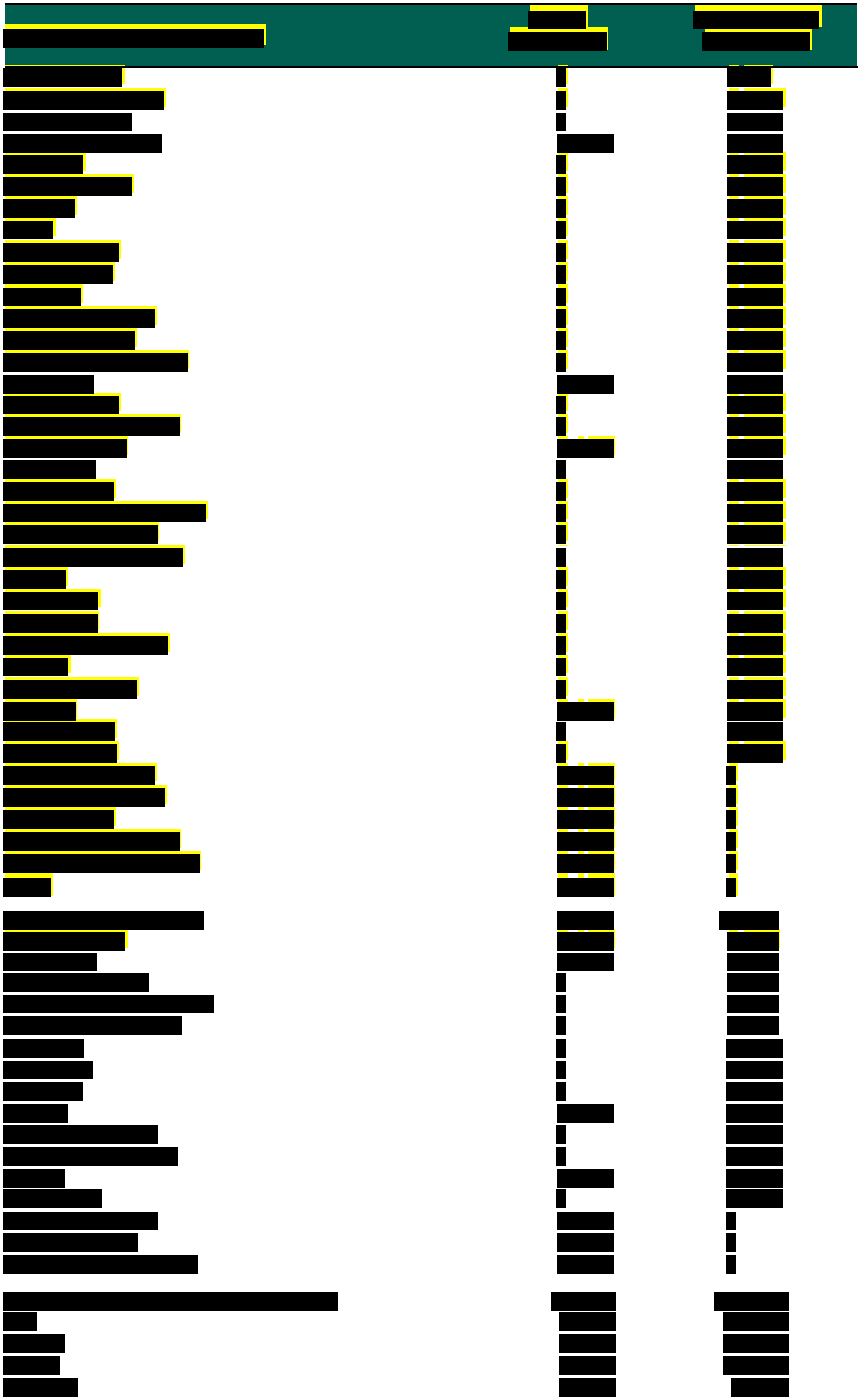

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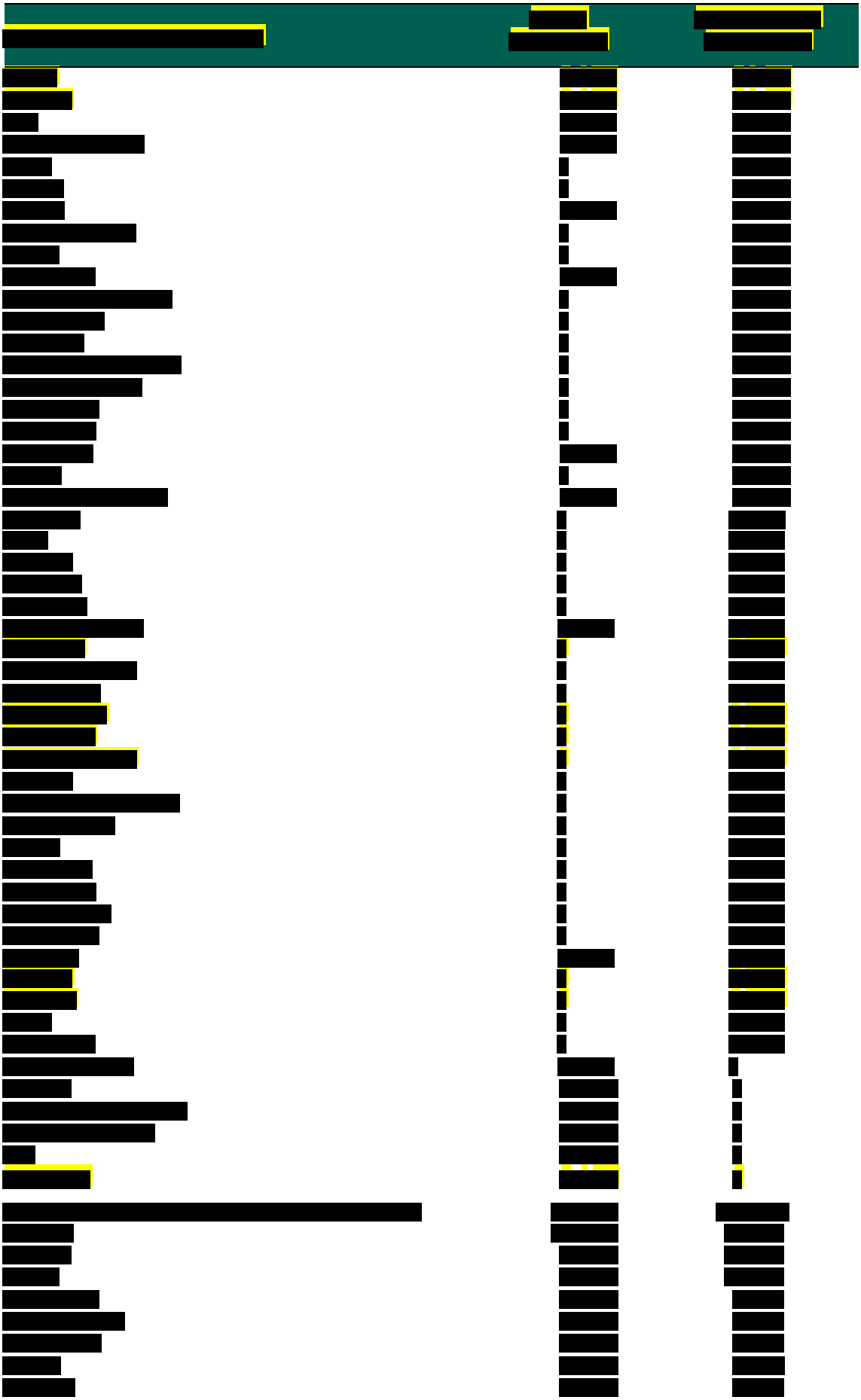

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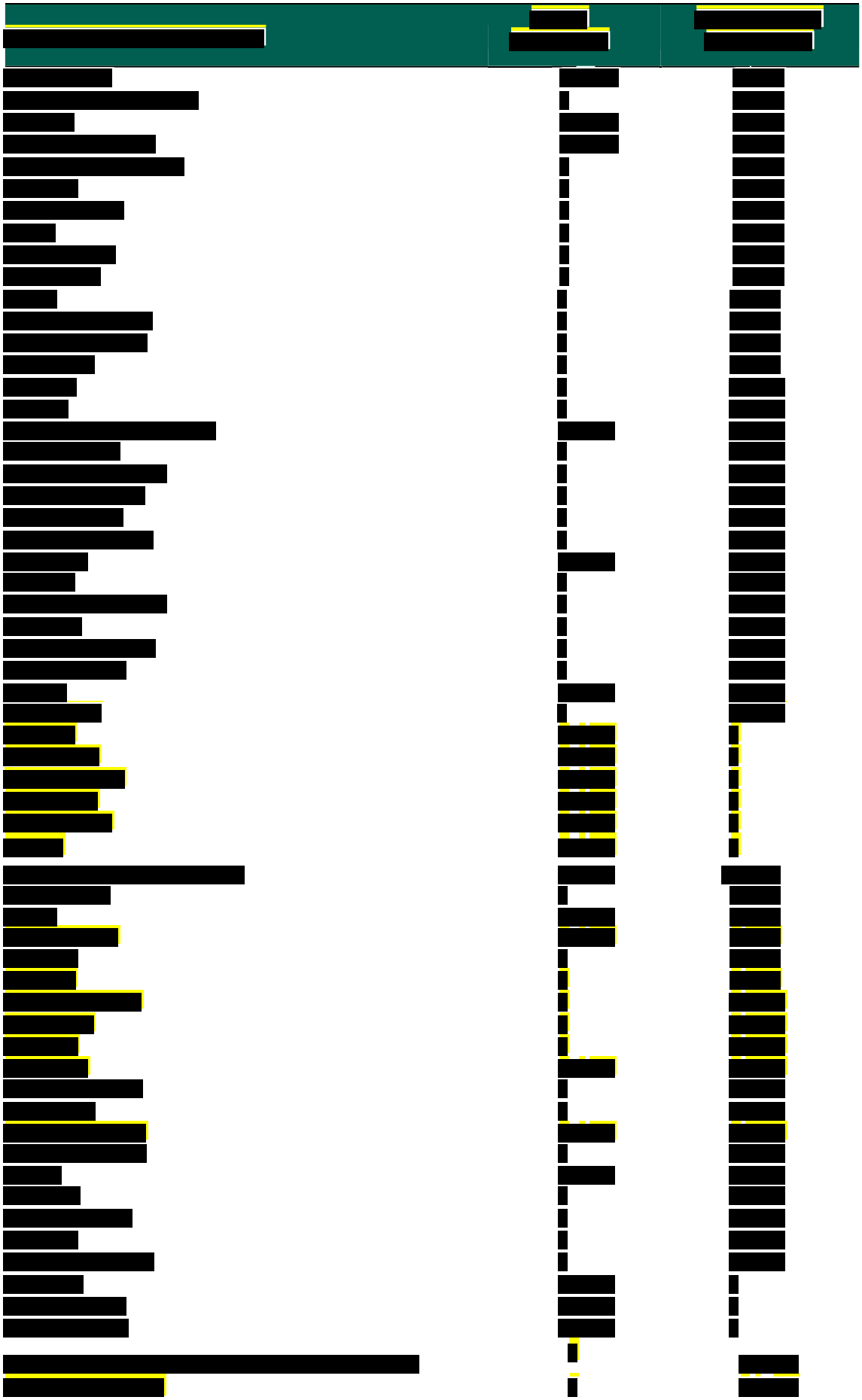

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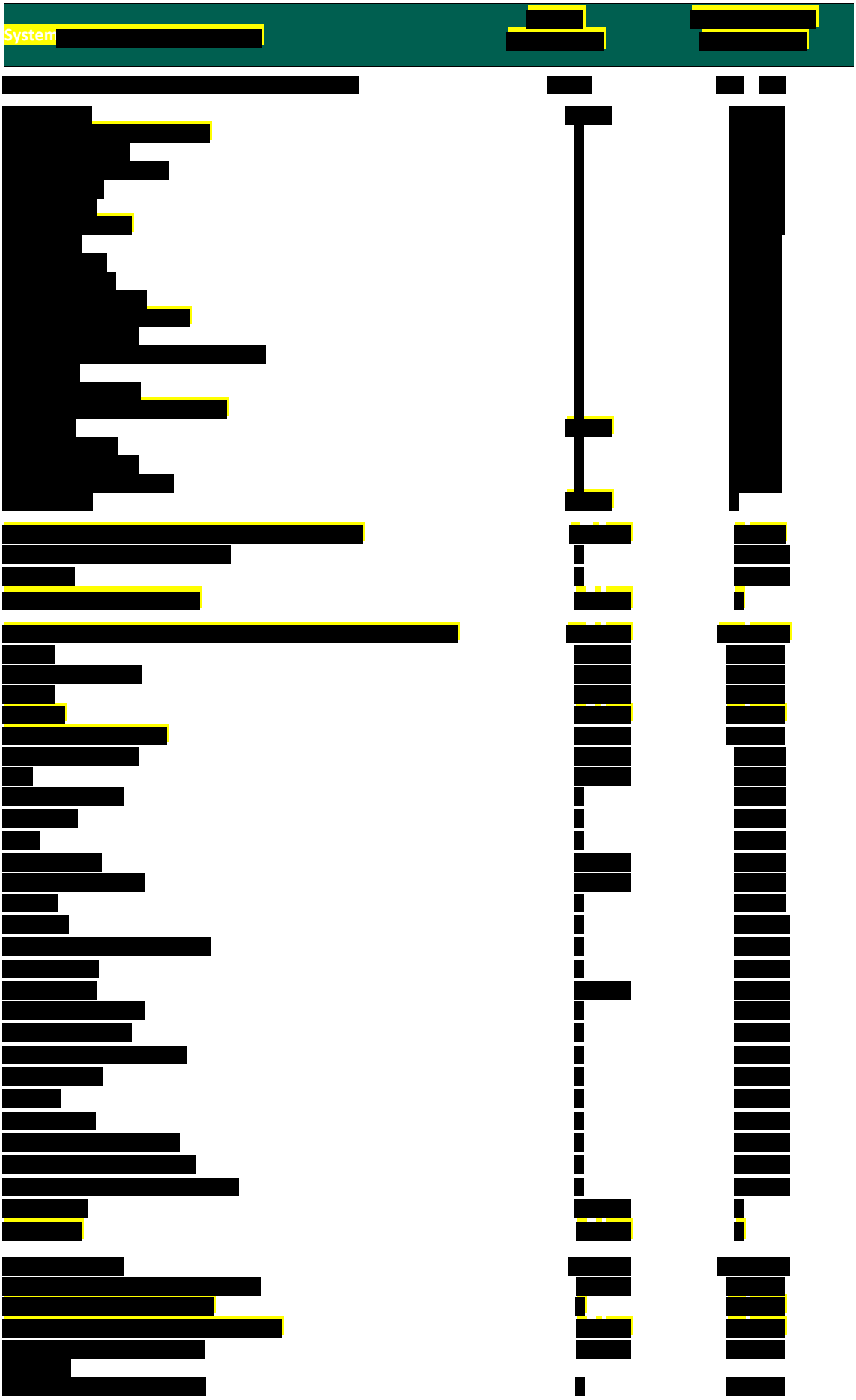

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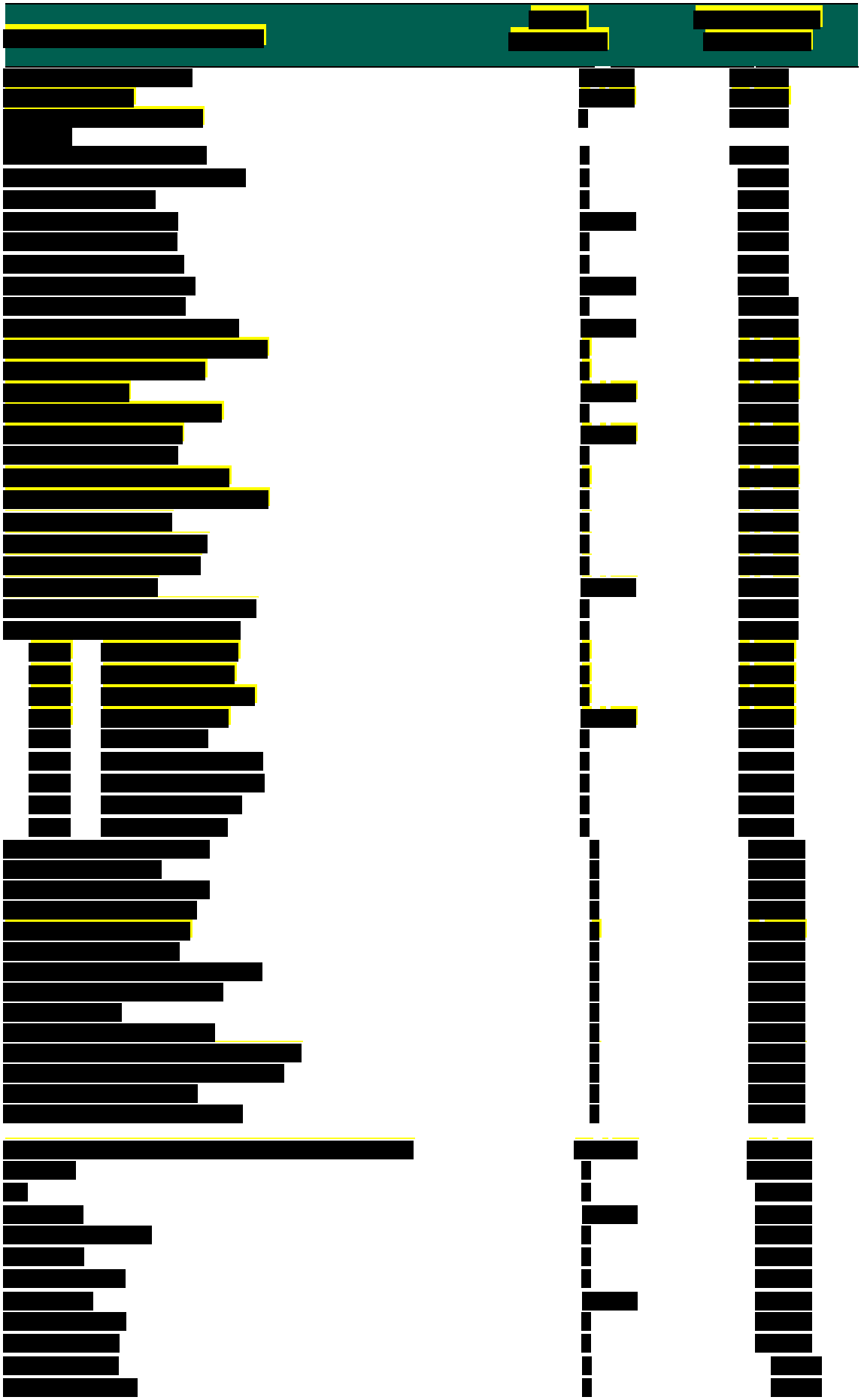

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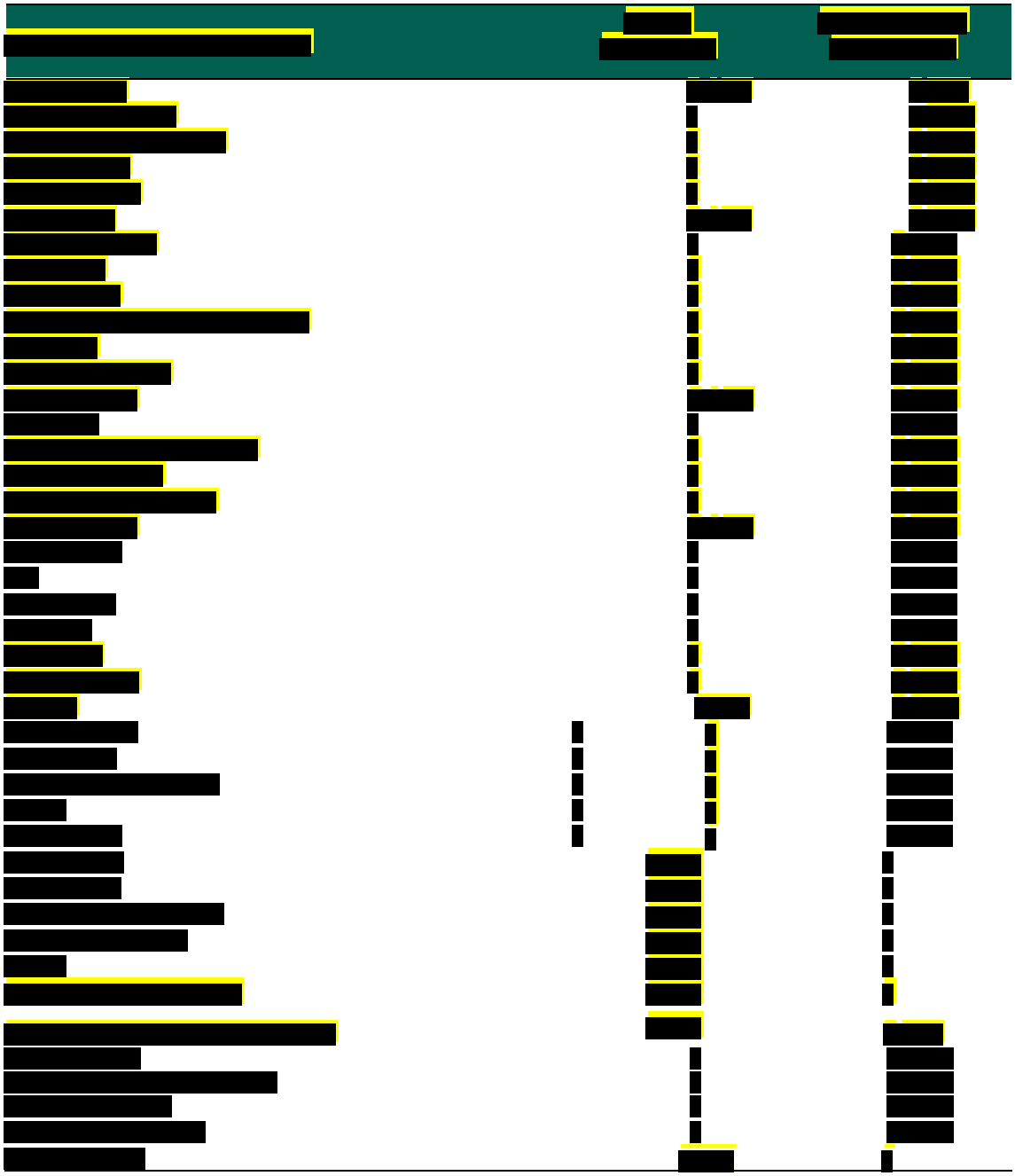

Notes:
The TEAE are defined regardless of the relationship to treatment. In the study TOUCHSTONE, the end period for TEAE collection is up to 30 days after last dose. For the TRUE NORTH study and OLE, the end period for TEAE collection is up to 90 days (+/-10) after last dose.
For the purpose of this analysis all the TEAEs are presented in the version 22.1 of the MedDRA dictionary, so the codification of TEAEs from TOUCSHTONE was upgraded from version 15.1.
Due to the nature of the randomized withdrawal design of TRUE NORTH and open label extension study, subjects may be included in both the ozanimod 1.0 mg and placebo treatment groups for this combined analysis. A total of 227 subjects who were treated with ozanimod 1 mg in TRUE NORTH Induction Period and were rerandomized to placebo in the Maintenance Period are also included in the total count of the "Placebo" group.

Source: BMS (2020)[49]

Appendix E.4 Network meta-analysis

Appendix E.4.1 Network meta-analysis: safety outcomes

Table E-11. Safety outcomes in the overall treatment populations

Trial name	Treatment	No. of patients	All AEs (%)	Serious AEs (%)	Withdrawals due to AEs (%)	Serious infections (%)
TRUE NORTH induction[27]	PBO	216	38.0	3.2	3.2	0.5
	OZA 1 mg	429	40.1	4.0	3.3	0.9
TRUE NORTH maintenance[27]	PBO	227	36.6	7.9	2.6	1.8
	OZA 1 mg	230	49.1	5.2	1.3	0.9
TOUCHSTONE[11]	PBO	65	40	9	6	NR
	OZA 0.5 mg	65	40	2	5	NR
	OZA 1 mg	67	39	4	1	NR
ULTRA 2[12]	PBO	260	83.8	12.3	13.1	1.9
	ADA 160/80/40 mg	257	82.9	12.1	8.9	1.6
ULTRA 2 induction[50]	PBO	246	66.3	8.5	7.3	1.2
	ADA 160/80/40 mg	247	58.3	6.1	4.0	1.2
PURSUIT-SC[13]	PBO	330	38.2	6.1	0.9	1.8
	GOL 100/50 mg	71	47.9	2.8	2.8	0.0
	GOL 200/100 mg	331	37.5	2.7	0.3	0.3
	GOL 400/200 mg	332	38.9	3.3	0.3	0.9
PURSUIT-M[14]	PBO	156	66.0	7.7	6.4	1.9
	GOL 50 mg	154	72.7	8.4	5.2	3.2
	GOL 100 mg	154	73.4	14.3	9.1	3.2
PURSUIT-J[15]	PBO	31	71.0	12.9	NR	NR
	GOL 100 mg	32	96.9	3.1	NR	NR
ACT 1[16]	PBO	121	85.1	25.6	9.1	4.1
	IFX 5 mg	121	87.6	21.5	8.3	2.5
	IFX 10 mg	122	91.0	23.8	9.0	6.6
ACT 2[16]	PBO	123	73.2	19.5	9.8	0.8
	IFX 5 mg	121	81.8	10.7	1.7	1.7
	IFX 10 mg	120	80.0	9.2	4.2	2.5
Kobayashi 2016[18]	PBO	104	90.4	18.3	7.7	1.9
	IFX 5 mg/kg	104	96.2	17.3	6.7	1.0
Kobayashi 2016 induction[18]	PBO	104	82.7	12.5	7.7	1.9
	IFX 5 mg/kg	104	81.7	8.7	4.8	1.0
Jiang 2015[17]	PBO	41	39.0	9.8	4.9	0.0
	IFX 3.5 mg/kg	41	39.0	4.9	0.0	0.0
	IFX 5 mg/kg	41	41.5	7.3	2.4	2.4
GEMINI 1[51]	VEDO 300 mg	620	80	12-13	NR	1.9
	PBO	275	80	12-13	NR	2.9
GEMINI 1 induction[19]	PBO	149	46	7	NR	2
	Cohort 1 VEDO 300 mg	225	40	2	NR	< 1

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Trial name	Treatment	No. of patients	All AEs (%)	Serious AEs (%)	Withdrawals due to AEs (%)	Serious infections (%)
	Cohort 2 VEDO 300 mg	521	47	4	NR	< 1
	Total VEDO 300 mg	746	45	3	NR	< 1
GEMINI 1 maintenance[19]	PBO	126	84	16	NR	3
	VEDO 300 mg Q8W	122	82	8	NR	2
	VEDO 300 mg Q4W	125	81	9	NR	2
VISIBLE 1[20]	PBO	56	76.8	10.7	4.9	0.0
	VEDO 108 mg Q2W	106	65.1	9.4	0.0	0.0
	VEDO 300 mg Q8W	54	75.9	13.0	2.4	2.4
Motoya 2019 induction[21]	PBO	82	52.4	4.9	2.4	2.4
	VEDO 300 mg	164	50.0	6.1	4.9	0.6
Motoya 2019 maintenance[21]	PBO	42	78.6	7.1	14.3	2.4
	VEDO 300 mg	41	87.8	9.8	4.9	2.4
UNIFI induction[22]	PBO	319	48.0	6.9	NR	1.6
	UST 6 mg/kg	320	50.6	3.4	NR	0.3
	UST 130 mg	321	41.4	3.7	NR	0.6
UNIFI maintenance[22]	PBO	175	78.9	9.7	11.4	2.3
	UST 90 mg Q8W	176	77.3	8.5	2.8	1.7
	UST 90 mg Q12W	172	69.2	7.6	5.2	3.5

ADA = adalimumab; AE = adverse event; GOL = golimumab; IFX = infliximab; NR = not reported; OZA = ozanimod; PBO = placebo; Q2W = every 2 weeks; Q4W = every 4 weeks; Q8W = every 8 weeks; Q12W = every 12 weeks; UST = ustekinumab; VEDO = vedolizumab.

Note: Italicised values were calculated using data reported in the articles.

Source: BMS Celgene data on file (2021)[26]

Table E-12. Safety outcomes in bio-naïve and bio-experienced patients

Trial name	Treatment	No. of patients	All AEs (%)	Serious AEs (%)	Withdrawals due to AEs (%)	Serious infections (%)
Bio-naïve patients						
PURSUIT-SC[13]	PBO	330	38.2	6.1	0.9	1.8
	GOL 100/50 mg	71	47.9	2.8	2.8	0.0
	GOL 200/100 mg	331	37.5	2.7	0.3	0.3
	GOL 400/200 mg	332	38.9	3.3	0.3	0.9
PURSUIT-M[14]	PBO	156	66.0	7.7	6.4	1.9
	GOL 50 mg	154	72.7	8.4	5.2	3.2
	GOL 100 mg	154	73.4	14.3	9.1	3.2
PURSUIT-J[15]	PBO	31	71.0	12.9	NR	NR
	GOL 100 mg	32	96.9	3.1	NR	NR
ACT 1[16]	PBO	121	85.1	25.6	9.1	4.1
	IFX 5 mg	121	87.6	21.5	8.3	2.5
	IFX 10 mg	122	91.0	23.8	9.0	6.6
ACT 2[16]	PBO	123	73.2	19.5	9.8	0.8
	IFX 5 mg	121	81.8	10.7	1.7	1.7

Trial name	Treatment	No. of patients	All AEs (%)	Serious AEs (%)	Withdrawals due to AEs (%)	Serious infections (%)
	IFX 10 mg	120	80.0	9.2	4.2	2.5
Kobayashi 2016[18]	PBO	104	90.4	18.3	7.7	1.9
	IFX 5 mg/kg	104	96.2	17.3	6.7	1.0
Kobayashi 2016 induction[18]	PBO	104	82.7	12.5	7.7	1.9
	IFX 5 mg/kg	104	81.7	8.7	6.7	1.0
Jiang 2015[17]	PBO	41	39.0	9.8	4.9	0.0
	IFX 3.5 mg/kg	41	39.0	4.9	0.0	0.0
	IFX 5 mg/kg	41	41.5	7.3	2.4	2.4
GEMINI 1 induction[52]	PBO	76	38	11	NR	3
	VEDO 300 mg	388	38	3	NR	0.5
GEMINI 1 maintenance[52]	PBO	76	75	16	NR	4
	Total VEDO 300 mg (Q4W + Q8W)	309	74	9	NR	1
Bio-experienced patients						
GEMINI 1 induction[52]	PBO	63	62	5	NR	3.0
	VEDO 300 mg	304	54	4	NR	0.7
GEMINI 1 maintenance[52]	PBO	63	84	11	NR	3
	Total VEDO 300 mg (Q4W + Q8W)	266	88	17	NR	3

ADA = adalimumab; AE = adverse event; GOL = golimumab; IFX = infliximab; NR = not reported; OZA = ozanimod; PBO = placebo; Q4W = every 4 weeks; Q8W = every 8 weeks; TOF = tofacitinib; UST = ustekinumab; VEDO = vedolizumab.

Source: BMS Celgene data on file (2021)[26]

Table E-13. Additional safety outcomes in the overall treatment populations

Trial name	Treatment	No. of patients	Injection site reactions (%)	Malignancies or other cancers (%)
TRUE NORTH induction[27]	PBO	216	NA	0
	OZA 1 mg	429	NA	0.2
TRUE NORTH maintenance[27]	PBO	227	NA	1.8
	OZA 1 mg	230	NA	2.6
TOUCHSTONE[11]	PBO	NR	NR	NR
	OZA 0.5 mg	NR	NR	NR
	OZA 1 mg	NR	NR	NR
ULTRA 2[12]	PBO	260	3.8	0
	ADA 160/80/40 mg	257	12.1	0.8
ULTRA 2 induction[50]	PBO	246	2.0	0.0
	ADA 160/80/40 mg	247	3.2	0.4
PURSUIT-SC[13,53]	PBO	330	1.5	0.3
	GOL 100/50 mg	71	5.6	NR
	GOL 200/100 mg	331	3.3	0.0
	GOL 400/200 mg	332	3.0	0.3

Trial name	Treatment	No. of patients	Injection site reactions (%)	Malignancies or other cancers (%)
PURSUIT-M[14]	PBO	156	1.9	0.6
	GOL 50 mg	154	1.9	2.6
	GOL 100 mg	154	7.1	2.6
PURSUIT-J[15]	PBO	31	18.8	NR
	GOL 100 mg	32	0.0	NR
ACT 1[16]	PBO	121	10.7	NR
	IFX 5 mg	121	9.9	NR
	IFX 10 mg	122	12.3	NR
ACT 2[16]	PBO	123	8.1	NR
	IFX 5 mg	121	11.6	NR
	IFX 10 mg	120	11.7	NR
Kobayashi 2016[18]	PBO	104	10.6	NR
	IFX 5 mg/kg	104	15.4	NR
Kobayashi 2016 induction[18]	PBO	104	8.7	NR
	IFX 5 mg/kg	104	10.6	NR
Jiang 2015[17]	PBO	41	4.9	NR
	IFX 3.5 mg/kg	41	4.9	NR
	IFX 5 mg/kg	41	7.3	NR
GEMINI 1 induction[19]	PBO	149	< 1	0
	Cohort 1 VEDO 300 mg	225	< 1	0
	Cohort 2 VEDO 300 mg	521	< 1	0
	Total VEDO 300 mg	746	< 1	0
GEMINI 1 maintenance[19]	PBO	126	2	2.0
	VEDO 300 mg Q8W	122	6	< 1
	VEDO 300 mg Q4W	125	11	NR
GEMINI 1[51]	VEDO 300 mg	620	NR	*0.2*
	PBO	275	NR	*1.1*
VISIBLE 1[20]	PBO	56	0	0.0
	VEDO 108 mg Q2W	106	10.4	0.0
	VEDO 300 mg Q8W	54	1.9	0.0
Motoya 2019 induction[21]	PBO	NR	2.4	NR
	VEDO 300 mg	NR	3.0	NR
Motoya 2019 maintenance[21]	PBO	NR	0	NR
	VEDO 300 mg	NR	0	NR
UNIFI induction[22]	PBO	319	1.9	0.0
	UST 6 mg/kg	320	0.9	0.0
	UST 130 mg	321	2.2	0.0
UNIFI maintenance[22]	PBO	175	2.3	0.6
	UST 90 mg Q8W	176	2.8	1.1
	UST 90 mg Q12W	172	0.6	1.2

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ADA = adalimumab; GOL = golimumab; IFX = infliximab; NR = not reported; OZA = ozanimod; PBO = placebo; Q2W = every 2 weeks; Q4W = every 4 weeks; Q8W = every 8 weeks; Q12W = every 12 weeks; UST = ustekinumab; VEDO = vedolizumab.

Note: Italicised values were calculated using data reported in the articles.

Source: BMS Celgene data on file (2021)[26]

Table E-14. Additional safety outcomes in bio-naïve patients

Trial name	Treatment	No. of patients	Injection site reactions (%)	Malignancies or other cancers (%)
TRUE NORTH induction[27]	PBO	NA	NA	NA
	OZA 1 mg	NA	NA	NA
TRUE NORTH maintenance[27]	PBO	NA	NA	NA
	OZA 1 mg	NA	NA	NA
TOUCHSTONE[11]	PBO	NR	NR	NR
	OZA 0.5 mg	NR	NR	NR
	OZA 1 mg	NR	NR	NR
ULTRA 2[12]	PBO	NR	NR	NR
	ADA 160/80/40 mg	NR	NR	NR
PURSUIT-SC[13,53]	PBO	330	1.5	0.3
	GOL 100/50 mg	71	5.6	NR
	GOL 200/100 mg	331	3.3	0.0
	GOL 400/200 mg	332	3.0	0.3
PURSUIT-M[14]	PBO	156	1.9	0.6
	GOL 50 mg	154	1.9	2.6
	GOL 100 mg	154	7.1	2.6
PURSUIT-J[15]	PBO	31	0.0	NR
	GOL 100 mg	32	18.8	NR
ACT 1[16]	PBO	121	10.7	NR
	IFX 5 mg	121	9.9	NR
	IFX 10 mg	122	12.3	NR
ACT 2 [16]	PBO	123	8.1	NR
	IFX 5 mg	121	11.6	NR
	IFX 10 mg	120	11.7	NR
Kobayashi 2016[18]	PBO	104	10.6	NR
	IFX 5 mg/kg	104	15.4	NR
Kobayashi 2016 induction[18]	PBO	104	8.7	NR
	IFX 5 mg/kg	104	10.6	NR
Jiang 2015[17]	PBO	41	4.9	NR
	IFX 3.5 mg/kg	41	4.9	NR
	IFX 5 mg/kg	41	7.3	NR
GEMINI 1 maintenance[52]	PBO	NR	NR	NR
	Total VEDO 300 mg (Q4W + Q8W)	NR	NR	NR
GEMINI 1 induction[52]	PBO	NR	NR	NR

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Trial name	Treatment	No. of patients	Injection site reactions (%)	Malignancies or other cancers (%)
	VEDO 300 mg	NR	NR	NR
VISIBLE 1[20]	PBO	NR	NR	NR
	VEDO 108 mg Q2W	NR	NR	NR
	VEDO 300 mg Q8W	NR	NR	NR
Motoya 2019 induction[21]	PBO	NR	NR	NR
	VEDO 300 mg	NR	NR	NR
Motoya 2019 maintenance[21]	PBO	NR	NR	NR
	VEDO 300 mg	NR	NR	NR
UNIFI Induction[22]	PBO	NR	NR	NR
	UST 6 mg/kg	NR	NR	NR
	UST 130 mg	NR	NR	NR
UNIFI maintenance[22]	PBO	NR	NR	NR
	UST 90 mg Q8W	NR	NR	NR
	UST 90 mg Q12W	NR	NR	NR

ADA = adalimumab; GOL = golimumab; IFX = infliximab; NR = not reported; OZA = ozanimod; PBO = placebo; Q2W = every 2 weeks; Q4W = every 4 weeks; Q8W = every 8 weeks; Q12W = every 12 weeks; TOF = tofacitinib; UST = ustekinumab; VEDO = vedolizumab.

Source: BMS Celgene data on file (2021)[26]

Table E-15. Safety outcomes in bio-experienced patients

Trial name	Treatment	No. of patients	Injection site reactions (%)	Malignancies or other cancers (%)
TRUE NORTH induction[27]	PBO	NR	NR	NR
	OZA 1 mg	NR	NR	NR
TRUE NORTH maintenance[27]	PBO	NR	NR	NR
	OZA 1 mg	NR	NR	NR
TOUCHSTONE[11]	PBO	NR	NR	NR
	OZA 0.5 mg	NR	NR	NR
	OZA 1 mg	NR	NR	NR
ULTRA 2[12]	PBO	NR	NR	NR
	ADA 160/80/40 mg	NR	NR	NR
GEMINI 1 induction[52]	PBO	NR	NR	NR
	VEDO 300 mg	NR	NR	NR
GEMINI 1 maintenance[52]	PBO	NR	NR	NR
	Total VEDO 300 mg (Q4W + Q8W)	NR	NR	NR
VISIBLE 1[20]	PBO	NR	NR	NR
	VEDO 108 mg Q2W	NR	NR	NR
	VEDO 300 mg Q8W	NR	NR	NR
Motoya 2019 induction[21]	PBO	NR	NR	NR
	VEDO 300 mg	NR	NR	NR
Motoya 2019 maintenance[21]	PBO	NR	NR	NR

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Trial name	Treatment	No. of patients	Injection site reactions (%)	Malignancies or other cancers (%)
	VEDO 300 mg	NR	NR	NR
UNIFI induction[22]	PBO	NR	NR	NR
	UST 6 mg/kg	NR	NR	NR
	UST 130 mg	NR	NR	NR
UNIFI maintenance[22]	PBO	NR	NR	NR
	UST 90 mg Q8W	NR	NR	NR
	UST 90 mg Q12W	NR	NR	NR

ADA = adalimumab; NR = not reported; OZA = ozanimod; PBO = placebo; Q2W = every 2 weeks; Q4W = every 4 weeks; Q8W = every 8 weeks; Q12W = every 12 weeks; UST = ustekinumab; VEDO = vedolizumab.

Source: BMS Celgene data on file (2021)[26]

Appendix E.5 Pooled safety analysis for relapsing multiple sclerosis

Appendix E.5.1 Treatment-emergent adverse events

Table E-16. Treatment-emergent adverse events in participants with relapsing multiple sclerosis who were treated with ozanimod 0.92 mg

	Phase 3 study population (N = 882)		Overall RMS population (N = 2,631)	
	Incidence, n (%)	IR/1000 PY[a]	Incidence, n (%)	IR/1000 PY[a]
Any TEAE	592 (67.1)	896.1 (825.4-971.3)	2,106 (80.0)	772.2 (739.5-805.9)
Severe TEAEs	22 (2.5)	16.5 (10.4-25.0)	129 (4.9)	18.7 (15.6-22.2)
Serious TEAEs	41 (4.6)	31.2 (22.4-42.4)	224 (8.5)	33.2 (29.0-37.9)
Permanent discontinuation for TEAEs	26 (2.9)	19.4 (12.7-28.5)	66 (2.5)	9.4 (7.3-11.9)
TEAEs in ≥ 5% of participants				
Nasopharyngitis	98 (11.1)	78.8 (64.0-96.1)	457 (17.4)	72.9 (66.3-79.9)
Headache	78 (8.8)	61.7 (48.8-77.0)	339 (12.9)	52.5 (47.0-58.4)
URTI	52 (5.9)	40.3 (30.1-52.8)	249 (9.5)	37.6 (33.1-42.6)
Lymphopenia	NA[b]	NA[b]	222 (8.4)	33.1 (28.9-37.8)
ALC decreased	NA[b]	NA[b]	181 (6.9)	26.6 (22.9-30.8)
GGT increased	40 (4.5)	30.5 (21.8-41.6)	174 (6.6)	25.8 (22.1-30.0)
Back pain	35 (4.0)	26.6 (18.5-37.0)	162 (6.2)	23.9 (20.3-27.8)
Hypertension	30 (3.4)	22.8 (15.4-32.5)	141 (5.4)	20.7 (17.4-24.4)
UTI	36 (4.1)	27.4 (19.2-37.9)	138 (5.2)	20.2 (17.0-23.9)
ALT increased	47 (5.3)	36.2 (26.6-48.1)	129 (4.9)	19.0 (15.8-22.5)
Influenza-like illness	44 (5.0)	34.4 (25.0-46.2)	65 (2.5)	9.4 (7.3-12.0)
Serious TEAEs in ≥ 2 participants				
Appendicitis	3 (0.3)	2.2 (0.5-6.5)	8 (0.3)	1.1 (0.5-2.2)
Uterine leiomyoma	1 (0.1)	0.7 (0.0-4.1)	8 (0.3)	1.1 (0.5-2.2)
Pyelonephritis acute	1 (0.1)	0.7 (0.0-4.1)	7 (0.3)	1.0 (0.4-2.0)

	Phase 3 study population (N = 882)		Overall RMS population (N = 2,631)	
	Incidence, n (%)	IR/1000 PY[a]	Incidence, n (%)	IR/1000 PY[a]
Intervertebral disc disorder	2 (0.2)	1.5 (0.2-5.4)	6 (0.2)	0.9 (0.3-1.9)
Depression	0	0 (0.0-2.7)	4 (0.2)	0.6 (0.2-1.5)
Intervertebral disc protrusion	1 (0.1)	0.7 (0.0-4.1)	4 (0.2)	0.6 (0.2-1.5)
Pneumonia	0	0 (0.0-2.7)	4 (0.2)	0.6 (0.2-1.5)
Uterine haemorrhage	0	0 (0.0-2.7)	4 (0.2)	0.6 (0.2-1.5)
Abortion spontaneous	1 (0.1)	0.7 (0.0-4.1)	3 (0.1)	0.4 (0.1-1.2)
Craniocerebral injury	1 (0.1)	0.7 (0.0-4.1)	3 (0.1)	0.4 (0.1-1.2)
Epilepsy	1 (0.1)	0.7 (0.0-4.1)	3 (0.1)	0.4 (0.1-1.2)
Headache	0	0 (0.0-2.7)	3 (0.1)	0.4 (0.1-1.2)

ALC = absolute lymphocyte count; ALT = alanine aminotransferase; CI = confidence interval; GGT = gamma-glutamyl transferase; IR = incidence rate; NA = not applicable; PY = person-year; RMS = relapsing multiple sclerosis; TEAE = treatment-emergent adverse event; URTI = upper respiratory tract infection; UTI = urinary tract infection.

[a] IR/1000 PY, study duration-adjusted incidence rate per 1,000 person-years, calculated as number of participants with a TEAE of interest/PY × 1,000, where PY was calculated as (date of first TEAE of interest – date of first dose of study drug + 1)/365.25; for participants without a TEAE of interest, time on study was the study duration (last date on study – date of first dose of study drug + 1)/365.25.

[b] Investigators in the phase 3 RMS studies were blinded to lymphocyte count data (a key pharmacodynamic effect of ozanimod); therefore, TEAEs related to lymphocyte counts were not reported.

Source: Selmaj et al. (2021)[40]

Appendix E.5.2 Cardiovascular effects

Table E-17. Hypertension, bradycardia, cardiac conduction abnormalities, and ischaemic heart conditions during long-term treatment with ozanimod 0.92 mg

	Phase 3 study population (N = 882)		Overall RMS population (N = 2,631)	
	Incidence, n (%)	IR/1000 PY[a] (95% CI)	Incidence, n (%)	IR/1000 PY[a] (95% CI)
Hypertension-related AEs	40 (4.5)	30.6 (21.8-41.6)	167 (6.3)	24.7 (21.1-28.7)
Hypertension	30 (3.4)	22.8 (15.4-32.5)	141 (5.4)	20.7 (17.4-24.4)
Hypertensive crisis	2 (0.2)	1.5 (0.2-5.4)	6 (0.2)[b]	0.9 (0.3-1.9)
Essential hypertension	1 (0.1)	0.7 (0.0-4.1)	1 (< 0.1)	0.1 (0.0-0.8)
Blood pressure increased	7 (0.8)	5.2 (2.1-10.8)	22 (0.8)	3.1 (2.0-4.7)
Blood pressure fluctuation	0	0 (0.0-2.7)	2 (0.1)	0.3 (0.0-1.0)
Bradycardias	14 (1.6)	10.5 (5.8-17.7)	33 (1.3)	4.7 (3.2-6.6)
Syncope	2 (0.2)[c]	1.5 (0.2-5.4)	16 (0.6)[c]	2.3 (1.3-3.7)
Bradycardia	7 (0.8)	5.2 (2.1-10.8)	10 (0.4)[d]	1.4 (0.7-2.6)
Sinus bradycardia	5 (0.6)	3.7 (1.2-8.7)	7 (0.3)[d]	1.0 (0.4-2.0)
Cardiac conduction abnormalities in ≥ 3 (0.2%) participants				
Palpitations	7 (0.8)	5.2 (2.1-10.8)	11 (0.4)	1.6 (0.8-2.8)
Atrioventricular block, first degree	5 (0.6)	3.7 (1.2-8.7)	12 (0.5)	1.7 (0.9-1.9)
Bundle branch block, right	1 (0.1)	0.7 (0.0-4.1)	6 (0.2)	0.9 (0.3-1.9)
Tachycardia	2 (0.2)	1.5 (0.2-5.4)	5 (0.2)	0.7 (0.2-1.7)

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	Phase 3 study population (N = 882)		Overall RMS population (N = 2,631)	
	Incidence, n (%)	IR/1000 PY[a] (95% CI)	Incidence, n (%)	IR/1000 PY[a] (95% CI)
Heart rate increased	1 (0.1)	0.7 (0.0-4.1)	4 (0.2)	0.6 (0.2-1.5)
Atrial fibrillation	0	0 (0.0-2.7)	3 (0.1)	0.4 (0.1-1.2)
Ischaemic heart conditions	0	0 (0.0-2.7)	11 (0.4)	1.6 (0.8-2.8)
Angina pectoris	0	0 (0.0-2.7)	6 (0.2)	0.9 (0.3-1.9)
Myocardial ischaemia	0	0 (0.0-2.7)	3 (0.1)	0.4 (0.1-1.2)
Myocardial infarction	0	0 (0.0-2.7)	2 (< 0.1)[e]	0.3 (0.0-1.0)
Angina unstable	0	0 (0.0-2.7)	1 (< 0.1)	0.1 (0.0-0.8)

AE = adverse event; CI = confidence interval; IR = incidence rate; PY = person-year; RMS = relapsing multiple sclerosis; TEAE = treatment-emergent adverse effect.

[a] IR/1000 PY, study duration-adjusted incidence rate per 1,000 person-years, calculated as number of participants with a TEAE of interest/PY × 1,000 where PY was calculated as (date of first TEAE of interest – date of first dose of study drug + 1)/365.25; for participants without a TEAE of interest, time on study was the study duration (last date on study – date of first dose of study drug + 1)/365.25.

[b] None of the reports of hypertensive crisis were classified as serious.

[c] One case of syncope (which occurred during a phase 3 trial) was considered serious.

[d] Five of the 10 participants with bradycardia and 3 of the 7 with sinus bradycardia experienced these events on day 1, following their initial dose of ozanimod.

[e] Both participants who experienced myocardial infarction had a history of hypertension, and 1 also had hyperlipidaemia and the other had chronic obstructive pulmonary disease. Both participants continued in the study with no change in ozanimod dosing.

Source: Selmaj et al. (2021)[40]

Appendix E.5.3 Hepatic effects

Table E-18. Hepatic laboratory abnormalities and treatment-emergent adverse events in participants with relapsing multiple sclerosis treated with ozanimod 0.92 mg

	Phase 3 study population (N = 882)	Overall RMS population (N = 2,631)
Based on laboratory testing	n = 878	n = 2,623
Maximum ALT		
≥ 3 × ULN, n (%)	48 (5.5)	102 (3.9)
≥ 5 × ULN, n (%)	14 (1.6)	25 (1.0)
≥ 10 × ULN, n (%)	4 (0.5)	9 (0.3)
Mean (SD) maximum change from baseline, IU/L	28.4 (61.0)	27.0 (66.3)
Maximum AST		
≥ 3 × ULN, n (%)	9 (1.0)	31 (1.2)
≥ 5 × ULN, n (%)	5 (0.6)	13 (0.5)
≥ 10 × ULN, n (%)	4 (0.5)	6 (0.2)
Mean (SD) maximum change from baseline, IU/L	13.7 (34.4)	12.8 (44.0)
Maximum bilirubin		
> 2 × ULN, n (%)	14 (1.6)	64 (2.4)
> 3 × ULN, n (%)	3 (0.3)	9 (0.3)
Mean (SD) maximum change from baseline, µmol/L	4.6 (4.9)	6.1 (5.4)

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	Phase 3 study population (N = 882)		Overall RMS population (N = 2,631)	
Hy's Law cases[a], n	0		0	
	N (%)	IR/1000 PY[b] (95% CI)	N (%)	IR/1000 PY[b] (95% CI)
Any Hepatobiliary TEAEs, n (%)	15 (1.7)	11.2 (6.3-18.5)	73 (2.8)	10.5 (8.3-13.2)
Hepatobiliary TEAEs in ≥ 3 participants, n (%)				
Hyperbilirubinemia	3 (0.3)	2.2 (0.5-6.5)	24 (0.9)	3.4 (2.2-5.1)
Cholecystitis chronic	1 (0.1)	0.7 (0.0-4.1)	7 (0.3)	1.0 (0.4-2.0)
Biliary dyskinesia	0	0 (0.0-2.7)	5 (0.2)	0.7 (0.2-1.7)
Hepatic cyst	0	0 (0.0-2.7)	5 (0.2)	0.7 (0.2-1.7)
Cholelithiasis	1 (0.1)	0.7 (0.0-4.1)	4 (0.2)	0.6 (0.2-1.5)
Chronic hepatitis	0	0 (0.0-2.7)	3 (0.1)	0.4 (0.1-1.2)
Hepatitis	0	0 (0.0-2.7)	3 (0.1)	0.4 (0.1-1.2)
Hepatitis toxic	2 (0.2)	1.5 (0.2-5.4)	3 (0.1)	0.4 (0.1-1.2)
Hypertransaminasemia	1 (0.1)	0.7 (0.0-4.1)	3 (0.1)	0.4 (0.1-1.2)

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CI = confidence interval; IR = incidence rate; IU = international unit; PY = person-year; RMS = relapsing multiple sclerosis; SD = standard deviation; TEAE = treatment-emergent adverse event; ULN = upper limit of normal.

[a] Hy's Law, defined as ALT or AST ≥ 3 × ULN plus total bilirubin > 2 × ULN without cholestasis and without alternative explanation, is used by the US Food and Drug Administration to identify drugs likely to cause severe drug-induced liver injury (Food and Drug Administration, 2009). An unblinded external panel of expert hepatologists reviewed all cases of concurrent ALT/AST elevations ≥ 3 × ULN and bilirubin > 2 × ULN and concluded that none met Hy's Law criteria due to alternate explanations and based on the pattern of abnormalities.

[b] IR/1000 PY, study duration-adjusted incidence rate per 1,000 person-years, calculated as number of participants with a TEAE of interest/PY × 1,000, where PY was calculated as (date of first TEAE of interest – date of first dose of study drug + 1)/365.25; for participants without a TEAE of interest, time on study was the study duration (last date on study – date of first dose of study drug + 1)/365.25.

Source: Selmaj et al. (2021)[40]

Appendix E.5.4 Macular oedema

Table E-19. Confirmed cases of macular oedema in all patients with relapsing multiple sclerosis treated with ozanimod

Case	Study	Treatment group	Time of onset relative to ozanimod initiation, days	Pre-existing risk factor or confounding factor	Action taken with study drug	Status
1	RADIANCE phase 3	Ozanimod 0.46 mg	211	History of macular oedema	Ozanimod withdrawn permanently	Resolved
2	RADIANCE phase 3	Ozanimod 0.46 mg	366	Central serous choroidopathy	Ozanimod withdrawn permanently	Resolved
3	SUNBEAM	Ozanimod 0.46 mg	182	Macular oedema secondary to ocular trauma	Ozanimod withdrawn permanently	Resolved
4	SUNBEAM	Ozanimod 0.46 mg	183	Prior unreported uveitis (intraocular inflammation)	Ozanimod withdrawn permanently	Resolved

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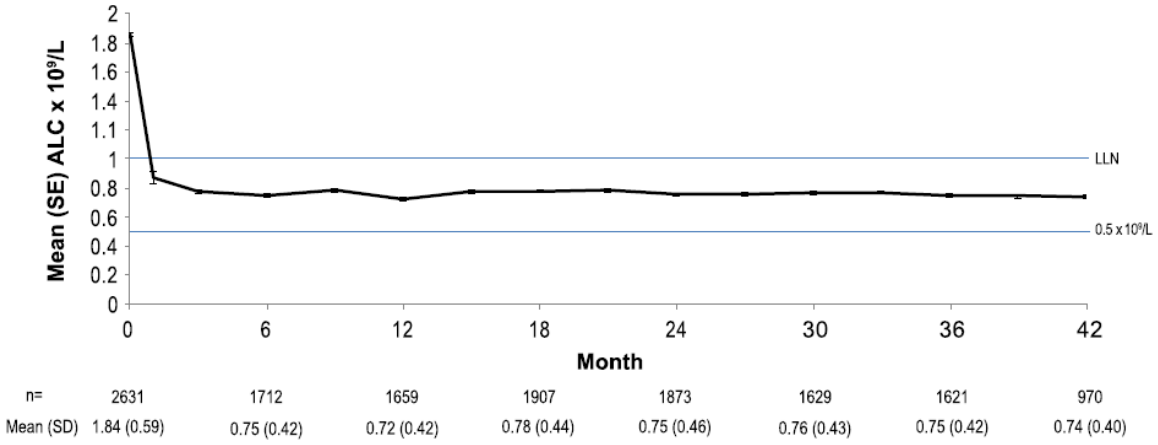
Case	Study	Treatment group	Time of onset relative to ozanimod initiation, days	Pre-existing risk factor or confounding factor	Action taken with study drug	Status
5	DAYBREAK	Ozanimod 0.92 mg	366	Pigment epithelial detachment with possible choroidal neovascularisation	No action taken	Resolving[a]
6	DAYBREAK	Ozanimod 0.92 mg	15	Uveitis	Ozanimod withdrawn permanently	Resolved
7	DAYBREAK	Ozanimod 0.92 mg	279	History of retinopathy and optic neuritis	Ozanimod withdrawn permanently	Resolved

[a] As of March 2020.

Source: Selmaj et al. (2021)[40]

Appendix E.5.5 Absolute lymphocyte count reductions

Figure E-4. Mean (standard error) absolute lymphocyte count by visit during treatment with ozanimod 0.92 mg: overall relapsing multiple sclerosis population



ALC = absolute lymphocyte count; LLN = lower limit of normal; SD = standard deviation; SE = standard error.

Source: Selmaj et al. (2021)[40]

Appendix E.5.6 Infections

Table E-20. Infections in participants with relapsing multiple sclerosis who were treated with ozanimod 0.92 mg

	Phase 3 study population (N = 882)		Overall RMS population (N = 2,631)	
	Incidence, n (%)	IR/1000 PY[a] (95% CI)	Incidence, n (%)	IR/1000 PY[a] (95% CI)
Any infection	310 (35.1)	300.5 (268.0-335.9)	1,278 (48.6)	270.1 (255.5-285.3)
Any serious infection[b]	9 (1.0)	6.7 (3.1-12.8)	44 (1.7)	6.3 (4.6-8.4)
Any opportunistic infection	16 (1.8)	12.0 (6.9-19.5)	113 (4.3)	16.4 (13.5-19.7)
Nasopharyngitis	98 (11.1)	78.8 (64.0-96.1)	457 (17.4)	72.9 (66.3-79.9)
URTI	52 (5.9)	40.3 (30.1-52.8)	249 (9.5)	37.6 (33.1-42.6)
UTI	36 (4.1)	27.4 (19.2-37.9)	138 (5.2)	20.2 (17.0-23.9)
Bronchitis	23 (2.6)	17.3 (11.0-26.0)	118 (4.5)	17.2 (14.2-20.6)

	Phase 3 study population (N = 882)		Overall RMS population (N = 2,631)	
	Incidence, n (%)	IR/1000 PY[a] (95% CI)	Incidence, n (%)	IR/1000 PY[a] (95% CI)
Pharyngitis	28 (3.2)	21.2 (14.1-30.6)	91 (3.5)	13.2 (10.6-16.2)
Respiratory tract infection	18 (2.0)	13.5 (8.0-21.4)	110 (4.2)	16.0 (13.1-19.2)
Respiratory tract infection viral	21 (2.4)	15.8 (9.8-24.2)	99 (3.8)	14.3 (11.7-17.5)
Influenza	9 (1.0)	6.7 (3.1-12.8)	73 (2.8)	10.5 (8.2-13.2)
Rhinitis	19 (2.2)	14.3 (8.6-22.4)	77 (2.9)	11.1 (8.8-13.9)
Sinusitis	13 (1.5)	9.8 (5.2-16.7)	76 (2.9)	10.9 (8.6-13.7)
Opportunistic infection in ≥ 2 participants[c]				
Oral herpes	6 (0.7)	4.5 (1.6-9.7)	40 (1.5)	5.7 (4.1-7.8)
Herpes zoster (including VZV)	5 (0.6)	3.7 (1.2-8.7)	37 (1.4)	5.3 (3.7-7.3)
Herpes simplex	1 (0.1)	0.7 (0.0-4.1)	12 (0.5)	1.7 (0.9-3.0)
Genital herpes	0	0 (0.0-2.7)	5 (0.2)	0.7 (0.2-1.7)
Fungal infection	0	0 (0.0-2.7)	4 (0.2)	0.6 (0.2-1.5)
Candida infection	0	0 (0.0-2.7)	3 (0.1)	0.4 (0.1-1.2)
Oral fungal infection	0	0 (0.0-2.7)	3 (0.1)	0.4 (0.1-1.2)
Herpes dermatitis	0	0 (0.0-2.7)	2 (0.07)	0.3 (0.0-1.0)
Genital fungal infection	1 (0.1)	0.7 (0.0-4.1)	2 (0.07)	0.3 (0.0-1.0)
Minimal postbaseline ALC < 0.5 × 10^9/L	480 (54.4)	542.5 (495.1-593.3)	1,669 (63.4)	450.6 (429.3-472.8)
Minimal postbaseline ALC < 0.2 × 10^9/L	29 (3.3)	21.9 (14.7-31.4)	182 (6.9)	26.7 (23.0-30.9)
ALC < 0.2 × 10^9/L around onset of any infection	2 (6.9)	1.5 (0.2-5.4)	18 (9.9)	2.6 (1.5-4.0)
ALC < 0.2 × 10^9/L around onset of serious infection[d]	0	0 (0.0-2.7)	1/182 (0.5) (pyelonephritis)	0.1 (0.0-0.8)
ALC < 0.2 × 10^9/L around onset of opportunistic infection[d]	0	0 (0.0-2.7)	1/182 (0.5) (pyelonephritis)	0.1 (0.0-0.8)

ALC = absolute lymphocyte count; CI = confidence interval; IR = incidence rate; PY = person-year; RMS = relapsing multiple sclerosis; TEAE = treatment-emergent adverse event; URTI = upper respiratory tract infection; UTI = urinary tract infection VZV = varicella zoster virus.

[a] IR/1000 PY, study duration-adjusted incidence rate per 1,000 person-years, calculated as number of participants with a TEAE of interest/PY × 1,000, where PY was calculated as (date of first TEAE of interest – date of first dose of study drug + 1)/365.25; for participants without a TEAE of interest, time on study was the study duration (last date on study – date of first dose of study drug + 1)/365.25.

[b] Serious infections occurring in > 2 participants can be found in Table E-16; a complete list of serious infections in participants with RMS who were treated with ozanimod 0.92 mg is available in Table E-21.

[c] Additional opportunistic infections that occurred in a single participant each (IR < 0.1/1000 PY) across all participants exposed to ozanimod 0.92 mg in any of the RMS trials included anal fungal infection, gastrointestinal candidiasis, oesophageal candidiasis, oral candidiasis, ophthalmic herpes simplex, herpes virus infection, nasal herpes, and varicella; 4 of these 8 infections occurred during the phase 3 trials.

[d] Participants who experienced an initial serious infection or opportunistic infection and had an ALC < 0.2 × 109/L at the laboratory visit prior to the event to either the time of the event or the assessment just after onset of the event.

Source: Selmaj et al. (2021)[40]

Table E-21. Serious infections

	Phase 3 study population (N = 882)		Overall RMS population (N = 2,631)	
	Incidence, n (%)	IR/1000 PY[a] (95% CI)	Incidence, n (%)	IR/1000 PY[a] (95% CI)
Any serious infection	9 (1.0)	6.7 (3.1-12.8)	44 (1.7)	6.3 (4.6-8.4)
Appendicitis	3 (0.3)	2.2 (0.5-6.5)	8 (0.3)	1.1 (0.5-2.2)
Pyelonephritis acute	1 (0.1)	0.7 (0.0-4.1)	7 (0.3)	1.0 (0.4-2.0)
Pneumonia	0	0 (0.0-2.7)	4 (0.2)	0.6 (0.2-1.5)
Bronchitis	0	0 (0.0-2.7)	2 (0.08)	0.3 (0.0-1.0)
Subcutaneous abscess	1 (0.1)	0.7 (0.0-4.1)	2 (0.08)	0.3 (0.0-1.0)
Lyme disease	0	0 (0.0-2.7)	2 (0.08)	0.3 (0.0-1.0)
Tonsillitis	1 (0.1)	0.7 (0.0-4.1)	2 (0.08)	0.3 (0.0-1.0)
UTI	1 (0.1)	0.7 (0.0-4.1)	2 (0.08)	0.3 (0.0-1.0)
Gastroenteritis	1 (0.1)	0.7 (0.0-4.1)	1 (0.04)	0.1 (0.0-0.8)
Postoperative abscess	1 (0.1)	0.7 (0.0-4.1)	1 (0.04)	0.1 (0.0-0.8)
Escherichia UTI	0	0 (0.0-2.7)	1 (0.04)	0.1 (0.0-0.8)
Acute sinusitis	0	0 (0.0-2.7)	1 (0.04)	0.1 (0.0-0.8)
Chronic hepatitis B	0	0 (0.0-2.7)	1 (0.04)	0.1 (0.0-0.8)
Dacryocystitis	0	0 (0.0-2.7)	1 (0.04)	0.1 (0.0-0.8)
HIV infection	0	0 (0.0-2.7)	1 (0.04)	0.1 (0.0-0.8)
Hepatitis A	0	0 (0.0-2.7)	1 (0.04)	0.1 (0.0-0.8)
Measles	0	0 (0.0-2.7)	1 (0.04)	0.1 (0.0-0.8)
Peritonitis	0	0 (0.0-2.7)	1 (0.04)	0.1 (0.0-0.8)
Pyelonephritis	0	0 (0.0-2.7)	1 (0.04)	0.1 (0.0-0.8)
Pyelonephritis chronic	0	0 (0.0-2.7)	1 (0.04)	0.1 (0.0-0.8)
Salpingitis	0	0 (0.0-2.7)	1 (0.04)	0.1 (0.0-0.8)
Toxic shock syndrome	0	0 (0.0-2.7)	1 (0.04)	0.1 (0.0-0.8)
URTI	0	0 (0.0-2.7)	1 (0.04)	0.1 (0.0-0.8)
Vestibular neuronitis	0	0 (0.0-2.7)	1 (0.04)	0.1 (0.0-0.8)
Chronic sinusitis	0	0 (0.0-2.7)	1 (0.04)	0.1 (0.0-0.8)
Diverticulitis	0	0 (0.0-2.7)	1 (0.04)	0.1 (0.0-0.8)

CI = confidence interval; HIV = human immunodeficiency virus; IR = incidence rate; PY = person-year; RMS = relapsing multiple sclerosis; TEAE = treatment-emergent adverse event; URTI = upper respiratory tract infection; UTI = urinary tract infection.

[a] IR/1000 PY, study duration-adjusted incidence rate per 1,000 person-years, calculated as number of participants with a TEAE of interest/PY × 1,000 where PY was calculated as (date of first TEAE of interest – date of first dose of study drug + 1)/365.25; for participants without a TEAE of interest, time on study was the study duration (last date on study – date of first dose of study drug + 1)/365.25.

Source: Selmaj et al. (2021)[40]

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Appendix E.5.7 Malignancies

Table E-22. Treatment-emergent malignancies by preferred term in participants with relapsing multiple sclerosis who were exposed to any dose of ozanimod (0.46 and/or 0.92 mg)

	Phase 3 study population (N = 882)		Overall RMS population (N = 2,631)	
	Incidence, n (%)	IR/1000 PY[a] (95% CI)	Incidence, n (%)	IR/1000 PY[a] (95% CI)
Treatment-emergent malignancies	8 (0.5)	298.2 (128.7-587.6)	25 (0.9)	289.3 (187.2-427.1)
Cutaneous	4 (0.2)	149.0 (40.6-381.6)	12 (0.4)	138.8 (71.7- 242.4)
Basal cell carcinoma	3 (0.2)	111.8 (23.0-326.6)	9 (0.3)	104.0 (47.6-197.5)
Keratoacanthoma	1 (0.06)	37.2 (0.9-207.4)	1 (0.04)	11.5 (0.3-64.3)
Squamous cell carcinoma	0	0 (0.0-2.7)	1 (0.04)	11.5 (0.3-64.3)
Malignant melanoma	0	0 (0.0-2.7)	1 (0.04)	11.5 (0.3-64.3)
NMSC	4 (0.2)	149.0 (40.6-381.6)	11 (0.4)	127.2 (63.5-227.6)
Noncutaneous	4 (0.2)	148.9 (40.6-381.4)	13 (0.5)	150.1 (79.9-256.7)
Breast cancer (women only)[b]	3/1,174 (0.3)	168.7 (34.8-493.0)	5/1,868 (0.3)	86.4 (28.0-201.5)
Cervix carcinoma	0	0 (0.0-2.7)	1 (0.04)	11.5 (0.3-64.3)
Testicular seminoma (pure) stage I[c]	1 (0.06)	37.2 (0.9-207.4)	1 (0.04)	11.5 (0.3-64.3)
Bile duct cancer[d]	0	0 (0.0-2.7)	1 (0.04)	11.5 (0.3-64.3)
Clear cell renal carcinoma	0	0 (0.0-2.7)	1 (0.04)	11.5 (0.3-64.3)
Glioblastoma	0	0 (0.0-2.7)	1 (0.04)	11.5 (0.3-64.3)
Malignant neoplasm	0	0 (0.0-2.7)	1 (0.04)	11.5 (0.3-64.3)
Pancreatic carcinoma metastatic	0	0 (0.0-2.7)	1 (0.04)	11.5 (0.3-64.3)
Papillary thyroid cancer	0	0 (0.0-2.7)	1 (0.04)	11.5 (0.3-64.3)
Treatment-emergent malignancies, excluding NMSC	4 (0.2)	148.9 (40.6-381.4)	14 (0.5)	161.7 (88.4-271.2)

CI = confidence interval (based on the Poisson distribution); IR = incidence rate; NMSC = non-melanoma skin cancer; PY = person-year; RMS = relapsing multiple sclerosis.

[a] IR/100,000 PY, study duration-adjusted incidence rate per 100,000 person-years, calculated as number of persons having the malignancy of interest/person-years × 100,000, where person-years = (date first malignancy of interest was documented – date of first dose of study drug + 1)/365.25; for participants not having the malignancy of interest, the time on study is the study duration (last date on study – first dose date of study drug +1)/365.25.

[b] Breast cancer includes cases using preferred terms of invasive breast cancer, breast cancer, and breast neoplasm.

[c] Diagnosed on study day 51.

[d] Diagnosis changed and confirmed after the data cutoff to hydatid cyst.

Source: Selmaj et al. (2021)[40]

Appendix E.5.8 Pulmonary function

Pulmonary function test (PFT) abnormalities were defined as forced expiratory volume in 1 second (FEV_1) or forced vital capacity (FVC) decrease to < 80% of baseline. PFT abnormalities were reported in 11.8% (n = 311) adults treated with ozanimod 0.92 mg across all RMS clinical trials, which included 10.2% (n = 90) participants treated with ozanimod 0.92 mg in the phase 3 studies. Of adults treated

with ozanimod 0.92 mg across all RMS trials, 9.4% (n = 242) had a FEV_1 < 80% of baseline at any visit and 6.7% (n = 171) for 2 consecutive postbaseline visits or on the last postbaseline visit. A reduction in FVC occurred in 7.9% (n = 204) of adults at any visit and 5.7% (n = 146) for 2 consecutive visits or on the last postbaseline visit. Pulmonary AEs were low with 1.5% (n = 39) events reported in adults receiving ozanimod 0.92 mg, which included 1 report (< 0.1%) of serious chronic obstructive pulmonary disease. Dyspnoea was reported in 0.4% (n = 10) participants exposed to ozanimod 0.92 mg across all RMS trials, with 1 participant discontinuing ozanimod due to dyspnoea.[40]

Appendix E.5.9 Potential drug interactions

Of patients were receiving ozanimod 0.92 or 0.46 mg, 20.6% (n = 573) did so with the following treatments concurrently:

- 12.2%: psychoanaleptic or psycholeptic drugs
- 7.8%: analgesics
- 2.0%: nasal preparations
- 1.5%: cough/cold preparations
- 0.7%: anaesthetics
- 0.1%: monoamine oxidase (MAO) inhibitor (moclobemide)

There were no reported cases of serotonin syndrome (preferred terms serotonin syndrome, neuroleptic malignant syndrome, hyperthermia malignant) or a hypertensive crisis (for those patients on an MAO inhibitor).[40]

Appendix E.5.10 Mortality

A total of 8 deaths occurred at the time of data cutoff:

- 3: malignancies
- 1: pneumonia
- 2: accidents (a drowning and a pedestrian-train accident)
- 1: pulmonary embolism after a 38-day hospitalisation for surgical repair of a lower limb fracture
- 1: as a result of chronic kidney failure approximately 10 months after prematurely discontinuing ozanimod 0.92 mg during phase 3 RADIANCE due to Guillain-Barre syndrome and posterior reversible encephalopathy syndrome[40]

Appendix E.5.11 Clinical rebound

Posttreatment follow-up is limited because most participants continued on treatment in the DAYBREAK trial at the time of data cutoff. At the time of the analysis, no posttreatment AEs indicative of rebound (MS flare) had been reported.[40]

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Appendix F. Comparative analysis of efficacy and safety

Appendix F.1 Induction results

Table F-1. Meta-analysis of studies comparing ozanimod to currently existing medications for patients with moderate-to-severe ulcerative colitis

Outcome	Studies included in the analysis	Treatment	Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
			Difference (risk difference)	Lower CrI	Upper CrI	Difference (relative risk)	Lower CrI	Upper CrI		
Induction – Clinical remission (Bio-naïve)	TRUE NORTH[24]	OZA vs. placebo	0.11	-0.03	0.39	2.66[a]	0.58	6.96	An NMA was conducted for an indirect comparison. Within the NMA, ORs were reported. The ORs were converted to RR to show the relative difference between treatments. In turn, the risk difference was calculated from the RR. The conversion from OR to RR used the formula provided in Appendix 2 of	No, because cost minimisation approach used.
	TRUE NORTH[24] PURSUIT-SC[13]	OZA vs. GOL 200/100 mg	0.02	-0.15	0.48	1.12[b]	0.17	3.69		
	TRUE NORTH[24] ACT 1[16] ACT 2[16] Jiang 2015[17] Kobayashi 2016[18]	OZA vs. INF 5 mg/kg	-0.09	0.29	-0.32	0.78[c]	1.75	0.17		
	TRUE NORTH[24] GEMINI 1[19] Motoya 2019[21]	OZA vs. VED 300 mg	-0.01	0.39	-0.19	0.96[d]	2.71	0.18		
Induction – Clinical response (Bio-naïve)	TRUE NORTH[24]	OZA vs. placebo	0.23	-0.09	0.53	1.78[a]	0.71	2.82		
	TRUE NORTH[24] PURSUIT-SC[13]	OZA vs. GOL 200/100 mg	0.03	-0.37	0.38	1.06[b]	0.28	1.75		
	TRUE NORTH[24] ACT 1[16] ACT 2[16] Jiang 2015[17] Kobayashi 2016[18]	OZA vs. INF 5 mg/kg	-0.08	0.20	-0.45	0.88[c]	1.28	0.35		

Outcome	Studies included in the analysis	Treatment	Absolute difference in effect: Difference (risk difference)	Absolute difference in effect: Lower CrI	Absolute difference in effect: Upper CrI	Relative difference in effect: Difference (relative risk)	Relative difference in effect: Lower CrI	Relative difference in effect: Upper CrI	Method used for quantitative synthesis	Result used in the health economic analysis?
	TRUE NORTH[24] GEMINI 1[19] Motoya 2019[21]	OZA vs. VED 300 mg	-0.01	0.33	-0.37	0.98 [d]	1.61	0.31	the Handbook for the Danish Medicines Council process and method of new medicines and indication extensions: Version 2.6.[54] Similarly, the calculation of absolute difference based on RR used the formula provided in Appendix 5.[54] The ACR used to calculate the relative risk and risk difference for each treatment comparison was taken from the largest phase 3 study.	
Induction – Clinical remission (Bio-experienced)	TRUE NORTH[24]	OZA vs. placebo	0.14	0.05	0.28	3.95 [a]	1.98	7.10		
	TRUE NORTH[24] ULTRA 2[12]	OZA vs. ADA 160/80/40 mg	0.13	0.00	0.37	2.46[e]	1.00	5.03		
	TRUE NORTH[24] UNIFI[22]	OZA vs. UST 6 mg/kg	-0.01	0.12	-0.07	0.95[f]	1.96	0.42		
	TRUE NORTH[24] GEMINI 1[19] Motoya 2019[21]	OZA vs. VED 300 mg	0.11	-0.01	0.32	2.12[d]	0.90	4.31		
Induction – Clinical response (Bio-experienced)	TRUE NORTH[24]	OZA vs. placebo	0.25	0.10	0.41	2.33 [a]	1.54	3.24		
	TRUE NORTH[24] ULTRA 2[12]	OZA vs. ADA 160/80/40 mg	0.21	0.00	0.40	1.57 [e]	1.00	2.09		
	TRUE NORTH[24] UNIFI[22]	OZA vs. UST 6 mg/kg	-0.01	0.16	-0.20	0.98 [f]	1.28	0.65		
	TRUE NORTH[24] GEMINI 1[19] Motoya 2019[21]	OZA vs. VED 300 mg	0.18	-0.02	0.37	1.46 [d]	0.94	1.94		
Induction – Serious Adverse Events (Overall)	TRUE NORTH[24] TOUCHSTONE[11]	OZA vs. placebo	0.00	-0.02	0.04	1.01[a]	0.49	2.15		
	TRUE NORTH[24] TOUCHSTONE[11] Suzuki 2014[5] ULTRA 1[7] ULTRA 2[12]	OZA vs. ADA 160/80/40 mg	0.07	0.25	-0.03	1.54[e]	3.09	0.71		

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Outcome	Studies included in the analysis	Treatment	Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
			Difference (risk difference)	Lower CrI	Upper CrI	Difference (relative risk)	Lower CrI	Upper CrI		
	TRUE NORTH[24] TOUCHSTONE[11] PURSUIT-SC[13]	OZA vs. GOL 200/100 mg	0.20	0.47	-0.04	1.73[b]	2.74	0.85		
	TRUE NORTH[24] TOUCHSTONE[11] Kobayashi 2016[18]	OZA vs. INF 5 mg/kg	0.04	0.25	-0.04	1.49[g]	3.84	0.49		
	TRUE NORTH[24] TOUCHSTONE[11] UNIFI[22]	OZA vs. UST 6 mg/kg	0.04	0.15	-0.01	2.05[f]	5.30	0.74		
	TRUE NORTH[24] TOUCHSTONE[11] GEMINI 1[19] Motoya 2019[21]	OZA vs. VED 300 mg	0.01	0.08	-0.01	1.47[d]	3.81	0.58		

ACR = assumed control group rate; ADA = adalimumab; CrI = credible interval; GOL = Golimumab; INF = infliximab; NA = not applicable; NMA = network meta-analysis; NR = not reported; OR = odds ratio; OZA = ozanimod; RR = relative risk; UST = ustekinumab; VED = vedolizumab.

[a] ACR taken from placebo arm of TRUE NORTH.

[b] ACR taken from GOL 200/100 mg arm of PURSUIT-SC.

[c] ACR taken from INF 5 mg arm of ACT 1.

[d] ACR taken from VED 300 mg arm of GEMINI 1.

[e] ACR taken from ADA arm of ULTRA 2.

[f] ACR taken from UST 6 mg/kg arm of UNIFI.

[g] ACR taken from INF 5 mg arm of Kobayashi 2016

Source: BMS Celgene data on file (2021)[26]

Appendix F.2 Maintenance results

Table F-2. Meta-analysis of studies comparing ozanimod to currently existing medications for patients with moderate-to-severe ulcerative colitis

Outcome	Studies included in the analysis	Treatment	Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
			Difference (risk difference)	Lower CrI	Upper CrI	Difference (relative risk)	Lower CrI	Upper CrI		
Maintenance - Corticosteroid-free remission (Bio-naive TT population)	ACT 1[16] Suzuki 2014[5] ULTRA 2[12]	INF 5 mg/kg vs ADA 40	0.06	-0.07	0.32	1.43[a]	0.49	3.36	An NMA was conducted for an indirect comparison. Within the NMA, ORs were reported. The ORs were converted to RR to show the relative difference between treatments. In turn, the risk difference was calculated from the RR. The conversion from OR to RR used the formula provided in Appendix 2 of the Handbook for the Danish Medicines Council process and method of new medicines and indication extensions: Version 2.6.[54] Similarly, the calculation of absolute difference based on RR used the formula provided in Appendix 5.[54] The ACR used to calculate the relative risk and risk difference for each treatment comparison was taken from the largest phase 3 study.	No, because cost minimisation approach used.
	ACT 1[16] Suzuki 2014[5] ULTRA 2[12] VARSITY[6]	INF 5 mg/kg vs VEDO 300 mg Q8W	0.19	-0.08	0.53	1.87[b]	0.63	3.46		
	ACT 1[16]	INF 5 mg/kg vs placebo	0.17	0.04	0.41	2.94[c]	1.40	5.59		
	VARSITY[6]	ADA 40 mg vs VEDO 300 mg Q8W	0.09	-0.05	0.28	1.42[b]	0.78	2.30		
	Suzuki 2014[5] ULTRA 2[12]	ADA 40 mg vs placebo	0.08	0.01	0.22	2.17[d]	1.12	4.14		
	Suzuki 2014[5] ULTRA 2[12] VARSITY[6]	VED 300 mg Q8W vs placebo	0.03	-0.03	0.17	1.44[e]	0.53	3.70		
Maintenance - Corticosteroid-free remission (Bio-naive RR population)	TRUE NORTH[24]	OZA vs. placebo	0.23	0.11	0.35	1.65[f]	1.30	1.99		
	TRUE NORTH[24] PURSUIT-M[14]	OZA vs. GOL 50 mg Q4W	0.06	-0.11	0.28	1.21[h]	0.62	1.99		
	TRUE NORTH[24] PURSUIT-J[15]	OZA vs. GOL 100 mg Q4W	0.09	-0.07	0.31	1.37[i]	0.70	2.32		

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Outcome	Studies included in the analysis	Treatment	Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
			Difference (risk difference)	Lower CrI	Upper CrI	Difference (relative risk)	Lower CrI	Upper CrI		
	PURSUIT-M[14]									
	TRUE NORTH[24] UNIFI[22]	OZA vs. UST 90 mg Q12W	0.06	-0.14	0.24	1.12[j]	0.70	1.53		
	TRUE NORTH[24] GEMINI 1[19] Motoya 2019[21]	OZA vs. VED 300 mg Q8W	0.00	-0.20	0.26	1.00[k]	0.45	1.72		
Maintenance - Corticosteroid-free remission (Bio-experienced TT population)	ULTRA 2[12]	ADA 40 vs placebo	0.16	-0.04	0.57	2.30[e]	0.65	5.54		
	VARSITY[6]	ADA 40 vs VEDO 300 Q8W	0.50	0.03	0.77	3.25[b]	1.14	4.45		
	ULTRA 2[12] VARSITY[6]	Placebo vs VEDO 300 Q8W	0.10	-0.04	0.82	2.97[e]	0.23	17.15		
Maintenance - Corticosteroid-free remission (Bio-experienced RR population)	TRUE NORTH[24]	OZA vs. placebo	0.30	0.08	0.51	2.07[f]	1.28	2.85		
	TRUE NORTH[24] UNIFI[22]	OZA vs. UST 90 mg Q12W	0.18	-0.07	0.48	1.67[j]	0.73	2.77		
	TRUE NORTH[24] GEMINI 1[19] Motoya 2019[21]	OZA vs. VED 300 mg Q8W	-0.12	0.27	-0.25	0.54[k]	2.04	0.05		
Maintenance - Endoscopic improvement (Bio-naïve TT population)	ACT 1[16] Suzuki 2014[5] ULTRA 2[12] VARSITY[6]	INF 5 mg/kg vs VEDO 300 mg	0.01	-0.17	0.21	1.02[b]	0.61	1.48		
	ACT 1[16]	INF 5 mg/kg vs ADA 40	0.14	-0.01	0.32	1.49[l]	0.95	2.12		

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Outcome	Studies included in the analysis	Treatment	Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
			Difference (risk difference)	Lower CrI	Upper CrI	Difference (relative risk)	Lower CrI	Upper CrI		
	Suzuki 2014[5] ULTRA 2[12]									
	ACT 1[16]	INF 5 mg/kg vs placebo	0.31	0.19	0.40	1.67[c]	1.41	1.88		
	VARSITY[6]	VEDO 300 mg Q8W vs ADA 40 mg	0.14	0.06	0.22	1.47[m]	1.19	1.75		
	Suzuki 2014[5] ULTRA 2[12] VARSITY[6]	VED 300 mg Q8W vs placebo	0.28	0.15	0.40	2.43[e]	1.76	3.10		
	Suzuki 2014[5] ULTRA 2[12]	ADA 40 vs placebo	0.16	0.07	0.27	1.56[d]	1.23	1.92		
Maintenance - Endoscopic improvement (Bio-naïve RR population)	TRUE NORTH[24]	OZA vs. placebo	0.20	0.08	0.31	1.65[f]	1.27	2.03		
	TRUE NORTH[24] PURSUIT-J[15]	OZA vs. GOL 100 mg Q4W	-0.34	-0.04	-0.54	0.46[n]	0.94	0.15		
	TRUE NORTH[24] GEMINI 1[19]	OZA vs. VED 300 mg Q8W	-0.18	0.03	-0.36	0.70[k]	1.04	0.39		
Maintenance - Endoscopic improvement (Bio-experienced TT population)	VARSITY[6]	VEDO 300 mg Q8W vs ADA 40 mg	0.07	-0.07	0.25	1.25[m]	0.73	1.93		
	ULTRA 2[12] VARSITY[6]	VED 300 mg Q8W vs placebo	0.10	-0.02	0.35	2.03[e]	0.78	4.55		
	ULTRA 2[12]	ADA 40 vs placebo	0.06	-0.02	0.21	1.56[e]	0.75	3.17		

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Outcome	Studies included in the analysis	Treatment	Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
			Difference (risk difference)	Lower CrI	Upper CrI	Difference (relative risk)	Lower CrI	Upper CrI		
Maintenance - Endoscopic improvement (Bio-experienced RR population)	TRUE NORTH[24]	OZA vs. placebo	0.20	0.04	0.40	2.14[f]	1.26	3.29		
	TRUE NORTH[24] UNIFI[22]	OZA vs. UST 90 mg Q12W	0.20	-0.03	0.45	1.76[j]	0.87	2.77		
	TRUE NORTH[24] GEMINI 1[19]	OZA vs. VED 300 mg Q8W	-0.24	0.06	-0.38	0.42[k]	1.14	0.09		
Maintenance – Serious adverse events (Overall)	TRUE NORTH[24]	OZA vs. placebo	-0.03	-0.05	0.02	0.65[f]	0.31	1.29		
	TRUE NORTH[24] PURSUIT-J[15] PURSUIT-M[14]	OZA vs GOL Pooled	-0.07	-0.11	0.03	0.54[o]	0.20	1.24		
	TRUE NORTH[24] UNIFI[22]	OZA vs. UST 90 mg	-0.01	-0.06	0.10	0.85[j]	0.30	2.17		
	TRUE NORTH[24] VISIBLE 1[20]	OZA vs. VED 108 mg SC	-0.01	-0.07	0.15	0.95[p]	0.30	2.60		
	TRUE NORTH[24] GEMINI 1[19] Motoya 2019[21] VISIBLE 1[20]	OZA vs. VED 300 mg IV	-0.01	-0.08	0.12	0.89[k]	0.35	2.00		
Serious adverse events in combined treatment phases in the overall population	TOUCHSTONE-Mixed (TT) True North-Ind True North-Maint (RR)	OZA vs placebo	-0.01	-0.03	0.02	0.79[f]	0.47	1.29		
	Suzuki 2014-Ind ULTRA 1-Ind	OZA vs ADA 160/80/40 mg	0.00	-0.05	0.08	0.96[a]	0.55	1.63		

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Outcome	Studies included in the analysis	Treatment	Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
			Difference (risk difference)	Lower CrI	Upper CrI	Difference (relative risk)	Lower CrI	Upper CrI		
	ULTRA 2-Mixed (TT) TOUCHSTONE-Mixed (TT) True North-Ind True North-Maint (RR)									
	PURSUIT-J-Maint (RR) PURSUIT-M-Maint (RR) PURSUIT-SC-Ind TOUCHSTONE-Mixed (TT) True North-Ind True North-Maint (RR)	OZA vs GOL pooled	-0.01	-0.12	0.13	0.95[q]	0.55	1.50		
	ACT 1-Mixed (TT) ACT 2-Mixed (TT) Jiang 2015-Mixed (TT) Kobayashi 2016-Mixed (TT) TOUCHSTONE-Mixed (TT)	OZA vs INF 5 mg/kg	0.01	0.12	-0.06	1.06[r]	1.72	0.61		

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Outcome	Studies included in the analysis	Treatment	Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
			Difference (risk difference)	Lower CrI	Upper CrI	Difference (relative risk)	Lower CrI	Upper CrI		
	True North-Ind True North-Maint (RR)									
	UNIFI-Ind TOUCHSTONE-Mixed (TT) True North-Ind True North-Maint (RR)	OZA vs UST 6 mg/kg	0.02	0.09	-0.01	1.63[s]	3.76	0.67		
	UNIFI-Maint (RR) TOUCHSTONE-Mixed (TT) True North-Ind True North-Maint (RR)	OZA vs UST 90 mg Q12W	0.00	0.11	-0.05	1.03[j]	2.31	0.42		
	VISIBLE 1-Maint (RR) TOUCHSTONE-Mixed (TT) True North-Ind True North-Maint (RR)	OZA vs VED 108 mg SC	0.02	0.18	-0.05	1.19[p]	2.88	0.46		
	GEMINI 1-Ind GEMINI 1-Maint (RR) Motoya 2019-Ind	OZA vs VED 300 mg IV	0.02	0.12	-0.04	1.16[k]	1.93	0.67		

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Outcome	Studies included in the analysis	Treatment	Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
			Difference (risk difference)	Lower CrI	Upper CrI	Difference (relative risk)	Lower CrI	Upper CrI		
	Motoya 2019-Maint (RR)									
	VISIBLE 1-Maint (RR)									
	TOUCHSTONE-Mixed (TT)									
	True North-Ind									
	True North-Maint (RR)									

ACR = American College of Rheumatology; ADA = adalimumab; CrI = credible interval; GOL = Golimumab; INF = infliximab; NA = not applicable; NMA = network meta-analysis; OR = odds ratio; OZA = ozanimod; Q12W = every 12 weeks; Q2W = every 2 weeks; Q4W = every 4 weeks; Q8W = every 8 weeks; RR = relative risk; SC = subcutaneous; UST = ustekinumab; VED = vedolizumab.

[a] ACR taken from ADA arm of ULTRA 2.

[b] ACR taken from VED 300 mg arm of VARSITY.

[c] ACR taken from placebo arm of ACT 1.

[d] ACT taken from placebo arm of Suzuki 2014.

[e] ACR taken from placebo arm of ULTRA 2.

[f] ACR taken from placebo arm of TRUE NORTH.

[h] ACR taken from GOL 50 mg Q4W arm of PURSUIT-M.

[i] ACR taken from GOL 100 mg Q4W arm of PURSUIT-M.

[j] ACR taken from UST 90 mg Q12W arm of UNIFI.

[k] ACR taken from VED 300 mg arm of GEMINI 1.

[l] ACT taken from ADA arm of Suzuki 2014.

[m] ACR taken from ADA arm of VARSITY.

[n] ACR taken from GOL 100 mg Q4W arm of PURSUIT-J.

[o] ACR taken from all GOL arm of PURSUIT-M

[p] ACR taken from VED 108 mg arm of VSIBLE 1.

[q] ACR taken from GOL arm of PURSUIT-SC

[r] ACR taken from INF 5 mg arm of ACT 1 and ACT 2.

[s] ACR taken from UST 6 mg/kg arm of UNIFI.

Source: BMS Celgene data on file (2021)[26]

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Appendix G. TRUE NORTH and TOUCHSTONE: additional study details

Appendix G.1 TRUE NORTH: statistical testing

Intention-to-treat (ITT) populations were used as the primary population for all efficacy analyses. The induction period ITT population consisted of all randomised patients from cohort 1 of the induction period who received ≥ 1 dose of the study drug and all enrolled patients from cohort 2 of the induction period who received ≥ 1 dose of the study drug. The maintenance period ITT population consisted of all randomised patients who received ≥ 1 dose of the study drug in the maintenance period. Safety populations were used to analyse safety data and consisted of all patients who received ≥ 1 dose of the study drug.[24]

Appendix G.1.1 TRUE NORTH: efficacy analyses—induction period

A 2-sided Cochran-Mantel-Haenszel test was used to analyse the primary efficacy endpoint (proportion of patients in clinical remission at week 10) and all secondary efficacy endpoints expressed as proportions of patients, with data stratified by corticosteroid use at screening (yes or no) and previous anti–tumour necrosis factor (anti-TNF) use (yes or no). An analysis of covariance (ANCOVA) model was used to analyse all secondary efficacy endpoints that were expressed as changes from baseline, with corticosteroid use at screening, previous use of anti-TNF therapy, and baseline value of the corresponding outcome included as covariates.[24]

Subgroup analyses were performed for clinical remission, clinical response, endoscopic improvement, mucosal healing at week 10 by corticosteroid use at screening (yes vs. no), previous use of anti-TNF therapy (yes vs. no), baseline total Mayo Score (≤ 9 vs. > 9), extent of colitis (left-sided vs. extensive), sex (female vs. male), age at screening (≤ median vs. > median), baseline faecal calprotectin (≤ 250 mg/kg vs. > 250 mg/kg), baseline absolute lymphocyte count (≤ 1,500 × 10^6/L vs. > 1,500 × 10^6/L), years since initial ulcerative colitis (UC) diagnosis (≤ 4 years vs. > 4 years), region (North America, Eastern Europe, Western Europe, Asia Pacific), baseline partial Mayo Score (≤ median vs. > median), baseline partial Mayo Score (≤ 7 vs. > 7), baseline endoscopic subscore (2 vs. 3), and moderate UC status at baseline (4-component Mayo Score of 6-10; yes vs. no).[24]

A hierarchical testing procedure was used to control the overall type I error rate for multiplicity, starting with the primary endpoint and followed by the 3 key secondary efficacy endpoints. Formal testing proceeded to the next outcome analysis if results from the previous analysis were significant (2-sided $P < 0.05$). If the results were not significant, all subsequent analyses were considered to be exploratory, with the corresponding *P* values being nominal. Other secondary efficacy endpoints were tested in a non-hierarchical manner without multiplicity adjustments.[24]

A post hoc analysis examined the change in rectal bleeding score (RBS) from baseline through week 10.[23]

Appendix G.1.2 TRUE NORTH: efficacy analyses—maintenance period

A 2-sided Cochran-Mantel-Haenszel test was used to analyse the primary efficacy endpoint (proportion of patients in clinical remission at week 52) and all secondary efficacy endpoints expressed as proportions of patients, with data stratified by clinical remission status at week 10 (3- or 4-component Mayo Score) of the induction period (yes or no) and corticosteroid use at week 10 of the induction period (yes or no). An ANCOVA model was used to analyse all secondary efficacy

endpoints that were expressed as changes from baseline, with clinical remission status at week 10 of the induction period, corticosteroid use at week 10 of the induction period, and baseline value of the corresponding outcome included as covariates.[24]

Subgroup analyses were performed for clinical remission, clinical response, endoscopic improvement, corticosteroid-free remission, and mucosal healing at week 52 by the subgroups analysed for the induction period in addition to clinical remission status at week 10 (in remission vs. not in remission) and corticosteroid use at week 10 (yes vs. no).[24]

A hierarchical testing procedure was used to control the overall type I error rate for multiplicity, starting with the primary endpoint and followed by the 6 key secondary efficacy endpoints. Formal testing proceeded to the next outcome analysis if results from the previous analysis were significant (2-sided $P < 0.05$). If the results were not significant, all subsequent analyses were considered to be exploratory, with the corresponding *P* values being nominal. Other secondary efficacy endpoints were tested in a non-hierarchical manner without multiplicity adjustments.[24]

Appendix G.1.3 TRUE NORTH: imputation—induction and maintenance periods

Non-responder imputation was used to handle missing values for the primary analyses, as well as for the analyses of all secondary efficacy endpoints that were proportions. Patients with missing week 10 efficacy data for the induction period and/or patients with missing week 52 efficacy data for the maintenance period were classified as non-responders. In addition, patients meeting criteria for treatment failure were considered non-responders using non-responder imputation for efficacy analyses. Treatment was considered to have failed for patients if any of the following occurred[24]:

- Any protocol-prohibited change in medications, including the following:
  - Postbaseline initiation of, or increase in, total daily dose level higher than the maximum dose taken between the screening and baseline visits in corticosteroids or 5-aminosalicylic acid dose to treat UC
  - Prolonged course of systemic corticosteroids for > 14 days for treatment of diseases other than UC
  - Initiation of an immunomodulator, including 6-mercaptopurine, azathioprine, anti-TNF agents, vedolizumab, or tofacitinib
- A colectomy (partial or total) or an ostomy
- Discontinuation of study drug for lack of therapeutic effect before the week 10 or week 52 efficacy evaluations

Appendix G.1.4 TRUE NORTH: post hoc analyses

Post hoc analyses were conducted for change in RBS from baseline at weeks 2, 4, 5, 6, 8, and 10 of the induction period using a mixed-effect model for repeated measures with the following main effects: previous anti-TNF use at screening, corticosteroid use at screening, treatment, and timepoint in weeks.

Post hoc analyses were also performed for the minimum clinically important difference (MCID) of the SF-36 Health Survey (SF-36) Physical Component Summary (PCS) and Mental Component Summary (MCS) scores for the induction and maintenance periods. The MCID for the SF-36 PCS and MCS was defined as a ≥ 5-point improvement in each summary score.

Appendix G.1.5 TRUE NORTH: significance analysis

The 2-sided $P < 0.05$ values calculated in the efficacy analyses were deemed nominally significant because no multiplicity adjustment was applied.[24]

Appendix G.2 TOUCHSTONE: statistical testing

The Cochran-Mantel-Haenszel chi-square test was used to analyse the rates of clinical remission, clinical response, and mucosal healing at weeks 8 and 32, with data stratified by previous use of anti-TNF therapy (yes or no). An ANCOVA model was used to analyse changes in the 4-component Mayo Score from baseline to week 8 and to week 32, with treatment arm, previous use of anti-TNF therapy, and baseline value of the corresponding outcome included as covariates. Non-parametric methods were used to analyse the changes from baseline in the absolute lymphocyte count and the concentrations of C-reactive protein, calprotectin, and lactoferrin.[11]

To control for multiplicity, a closed hierarchical procedure was used for the primary and secondary efficacy endpoints. The order of hierarchical testing was as follows: clinical remission rates at week 8 in the ozanimod 1 mg arm versus the placebo arm, clinical remission rates at week 8 in the ozanimod 0.5 mg arm versus the placebo arm, followed by each major secondary efficacy endpoint in order (clinical response, change in Mayo Score from baseline, and mucosal healing at week 8), with comparisons for the 1-mg dose ranked before those for the 0.5-mg dose. Formal testing proceeded to the next outcome analysis if results from the previous analysis were significant (2-sided $P < 0.05$); if the results were not significant, all subsequent analyses were considered to be exploratory, with the corresponding *P* values being nominal.[11]

Intention-to-treat analyses were used for efficacy endpoints. Non-responder imputation was used to handle missing values for the primary analysis, as well as for the analyses of all secondary efficacy endpoints that were proportions. Patients who did not continue to the maintenance period were classified as non-responders at week 32. Last observation carried forward imputation was used to handle missing values for the analyses of changes from baseline in the Mayo Score and concentrations of C-reactive protein, calprotectin, and lactoferrin.[11]

Prespecified subgroup analyses were performed for clinical remission at week 8 by previous use of anti-TNF therapy (yes or no), age (less than the median or at least as old as the median), sex, colonic area involved (left side or extensive), and baseline 4-component Mayo Score (≤ 8 or > 8).[11]

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Appendix G.3 Pooled relapsing multiple sclerosis safety data

Table G-1. Pooled relapsing multiple sclerosis: inclusion and exclusion criteria

RADIANCE (Phase 2)[55,56] NCT01628393	RADIANCE (Phase 3)[57] NCT02047734	SUNBEAM[58] NCT02294058	DAYBREAK[59,40] NCT02576717
Key inclusion criteria			
▪ Aged 18-55 years ▪ Relapsing MS fulfilling the McDonald criteria ▪ EDSS score of 0-5 ▪ Detection of brain lesions with MRI consistent with MS ▪ 1 or more relapses in the previous 12 months, or 1 or more relapses in the past 24 months and 1 or more gadolinium-enhancing MRI lesions in the previous 12 months ▪ Clinical stability without relapse or systemic corticosteroid treatment in the past month ▪ Positive varicella zoster virus serology	▪ Aged 18-55 years ▪ MS according to 2010 McDonald criteria ▪ A relapsing clinical course (relapsing-remitting, progressive-relapsing, or secondary progressive) ▪ Brain MRI lesions consistent with MS ▪ An EDSS score of 0.0-5.0 ▪ At least 1 relapse within 12 months before screening or at least 1 relapse within 24 months before screening plus at least 1 gadolinium-enhancing lesion within the 12 months before randomisation ▪ Positive varicella zoster virus immunoglobulin G antibody status or varicella zoster virus vaccination at least 30 days before randomisation	▪ Aged 18-55 years ▪ Diagnosed with MS per 2010 McDonald criteria ▪ Are lapsing clinical course (relapsing-remitting, secondary progressive, or progressive-relapsing) ▪ History of brain MRI lesions consistent with MS ▪ Baseline EDSS score of 0.0-5.0 ▪ At least 1 relapse in the 12 months before screening or at least 1 relapse in the 24 months before screening plus at least 1 gadolinium-enhancing lesion in the 12 months before randomisation ▪ Participants had to have no history of relapse or systemic corticosteroid or adrenocorticotrophic hormone use from 30 days before screening up to randomisation and positive varicella zoster virus immunoglobulin G antibody status or varicella zoster virus vaccination at least 30 days before randomisation	▪ Participant in 1 of the parent trials ▪ Aged 18-55 years ▪ MS diagnosed by 2010 McDonald criteria ▪ Relapsing clinical course ▪ History of brain MRI lesions consistent with MS ▪ EDSS score of 0-5.0 (phase 2 and 3) or 0-6.0 (phase 1)

RADIANCE (Phase 2)[55,56] NCT01628393	RADIANCE (Phase 3)[57] NCT02047734	SUNBEAM[58] NCT02294058	DAYBREAK[59,40] NCT02576717
Key exclusion criteria			
▪ Primary progressive course ▪ Disease duration > 15 years with EDSS score of ≤ 2.0 ▪ Clinically relevant cardiovascular disease ▪ Resting heart rate of less than 55 bpm ▪ Treatment with drugs known to alter heart rate or cardiac conduction (i.e., β blockers, calcium-channel blockers, and class Ia or class III antiarrhythmic drugs) ▪ Diabetes mellitus, uveitis, or other clinically significant medical illnesses or laboratory abnormalities	▪ Primary progressive MS ▪ Disease duration > 15 years and an EDSS of ≤ 2.0 ▪ Previous inability to tolerate interferon beta ▪ Specific cardiovascular conditions (e.g., recent myocardial infarction, stroke, or prolonged QTcF) ▪ Resting heart rate less than 55 bpm at screening ▪ Previous treatment with lymphocyte-depleting therapies or lymphocyte-trafficking blockers ▪ Any active infection	▪ Primary progressive MS ▪ Disease duration > 15 years with an EDSS of ≤ 2.0 ▪ Contraindications to MRI or gadolinium contrast ▪ Previous inability to tolerate interferon beta ▪ Resting heart rate less than 55 bpm at screening ▪ Specific cardiac conditions (e.g., recent myocardial infarction, stroke, prolonged QTcF) ▪ Previous treatment with lymphocyte-depleting therapies or lymphocyte-trafficking blockers ▪ Active infections	▪ Not stated in published study results

bpm = beats per minute; EDSS = Expanded Disability Status Scale; MRI = magnetic resonance imaging; MS = multiple sclerosis; QTcF = Fridericia-corrected QT interval.

Table G-2. Pooled relapsing multiple sclerosis: schedule of safety assessments

	Phase 1 (NCT02797015)	Phase 2 RADIANCE (NCT01628393)	Phase 2 RADIANCE blinded extension period[a]	Phase 3 RADIANCE (NCT02047734)	Phase 3 SUNBEAM (NCT02294058)	Open-label extension study DAYBREAK (NCT02576717)
Monitoring of TEAEs and serious TEAEs	Throughout each study (each study visit)					
Vital signs[d]	Screening; days 1, 5, 8, 28, 56, 85; early termination or EOS[b]	Screening; days 1, 5,[e] 29, 57, 85, 113, 141; EOT-day 169[e]	Day 183,[f] Q12 weeks, EOS, unscheduled relapse visit, early termination, F/U visit	Screening; days 1, 15, 92, 183, 274, 365, 456, 547, 638, 729; unscheduled relapse visit; early termination; F/U visit	Screening; days 1,[g] 15, 92, 183, 274; EOT-day 365; unscheduled relapse visit; early termination; F/U visit	Day 1,[c] Q3 months, unscheduled relapse visit, early termination or EOS, safety F/U visit
Physical examination	Screening, early termination or EOS[b]	Screening, EOT-day 169	EOS, early termination	Screening, days 365 and 729, early termination	Screening, day 365, early termination	Day 1,[c] Q12 months, early termination or EOS

	Phase 1 (NCT02797015)	Phase 2 RADIANCE (NCT01628393)	Phase 2 RADIANCE blinded extension period[a]	Phase 3 RADIANCE (NCT02047734)	Phase 3 SUNBEAM (NCT02294058)	Open-label extension study DAYBREAK (NCT02576717)
12-lead ECG[h]	Screening; days 1, 5, 8, 28, 56, 85	Screening; days 1, 5,[e] 29, 85, EOT-day 169[e]	Day 183,[f] Q12 weeks, EOS, early termination, F/U visit	Screening; days 1, 15, 365, 729; early termination; F/U visit	Screening; day 1,[g] day 15, EOT-day 365 (unless done within previous 6 months), early termination, F/U visit	Day 1, Q12 months, early termination or EOS, safety F/U visit
Complete blood count	Screening; predose on days 1, 5, 8, 28, 56, 85; postdose on days 1, 2, 3, and 4-6; early termination or EOS[b]	Screening; days 1, 29, 85; EOT-day 169	Q12 weeks, EOS, unscheduled relapse visit, early termination, F/U visit	Screening; days 1, 92, 183, 274, 365, 456, 547, 638, 729; unscheduled relapse visit; early termination; F/U visit	Screening; days 1, 92, 183, 274; EOT-day 36; unscheduled relapse visit; early termination; F/U visit	Day 1,[c] Q3 months, early termination or EOS, ALC F/U visit (Q14 days after last dose), safety F/U visit
Chemistry	Screening; predose on days 1, 28, 85; early termination or EOS[b]	Screening; days 1, 29, 85; EOT-day 169	Q12 weeks, EOS, unscheduled relapse visit, early termination, F/U visit	Screening; days 1, 92, 183, 274, 365, 456, 547, 638, 729; unscheduled relapse visit; early termination; F/U visit	Screening; days 1, 92, 183, 274; EOT-day 365; unscheduled relapse visit; early termination; F/U visit	Day 1,[c] Q3 months, early termination or EOS, ALC F/U visit (Q14 days after last dose), safety F/U visit
LFTs	Screening; predose on days 1, 28, 85; early termination or EOS[b]	Screening; days 1, 29, 85; EOT-day 169	Q12 weeks, EOS, unscheduled relapse visit, early termination, F/U visit	Screening; days 1, 92, 183, 274, 365, 456, 547, 638, 729; unscheduled relapse visit; early termination; F/U visit	Screening; days 1, 15, 92, 183, 274; EOT-day 365; unscheduled relapse visit; early termination F/U visit	Day 1,[c] Q3 months, early termination or EOS, ALC follow-up visit (Q14 days after last dose), safety F/U visit
Urinalysis	Screening, early termination or EOS[b]	Screening, EOT-day 169	Q12 weeks, EOS, unscheduled relapse visit, early termination, F/U visit	Screening; days 1, 92, 183, 274, 365, 456, 547, 638, 729; unscheduled relapse visit; early termination F/U visit	Screening; days 1, 92, 183, 274; EOT-day 365; unscheduled relapse visit; early termination; F/U visit	Day 1,[c] Q3 months, early termination or EOS, ALC F/U visit (Q14 days after last dose), safety F/U visit
Pulmonary function tests[j]		Screening, day 85, EOT-day 169	Q12 weeks, EOS, early termination	Screening; days 92, 183, 365, 729; early termination	Screening, days 92 and 183, EOT-day 365, (unless done within previous 6 months), early termination	Day 1,[c] Q12 months, early termination or EOS

	Phase 1 (NCT02797015)	Phase 2 RADIANCE (NCT01628393)	Phase 2 RADIANCE blinded extension period[a]	Phase 3 RADIANCE (NCT02047734)	Phase 3 SUNBEAM (NCT02294058)	Open-label extension study DAYBREAK (NCT02576717)
Optical coherence tomography[k]		Screening, EOT-day 169	EOS, early termination	Screening; days 183, 365, 729; early termination	Screening, day 183, EOT-day 365 (unless done within previous 6 months), early termination	Day 1,[c] Q12 months, early termination or EOS
Skin examination		Screening, day 169		Screening, days 365 and 729, early termination	Screening; EOT-day 365 (unless done within previous 6 months) early termination	Day 1,[c] Q12 months, early termination or EOS
Serum/urine pregnancy test (WOCBP only)	Screening; days 1, 28, 56, 85; early termination or EOS[b]	Screening; days 1, 29, 57, 85, 113, 141; EOT-day 169	Q12 weeks, EOS, early termination, F/U visit	Screening; days 1, 92, 183, 274, 365, 456, 547, 638, 729; early termination, F/U visit	Screening; days 1, 92, 183, 274; EOT-day 365; early termination; F/U visit	Day 1,[c] Q3 months, early termination or EOS, safety F/U visits (28 and 75 day after last dose)

ALC = absolute lymphocyte count; ECG = electrocardiogram; EOS = end of study; EOT = end of treatment; LFT = liver function test; NCT = National Clinical Trial number; Q = every; TEAE = treatment-emergent adverse event; WOCBP = women of childbearing potential.

[a] At week 24 of the phase 2 trial, participants could enter a 2-year dose-blinded extension period.

[b] An EOS evaluation was performed for participants who completed the study; this evaluation occurred at least 7 days after the last dose for participants enrolling in DAYBREAK, or 28 days after the last dose for those not enrolling in DAYBREAK. For participants who withdrew from treatment prior to study completion for any reason, an EOS evaluation was performed as soon as possible after the decision to permanently discontinue treatment was made.

[c] Only if not performed at the EOT visit of the parent trial or not within the timeframe prior to the EOT visit specified by the parent trial protocol.

[d] Vital signs were collected predose and every hour for 6 hours after the initial dose with the exception of participants entering DAYBREAK from phase 1 or phase 2 RADIANCE who did not require dose escalation. For these participants, the EOT vital signs from phase 2 RADIANCE or EOS vital signs from phase 1 were used as the baseline vital signs for DAYBREAK.

[e] In phase 2 RADIANCE, 6-hour postdose monitoring was performed on day 5 only for the first 75 participants. At the week 24 visit (day 169), cardiac monitoring procedures were performed for participants who continued in the extension period following the first dose of that period.

[f] A visit for safety assessments was performed 14 days after the first dose of study medication.

[g] The first-dose cardiac monitoring strategy was repeated at day 5 or at day 8 if any cardiac safety issues were observed at the prior day of dose escalation.

[h] ECG was performed predose and 6 hours postdose, with the exceptions of participants who entered DAYBREAK from phase 1 or phase 2 RADIANCE who did not require dose escalation.

[I] Began 15 min before dosing and continued for 24 hours after dosing.

[J] Pulmonary function tests include forced expiratory volume in 1 second and forced vital capacity measurements at all the above indicated visits.

Source: Selmaj et al. (2021)[40]

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Appendix H. Summary of product characteristics (SmPC) for ozanimod

Please see the separate attachment.

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Appendix I. Description of comparators

Appendix I.1 Description of comparators

Infliximab, golimumab, and vedolizumab (IV and SC) constituted the best treatment options for bio-naïve patients with moderately to severely active UC in the DMC treatment guidance for BTSDs for UC.[60] Adalimumab, infliximab, golimumab, vedolizumab (IV and SC), and ustekinumab were considered the best treatment options for BTSD-experienced patients with moderately to severely active UC. Therefore, BMS considers these therapies to be the appropriate comparators for ozanimod, and Table I-1 to Table I-5 includes summary tables for these comparator products.

Table I-1. Description of adalimumab

Generic name (ATC code)	Adalimumab (L04AB04)
Mode of action	Adalimumab is a fully human IgG1 monoclonal antibody that specifically binds to TNF-α. The mechanism of action is based on both the neutralisation of TNF-α bioactivity and the induction of apoptosis of TNF-expressing mononuclear cells.
Pharmaceutical form	Clear, colourless solution for injection.
Posology	The recommended adalimumab induction dosage regimen for adults with moderate-to-severe UC is 160 mg at week 0 (given as four 40 mg injections in 1 day or as two 40 mg injections per day for 2 consecutive days) and 80 mg at week 2 (given as two 40 mg injections in 1 day). After induction treatment, the recommended dosage is 40 mg every other week via subcutaneous injection. Some patients who experience a decrease in their response to adalimumab 40 mg every other week may benefit from an increase in dosage to 40 mg adalimumab every week or 80 mg every other week.
Method of administration	Subcutaneous injection
Dosing	▪ Available in 20 mg/0.2 mL and 40 mg/0.4 mL syringe ▪ 40 mg/0.4 mL pen
Should the pharmaceutical be administered with other medicines?	No
Treatment duration	Available data suggest that clinical response is usually achieved within 2-8 weeks of treatment. Adalimumab therapy should not be continued in patients who do not respond within this period.
Necessary monitoring, both during administration and during the treatment period	Patients must be monitored closely for infections, including tuberculosis, before, during, and after treatment with adalimumab. Patients should be tested for hepatitis B virus infection before initiating treatment with adalimumab.
Additional tests or investigations	Not applicable
Packaging	▪ 20 mg/0.2 mL: 2 syringes ▪ 40 mg/0.4 mL: 2 syringes ▪ 40 mg/0.4 mL: 2 pens

ATC = Anatomical Therapeutic Chemical Classification System; IgG1 = immunoglobulin G1; TNF = tumour necrosis factor; UC = ulcerative colitis.

Sources: Humira SmPC (2021)[61]; Danish Medicines Agency (2021)[62]

Golimumab is indicated for the treatment of moderately to severely active UC in adults who have had an inadequate response to conventional therapy, including corticosteroids and 6-MP or azathioprine, or who are intolerant to or have medical contraindications for such therapies (Table I-2).[63]

Table I-2. Description of golimumab

Generic name (ATC code)	Golimumab (L04AB06)
Mode of action	Golimumab us a human monoclonal antibody that binds to both the soluble and transmembrane bioactive forms of human TNF-α. This interaction prevents the binding of TNF-α to its receptors, thereby inhibiting the biologic activity of TNF-α.
Pharmaceutical form	▪ Solution for injection in prefilled pen. ▪ Solution for injection in prefilled syringe. ▪ The solution is clear to slightly opalescent, colourless to light yellow.
Posology	▪ Patients with body weight < 80 kg: golimumab given as an initial dose of 200 mg, followed by 100 mg at week 2. Patients who have an adequate response should receive 50 mg at week 6 and every 4 weeks thereafter. Patients who have an inadequate response may benefit from continuing with 100 mg at week 6 and every 4 weeks thereafter. ▪ Patients with body weight ≥ 80 kg: golimumab given as an initial dose of 200 mg, followed by 100 mg at week 2, then 100 mg every 4 weeks thereafter.
Method of administration	Subcutaneous injection
Dosing	▪ Available in 50 mg syringe ▪ 45 mg/0.45 mL pen ▪ 50 mg pen ▪ 100 mg pen
Should the pharmaceutical be administered with other medicines?	No
Treatment duration	Available data suggest that clinical response is usually achieved within 12-14 weeks of treatment (after 4 doses). Continued therapy should be reconsidered in patients who show no evidence of therapeutic benefit within this period.
Necessary monitoring, both during administration and during the treatment period	Patients must be monitored closely for infections, including tuberculosis, before, during, and after treatment with golimumab. Patients should be tested for hepatitis B virus infection before initiating treatment with golimumab. Golimumab should be used with caution in patients with mild heart failure (NYHA class I/II). Patients should be closely monitored, and golimumab must be discontinued in patients who develop new or worsening symptoms of heart failure.
Additional tests or investigations	Not applicable

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Generic name (ATC code)	Golimumab (L04AB06)
Packaging	▪ 50 mg syringe: 1 syringe ▪ 45 mg/0.45 mL pen: 1 pen ▪ 50 mg pen: 1 pen ▪ 100 mg pen: 1 pen

ATC = Anatomical Therapeutic Chemical Classification System; NYHA = New York Heart Association; TNF = tumour necrosis factor.

Sources: Simponi SmPC (2021)[63]; Danish Medicines Agency (2021)[64]

Infliximab is indicated for the treatment of moderately to severely active UC in adults who have had an inadequate response to conventional therapy, including corticosteroids and 6-MP or azathioprine, or who are intolerant to or have medical contraindications for such therapies (Table I-3).[65]

Table I-3. Description of infliximab

Generic name (ATC code)	Infliximab (L04AB02)
Mode of action	Infliximab is a TNF-α blocker and a chimeric monoclonal IgG1 antibody. TNF-α is a key proinflammatory cytokine involved in inflammatory diseases. Its hyperactivity and enhanced signalling pathways can be observed in inflammatory diseases in which it activates further proinflammatory cascades. By binding to both the soluble subunit and the membrane-bound precursor of TNF-α1, infliximab disrupts the interaction of TNF-α with its receptors and may cause lysis of cells that produce TNF-α1.
Pharmaceutical form	Powder for concentrate for solution for infusion. The powder is a freeze-dried white pellet.
Posology	5 mg/kg given as an intravenous infusion followed by additional 5 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter.
Method of administration	Intravenous infusion
Dosing	Available in 100 mg vials
Should the pharmaceutical be administered with other medicines?	No
Treatment duration	Available data suggest that the clinical response is usually achieved within 14 weeks of treatment (i.e., 3 doses). Continued therapy should be carefully reconsidered in patients who show no evidence of therapeutic benefit within this period.
Necessary monitoring, both during administration and during the treatment period	Patients must be monitored closely for infections, including tuberculosis, before, during, and after treatment with infliximab. Patients with mild heart failure (NYHA class I/II) should be closely monitored.
Additional tests or investigations	Before starting treatment with infliximab, all patients must be evaluated for both active and inactive ("latent") tuberculosis. Patients should be tested for hepatitis B virus infection before initiation of treatment.
Packaging	▪ 100 mg: 1 vial

ATC = Anatomical Therapeutic Chemical Classification System; IgG1 = immunoglobulin G1; NYHA = New York Heart Association; TNF = tumour necrosis factor.

Sources: Remicade SmPC (2021)[65]; Danish Medicines Agency (2021)[66]

Ustekinumab is indicated for the treatment of adults with moderately to severely active UC who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a biologic or have medical contraindications to such therapies (Table I-4).[67]

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Table I-4. Description of ustekinumab

Generic name (ATC code)	Ustekinumab (L04AC05)
Mode of action	Ustekinumab is a human IgG1k monoclonal antibody that binds with specificity to the p40 protein subunit used by both the IL-12 and IL-23 cytokines. IL-12 and IL-23 are naturally occurring cytokines that are involved in inflammatory and immune responses such as natural killer cell activation and CD4+ T-cell differentiation and activation.
Pharmaceutical form	▪ Concentrate for solution for infusion ▪ Solution for injection ▪ Solution for injection in prefilled syringe ▪ The solution is clear, colourless to light yellow
Posology	Ustekinumab is to be initiated with a single intravenous dose based on body weight: ≤ 55 kg: 260 mg; > 55 kg to ≤ 85 kg: 390 mg; > 85 kg: 520 mg. The first 90 mg subcutaneous dose should be given at week 8 after the intravenous dose. After this, dosing every 12 weeks is recommended. Patients who lose response on dosing every 12 weeks may benefit from an increase in dosing frequency to every 8 weeks. Patients may subsequently be dosed every 8 weeks or every 12 weeks according to clinical judgement.
Method of administration	Intravenous and subcutaneous injection
Dosing	Available in 130 mg concentrate for solution vials, 45 mg/0.5 mL solution for injection vial, 45 mg/ 0.5 mL prefilled syringe, and 90 mg/1 mL prefilled syringe.
Should the pharmaceutical be administered with other medicines?	No
Treatment duration	Consideration should be given to discontinuing treatment in patients who show no evidence of therapeutic benefit 16 weeks after the intravenous induction dose or 16 weeks after switching to the 8-weekly maintenance dose.
Necessary monitoring, both during administration and during the treatment period	Before initiating treatment with ustekinumab, patients should be evaluated for tuberculosis infection. All patients, in particular those aged > 60 years, patients with a medical history of prolonged immunosuppressant therapy, or those with a history of psoralen and ultraviolet A treatment, should be monitored for the appearance of non-melanoma skin cancer.
Additional tests or investigations	Not applicable
Packaging	▪ 130 mg concentrate for solution: 1 vial ▪ 45 mg/0.5 mL solution for injection: 1 vial ▪ 45 mg/0.5 mL prefilled syringe: 1 prefilled syringe ▪ 90 mg/1 mL prefilled syringe: 1 prefilled syringe

ATC = Anatomical Therapeutic Chemical Classification System; IgG1 = immunoglobulin G1; IL = interleukin.

Sources: Stelara SmPC (2021)[67]; Danish Medicines Agency (2021)[68]

Vedolizumab is indicated for the treatment of adult patients with moderately to severely active UC who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a TNF-α antagonist (Table I-5).[69]

Table I-5. Description of vedolizumab

Generic name (ATC code)	Vedolizumab (L04AA33)
Mode of action	Vedolizumab is a recombinant humanised IgG1 monoclonal antibody directed against the human lymphocyte α4β7 integrin, a key mediator of gastrointestinal inflammation. By blocking its primary target, α4β7 integrin, vedolizumab reduces inflammation in the gut.
Pharmaceutical form	▪ Powder for concentrate for solution for infusion. White to off-white lyophilised cake or powder. ▪ 108 mg solution for injection in a prefilled syringe. ▪ 108 mg solution for injection in a prefilled pen.
Posology	▪ The recommended dose regimen of intravenous vedolizumab is 300 mg administered by intravenous infusion at 0, 2, and 6 weeks and then every 8 weeks thereafter. ▪ Some patients who have experienced a decrease in their response may benefit from an increase in dosing frequency to intravenous vedolizumab 300 mg every 4 weeks. ▪ The recommended dose regimen of subcutaneous vedolizumab as a maintenance treatment, following at least 2 intravenous infusions, is 108 mg administered by subcutaneous injection once every 2 weeks. The first subcutaneous dose should be administered in place of the next scheduled intravenous dose and every 2 weeks thereafter.
Method of administration	▪ Intravenous infusion ▪ Subcutaneous injection
Dosing	Available in 300 mg vials, 108 mg prefilled syringes, and 108 mg prefilled pens
Should the pharmaceutical be administered with other medicines?	No
Treatment duration	Therapy for patients with UC should be discontinued if no evidence of therapeutic benefit is observed by week 10.
Necessary monitoring, both during administration and during the treatment period	▪ Intravenous vedolizumab should be administered in a healthcare setting equipped to allow management of acute hypersensitivity reactions, including anaphylaxis, if they occur. Appropriate monitoring and medical support measures should be available for immediate use when administering intravenous vedolizumab. All patients should be observed continuously during each infusion. For the first 2 infusions, they should also be observed for approximately 2 hours after completion of the infusion for signs and symptoms of acute hypersensitivity reactions. For all subsequent infusions, patients should be observed for approximately 1 hour after completion of the infusion. ▪ Patients should be monitored closely for infections before, during, and after treatment. ▪ Healthcare professionals should monitor patients on vedolizumab for any new onset or worsening of neurological signs and symptoms. If progressive multifocal leukoencephalopathy; is suspected, treatment with vedolizumab must be withheld; if confirmed, treatment must be permanently discontinued.
Additional tests or investigations	Not applicable
Packaging	▪ 300 mg powder for concentrate: 1 vial ▪ 108 mg syringe: 1 syringe ▪ 108 mg pen: 1 pen

ATC = Anatomical Therapeutic Chemical Classification System; IgG1 = immunoglobulin G1; UC = ulcerative colitis.

Sources: Entyvio SmPC (2021)[69]; Danish Medicines Agency (2021)[70]

Appendix J. Extrapolation

Not applicable as a cost-minimisation approach was used.

Appendix K. Literature search for HRQoL data

Not applicable because HRQoL data are not used in economic evaluation due to the cost-minimisation approach.

Appendix L. Mapping of HRQoL data

Not applicable because a cost-minimisation approach was used. Probabilistic sensitivity analyses

Appendix M. Probabilistic sensitivity analyses

Probabilistic sensitivity analyses were not conducted because a cost-minimisation approach was used.

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Appendix N. NMA additional details

Appendix N.1 Trial eligibility

Table N-1. Summary of trial eligibility criteria

Trial	Inclusion criteria	Exclusion criteria
True North [10]	▪ Aged 18 to 75 years ▪ UC diagnosed for ≥ 3 months ▪ Active UC based on Mayo Score of 6 to 12, with endoscopic subscore of ≥ 2, a rectal bleeding score of ≥ 1, and a stool frequency score of ≥ 1 ▪ Currently receiving treatment with ≥ 1 of the: oral ASAs, prednisone, budesonide	▪ Severe extensive colitis, Crohn's disease or indeterminate colitis ▪ Treatment with biologic agent within 8 weeks or 5 elimination half-lives prior to randomisation ▪ Treatment with CSP, TAC, sirolimus, or MMF within 16 weeks of screening or TOF within 2 weeks
TOUCHSTONE [11]	▪ Aged 18 to 75 years ▪ UC diagnosed for ≥ 2 months ▪ Active UC based on Mayo Score of 6 to 12, with endoscopic subscore of ≥ 2 ▪ If receiving biologic agents or AZA, MP, or methotrexate, must have discontinued these agents 5 half-lives before starting the trial regimen and 4 weeks before their screening endoscopy	▪ Fulminant colitis, Crohn's disease or indeterminate colitis ▪ Treatment with CSP, TAC, sirolimus or MMF within 16 weeks ▪ Treatment with a biologic or investigational agent within 5 half-lives ▪ Treatment with topical rectal mesalamine or CSs within 2 weeks
ULTRA 1 [7]	▪ Aged ≥ 18 years ▪ UC diagnosed for at least 90 days ▪ Active UC based on Mayo Score of 6 to 12, with endoscopic subscore of ≥ 2 despite concurrent and stable treatment with oral CSs and/or IMMs	▪ Fulminant colitis and/or toxic megacolon, Crohn's disease, indeterminate colitis ▪ Treatment with IFX, ADA or other anti-TNF agent or biologic agent ▪ Treatment with CSP, TAC, or MMF within 30 days
ULTRA 2 [12]	▪ Aged ≥ 18 years ▪ UC diagnosed for at least 90 days ▪ Active UC based on Mayo Score of 6 to 12, with endoscopic subscore of ≥ 2 despite concurrent and stable treatment with oral CSs and/or IMMs ▪ Failed to respond, or intolerance to CSs or IMMs	▪ Fulminant colitis and/or toxic megacolon, Crohn's disease, indeterminate colitis ▪ Treatment with IFX, ADA or other anti-TNF agent or biologic agent ▪ Treatment with CSP, TAC, or MMF within 30 days
Suzuki 2014 [5]	▪ Aged ≥ 15 years ▪ Active UC based on Mayo Score of 6 to 12, with endoscopic subscore of ≥ 2 despite concurrent and stable treatment with oral CSs and/or IMMs	▪ Indeterminate colitis, Crohn's disease ▪ Treatment with anti-TNF therapies or other biologic agents ▪ Treatment with CS injection, CSP, TAC, or MMF within 4 weeks ▪ Discontinuation of oral CSs within 2 weeks

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Trial	Inclusion criteria	Exclusion criteria
SERENE-UC[71]	▪ Aged 18 to 75 years ▪ UC diagnosed for ≥ 90 days ▪ Active UC based on Mayo Score of 6 to 12, with endoscopic subscore of ≥ 2 despite concurrent and stable treatment with oral CSs and/or IMMs	▪ Fulminant colitis and/or toxic megacolon, Crohn's disease, indeterminate colitis ▪ Treatment with anti-TNF therapies other than IFX, TOF or VEDO ▪ Treatment within IFX: within 56 days of baseline or with no clinical response to IFX at any time
PURSUIT-SC [13]	▪ Mayo Score 6-12 and endoscopic subscore ≥ 2 ▪ Inadequate response to, or had failed to tolerate, ≥ 1 of following conventional therapies: oral ASAs, oral CSs, AZA, and/or MP; or CS dependent ▪	▪ Prior use within 12 months of biologic anti-TNF agent(s) natalizumab or other agents targeting the a-4 integrin, B-cell depleting agents (rituximab), or T-cell depleting agents (alemtuzumab, visilizumab) ▪ Prior use of oral CSs at a dose > 40 mg prednisone or its equivalent per day ▪ Treatment with CSP, TAC, sirolimus, or MMF within 8 weeks
PURSUIT M [14]	▪ Mayo Score 6-12 and endoscopic subscore ≥ 2 ▪ Inadequate response to, or had failed to tolerate, ≥ 1 of following conventional therapies: oral ASAs, oral CSs, AZA, and/or MP; or CS dependent	▪ Prior use within 12 months of biologic anti-TNF agent(s) natalizumab or other agents targeting the a-4 integrin, B-cell depleting agents (rituximab), or T-cell depleting agents (alemtuzumab, visilizumab) ▪ Prior use of oral CSs at a dose > 40 mg prednisone or its equivalent per day ▪ Receipt of CSP, TAC, sirolimus, or MMF within 8 weeks ▪ Patients receiving 5-ASAs, IMMs, CSs at baseline of the PURSUIT-IV or PURSUIT-SC studies had to have maintained doses throughout induction
PURSUIT J [15]	▪ Mayo Score 6-12 and endoscopic subscore ≥ 2 ▪ Inadequate response to, or had failed to tolerate, ≥ 1 of following conventional therapies: oral ASAs, oral CSs, AZA, and/or MP; or CS dependent ▪ Naïve to anti-TNF therapy	▪ Severe and extensive colitis requiring colectomy, or colitis limited to 20 cm of colon ▪ Any prior abdominal surgery ▪ Patients having presence of fistula or adenomatous colonic polyps
ACT 1 [16]	▪ Mayo Score 6-12 and endoscopic subscore ≥ 2 ▪ Inadequate response to, or had failed to tolerate, ≥ 1 of following conventional therapies: oral ASAs, oral CSs, AZA, and/or MP; or CS dependent	▪ Indeterminate colitis or Crohn's disease ▪ Treatment with rectally administered CSs or medications containing ASAs within 2 weeks of screening ▪ Prior exposure to IFX or other anti-TNF agent
ACT 2 [16]	▪ Mayo Score 6-12 and endoscopic subscore ≥ 2 ▪ Inadequate response to, or had failed to tolerate, ≥ 1 of following conventional therapies: oral ASAs, oral CSs, AZA, and/or MP; or CS dependent	▪ Indeterminate colitis or Crohn's disease ▪ Treatment with rectally administered CSs or medications containing ASAs within 2 weeks of screening ▪ Prior exposure to IFX or other anti-TNF agent

Trial	Inclusion criteria	Exclusion criteria
UC-SUCCESS [31]	▪ Aged ≥ 18 years (increased to ≥ 21 years after the study started) ▪ Mayo Score of 6-12 at baseline ▪ Naïve to anti-TNF therapy ▪ Responded inadequately to a course of CSs with or without mesalamine within 12 weeks ▪ Either AZA-naïve or free from AZA treatment for at least 3 months	▪ Hospitalisation for extensive severe UC ▪ Experienced recent gastrointestinal surgery, bowel obstruction, stricture of the colon ▪ Previous colonic resection, documented colonic dysplasia, previous tuberculosis or other granulomatous infection ▪ Recent episode of an opportunistic infection (within 2 months of screening)
Jiang 2015 [17]	▪ Mayo Score 6-12 and endoscopic subscore ≥ 2 ▪ Inadequate response to, or had failed to tolerate, ≥ 1 of following conventional therapies: oral ASAs, oral CSs, AZA, and/or MP; or CS dependent	▪ Indeterminate colitis or Crohn's disease ▪ Treatment with rectally administered CSs or drugs containing ASAs within 2 weeks ▪ Prior exposure to IFX or other anti-TNF agents
Kobayashi 2016 [18]	▪ Mayo Score 6-12 and endoscopic subscore ≥ 2 ▪ Inadequate response to, or had failed to tolerate, ≥ 1 of following conventional therapies: oral ASAs, oral CSs, AZA, and/or MP; or CS dependent	▪ Recent bowel surgery or complications ▪ Bowel complications: stricture, fistula, or dysplasia ▪ Treatment with other biologics, methotrexate, calcineurin inhibitors, or cytapheresis within the previous 18 months ▪ Serious medical conditions such as chronic heart failure or latent infectious diseases
Probert 2003 [32]	▪ Aged ≥ 18 years ▪ Ulcerative colitis symptom score of ≥ 6 and a sigmoidoscopy score of ≥ 2 on the Baron scale ▪ Failed to respond to conventional treatment with glucocorticoids ▪ Biopsy showing histological changes of acute ulcerative colitis	▪ Crohn's disease ▪ Patients with severe disease ▪ Prior treatment with CSP, any therapeutic agent used to directly reduce TNF, or any investigational drug within 3 months ▪ Initiation of treatment within prior 3 months with 6-MP or AZA
Sands 2001 [33]	▪ Aged 18 to 65 years ▪ UC diagnosis for least 2 weeks ▪ Severe active UC based on modified Truelove and Witts classification ▪ Received at least 7 days of CS therapy (40 to 60 mg/day, prednisone equivalent), of which at least 5 days included intravenous administration	▪ UC so severe endoscopy was contraindicated ▪ Toxic megacolon, perforation of colon
GEMINI 1 [19]	▪ Aged 18 to 80 years ▪ Mayo Score of 6-12 with a sigmoidoscopy subscore of ≥ 2 ▪ Loss of response to, inadequate response to or intolerance to ≥ 1 of: IMMs, anti-TNF or CSs	▪ Toxic megacolon, abdominal abscess, symptomatic colonic stricture, stoma, a history of colectomy ▪ Treatment with anti-TNF agents within 60 days ▪ Treatment with CSP, thalidomide, or investigational drugs within 30 days ▪ Prior treatment with VEDO, natalizumab, efalizumab, or rituximab

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Trial	Inclusion criteria	Exclusion criteria
VARSITY [6]	▪ Aged 18 to 85 years ▪ UC diagnosis for at least 3 months ▪ Mayo Score of 6-12 and endoscopic subscore ≥ 2 ▪ No prior treatment with VEDO ▪ Naïve to anti-TNF therapy or discontinuation of anti-TNF therapy (except ADA) for reasons other than safety ▪ No response or loss of response to conventional treatments	▪ Crohn's disease or indeterminate colitis ▪ Treatment with biologic or biosimilar agent within 60 days or 5 half-lives prior to the screening ▪ Prior treatment with natalizumab, EFA, ADA, AMG-181, anti-mucosal addressing cell adhesion molecule-1 antibodies, rituximab, VEDO
VISIBLE 1 [20]	▪ Aged 18 to 80 years ▪ UC diagnosis for at least 6 months ▪ Mayo Score of 6-12 with endoscopic subscore of ≥ 2 ▪ Inadequate response to, loss of response to, or intolerance to at least ≥ 1 of: CS, IMM, or anti-TNF therapy	▪ Abdominal abscess, toxic megacolon, subtotal or total colectomy, unresected adenomatous colonic polyps, colonic mucosal dysplasia ▪ Prior exposure to any anti-integrin therapies, anti-MAdCAM-1 antibodies, or rituximab ▪ Exposure to any biologics within 60 days or 5 half-lives of screening (whichever was longer) ▪ Exposure to any nonbiologic therapies within 30 days or 5 half-lives of screening (whichever was longer)
Motoya 2019 [21]	▪ Aged 15 to 80 years ▪ UC diagnosis for ≥ 6 months ▪ Mayo Score of 6-12 with endoscopic subscore of ≥ 2 ▪ No use or treatment failure with CSs, IMMs or anti-TNF agents within 5 years	▪ Previously treated with VEDO, natalizumab, EFA, or rituximab
UNIFI [22]	▪ Aged ≥ 18 years ▪ UC diagnosis for ≥ 4 months ▪ Mayo Score 6-12 and endoscopic subscore ≥ 2 ▪ Inadequate response to or unacceptable side effects from anti-TNFs, VEDO, or conventional (i.e., nonbiologic) therapy	▪ Previous treatment with interleukin-12 or interleukin-23 antagonists ▪ Previous TNF antagonist therapy not discontinued for < 8 weeks, and VEDO not discontinued for at least 4 months ▪ Conventional therapies not discontinued for at least 2 to 4 weeks

Abbreviations: ADA = adalimumab; AMG-181 = abrilumab; ASA = aminosalicylic acid; AZA = azathioprine; CS = corticosteroid; CSP = cyclosporine; EFA = efalizumab; IFX = infliximab; IMM = immunomodulator; MP = mercaptopurine ; MMF = mycophenolate mofetil; TAC = tacrolimus; TNF = tumour necrosis factor; TOF = tofacitinib; UC = ulcerative colitis; VEDO = vedolizumab.

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Appendix N.2 Study design

Table N-2. Duration of induction and maintenance phases

Drug	Trials	Induction duration & timepoint	Maintenance duration	Maintenance timepoint
Ozanimod	True North [10]	10 weeks	42 weeks	52 weeks
	TOUCHSTONE [11]	8 weeks*	24 weeks	32 weeks
Adalimumab	ULTRA 1 [7]	8 weeks	NA	NA
	ULTRA 2 [12]	8 weeks	44 weeks	52 weeks
	SERENE-UC [31]	8 weeks	44 weeks	52 weeks
	Suzuki 2014 [5]	8 weeks	44 weeks	52 weeks
Golimumab	PURSUIT-SC [13]; PURSUIT M [14]; PURSUIT J [15]	6 weeks	54 weeks	60 weeks
Infliximab	ACT 1 [16];	8 weeks	46 weeks	54 weeks
	ACT 2 [16]	8 weeks	22 weeks	30 weeks
	UC-SUCCESS [31]	8 weeks[a]	NA	NA
	Jiang 2015 [17];	8 weeks	22 weeks	30 weeks
	Kobayashi 2016 [18]	8 weeks	22 weeks	38 weeks
	Probert 2003[32]	6 weeks[b]	NA	NA
	Sands 2001[33]	2 weeks[c]	NA	NA
Vedolizumab	GEMINI 1 [19]	6 weeks	46 weeks	52 weeks
	VARSITY [6]	14 weeks	38 weeks	52 weeks
	VISIBLE 1 [20]	6 weeks[e]	46 weeks	52 weeks
	Motoya 2019 [21]	10 weeks	46 weeks	60 weeks
Ustekinumab	UNIFI [22]	8 weeks	44 weeks	52 weeks

Timepoints coloured in orange represent a timepoint that was not eligible for inclusion in the NMA.

* 9 weeks including the 1-week dose escalation phase.

[a] Extended induction data available at week 16.

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[b] Extended induction data available at week 8.

[c] Extended induction data available at week 12.

Table N-3. Handling of induction responders and non-responders in trials with a re-randomised maintenance phase

Trial	Active agent	Open label induction cohort	Re-randomisers active responders	Re-randomisers placebo responders	Handling of non-responders*
True North	Ozanimod	Included as a separate cohort from randomised induction cohort	Yes	No; patients remain on placebo	Receive open-label active treatment
GEMINI	Vedolizumab	Included as a separate cohort from randomised induction cohort	Yes	No; patients remain on placebo	Receive open-label active treatment
UNIFI	Ustekinumab	No	Yes	Only delayed responders[a]	Receive open-label active treatment
OCTAVE SUSTAIN	Tofacitinib	No	Yes	Yes	Receive open-label active treatment
PURSUIT-M	Golimumab	No	Yes	No; patients remain on placebo	Receive open-label active treatment
PURSUIT-J	Golimumab	Included as the only induction cohort	Yes	No; patients remain on placebo	Receive open-label active treatment
Motoya 2019	Vedolizumab	Included as a separate cohort from randomised induction cohort	Yes	No; patients remain on placebo	Receive open-label active treatment
VISIBLE 1	Vedolizumab	Included as the only induction cohort	Yes	No; patients remain on placebo	Receive open-label active treatment

* In such cases, the non-responder group is analysed separately from the responder group in the maintenance phase.

[a] Defined as those who did not have a response to intravenous placebo and who then received an induction dose of intravenous ustekinumab (6 mg per kilogram of body weight) at week 8 and had a response at week 16. Patients who had a response to intravenous placebo in the induction trial at week 8 entered the maintenance trial but did not undergo randomisation (i.e., continued placebo).

Appendix N.3 Biologic subgroup definitions

Table N-4. Summary of biologic subgroup data in mixed-population trials

			Biologic-naïve patients		Biologic experienced patients	
UC therapy	Trials	Prior biologics	Biologic non-exposed	Biologic non-failure	Biologic exposed	Biologic failure
Ozanimod	True North	UST, VEDO, Anti-TNF	Available (Anti-TNF: 65.0%; Non-anti-TNF: 77.3%)*	NR	Available (Anti-TNF: 35.0%; Non-anti-TNF: 22.7%)*	NR
	TOUCHSTONE	UST, VEDO, Anti-TNF	NR	NR	NR	NR
Adalimumab	ULTRA 2[a]	Anti-TNF (excluding ADA)	Available (59.7%)		Available (40.3%)	
Vedolizumab	GEMINI 1	Anti-TNF	Available (51.8%)	NR	NR	Available (48.2%)
	Motoya 2019	Anti-TNF	Available (48.8%)	NR	Available (51.2%)	NR
	VARSITY	Anti-TNF (excluding ADA)	Available (79.2%)	NR	Available (20.8%)	NR
	VISIBLE 1	Anti-TNF	Available (61.1%)	NR	Available (38.9%)	NR
Ustekinumab	UNIFI	VEDO, Anti-TNF	Available (46.1%)	Available (48.9%)	NR	Available (51.1%)
Tofacitinib	Study A3921063	Anti-TNF	Available (69.6%)	NR	Available (30.4%)	NR
	OCTAVE 1	Anti-TNF	Available (46.6%)	Available (48.6%)	Available (53.4%)	Available (51.4%)
	OCTAVE 2	Anti-TNF	Available (44.8%)	Available (47.9%)	Available (55.3%)	Available (52.2%)
	OCTAVE SUSTAIN	Anti-TNF	NR	Available (55.3%)	NR	Available (44.7%)

[a] All biologic-exposed patients were biologic-failures.

*Percentage of patients at induction baseline.

Blue background indicates that the subgroup data was selected for use in the NMA. TOUCHSTONE was included in the biologic-naïve NMA as a sensitivity as it was 82% naïve.

Abbreviations: ADA = adalimumab; NR = not reported; TNF = tumour necrosis factor; UST = ustekinumab; VEDO = vedolizumab

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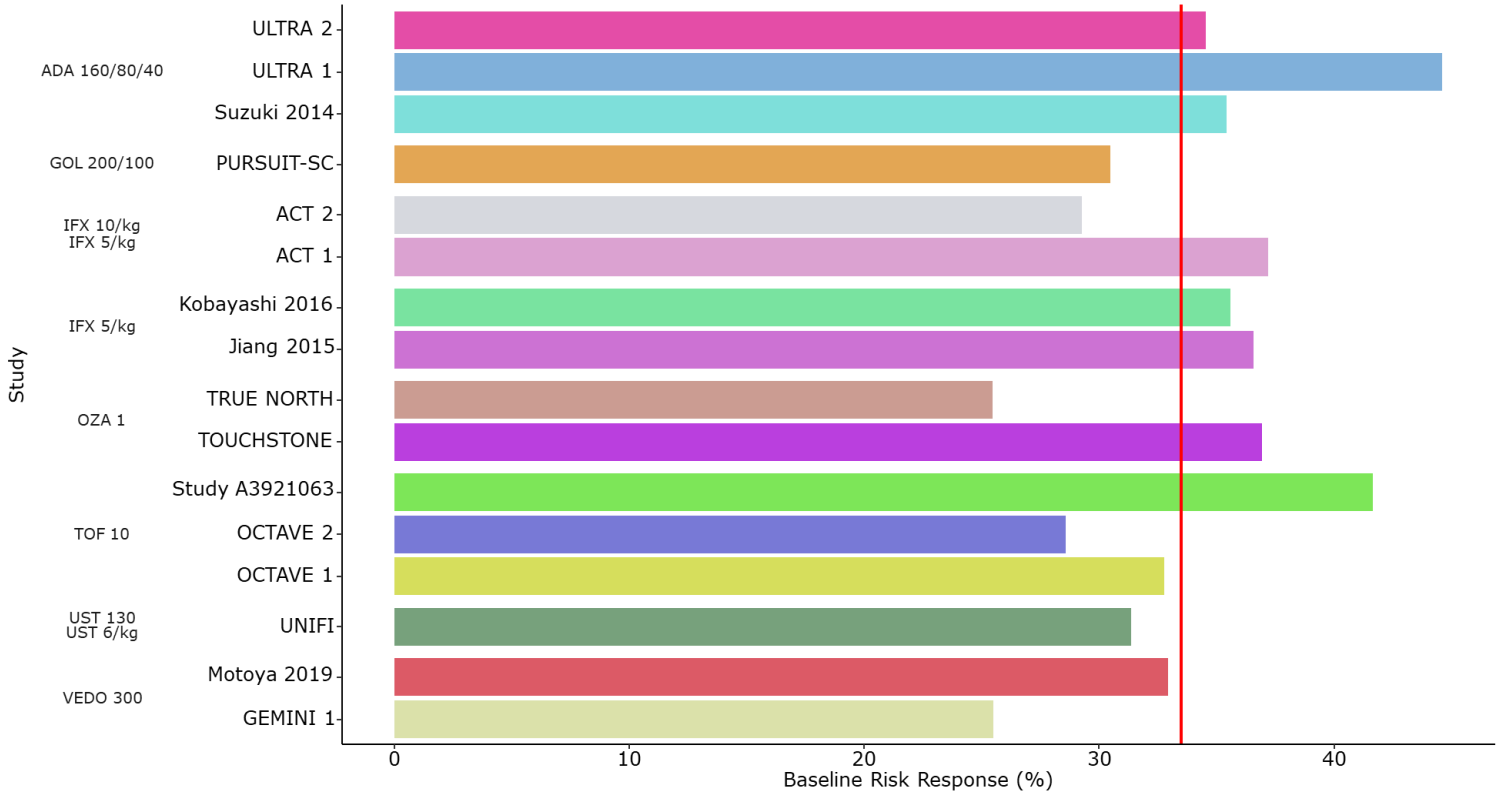
Appendix N.4 Placebo response assessment

Appendix N.4.1 Clinical response

Figure N-1. Placebo rates for clinical response at induction in the overall population



Note: red line represents the average placebo response across all trials. Baseline risk is equivalent to placebo response.

Abbreviations: ADA = adalimumab; GOL = golimumab; IFX = infliximab; OZA = ozanimod; PBO = placebo; TOF = tofacitinib; UST = ustekinumab; VEDO = vedolizumab.

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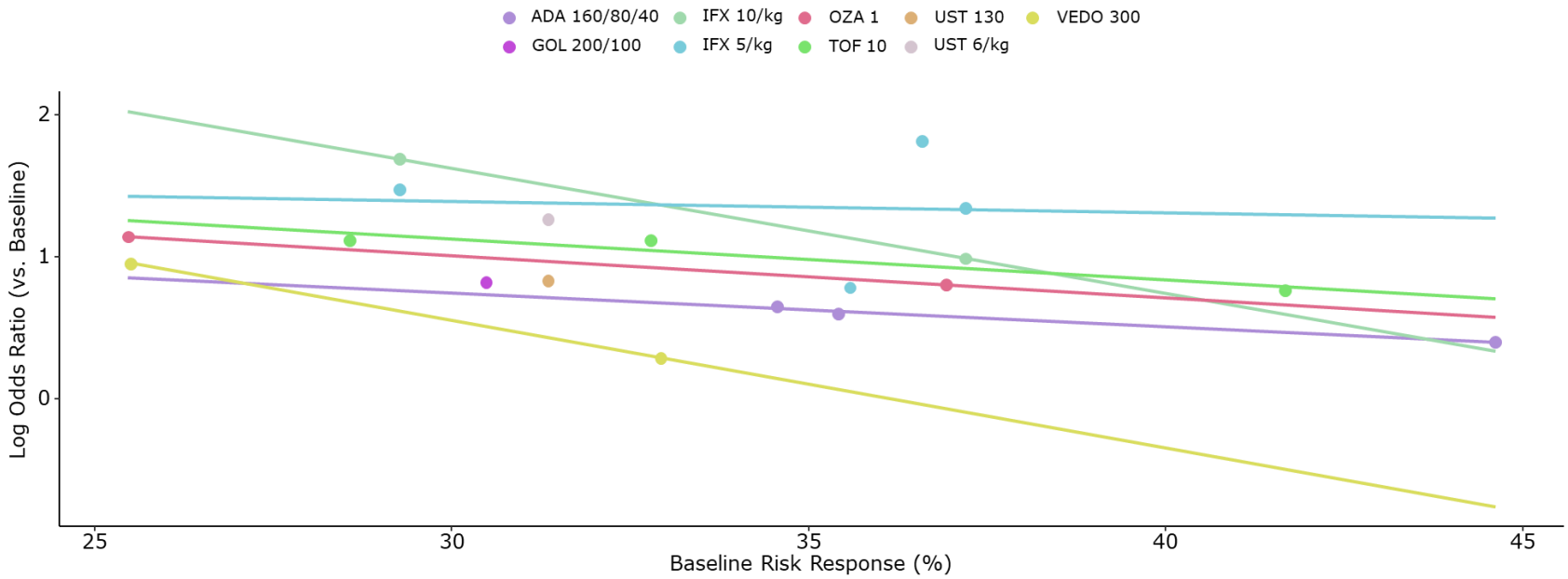
Figure N-2. Placebo response versus treatment effect for clinical response at induction in the overall population



Plot of treatment effects organised by treatment on the log odds scale versus placebo response. Baseline risk is equivalent to placebo response. Lines are only presented when ≥ 2 data points are available.

Abbreviations: ADA = adalimumab; GOL = golimumab; IFX = infliximab; OZA = ozanimod; PBO = placebo; TOF = tofacitinib; UST = ustekinumab; VEDO = vedolizumab.

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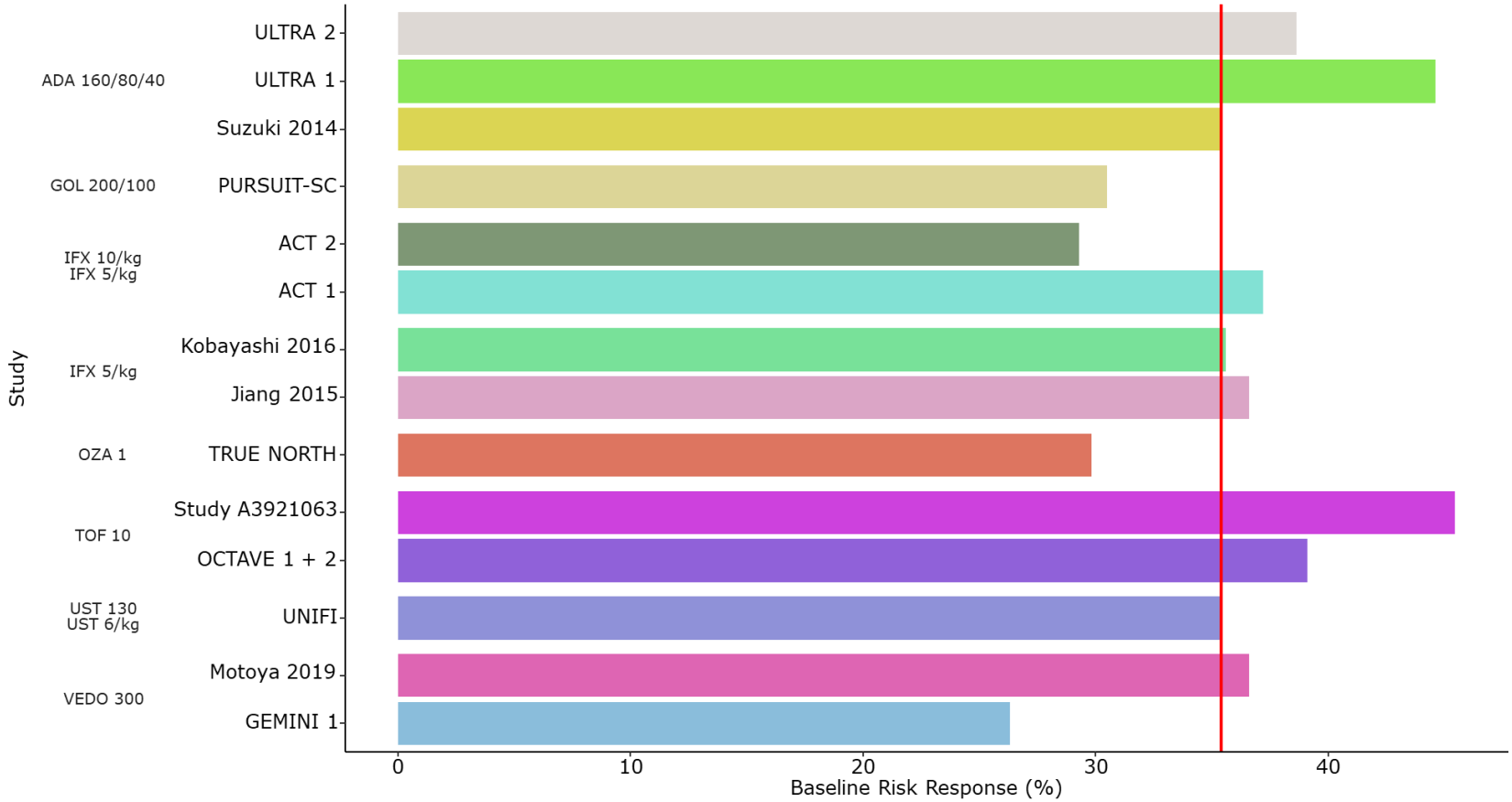
Figure N-3. Placebo rates for clinical response at induction in the bio-naïve population



Note: red line represents the average placebo response across all trials. Baseline risk is equivalent to placebo response.

Abbreviations: ADA = adalimumab; GOL = golimumab; IFX = infliximab; OZA = ozanimod; PBO = placebo; TOF = tofacitinib; UST = ustekinumab; VEDO = vedolizumab.

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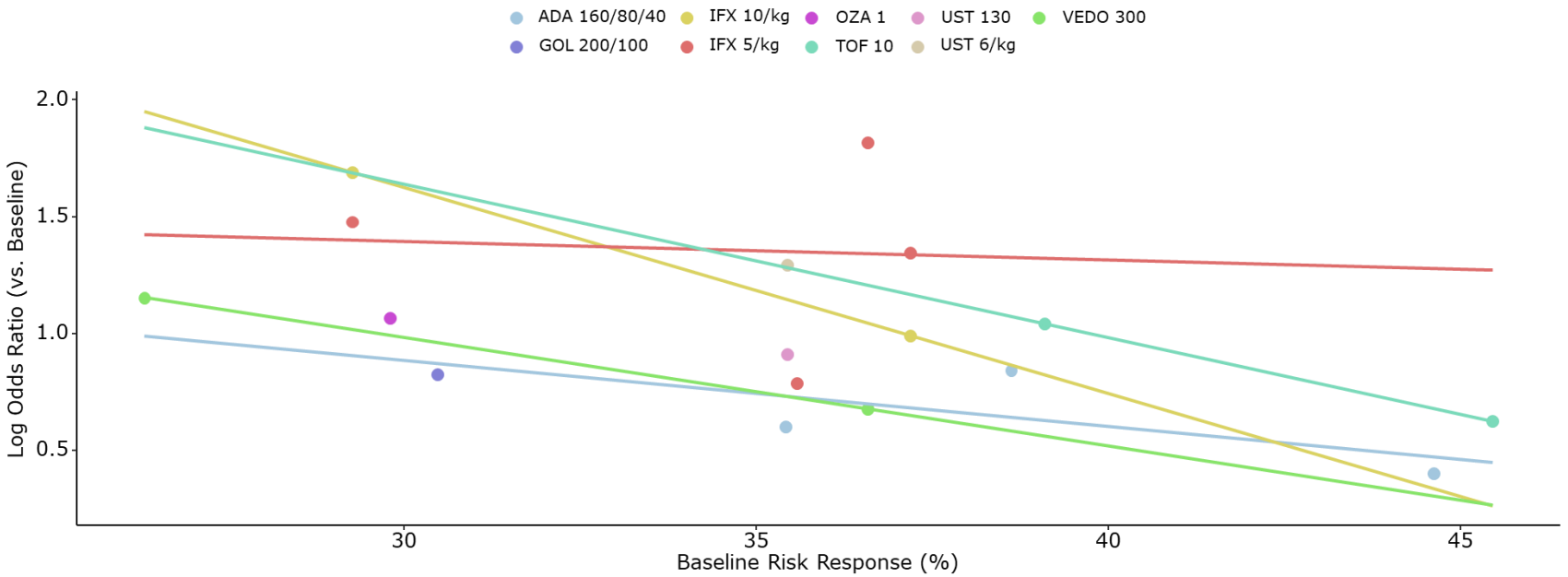
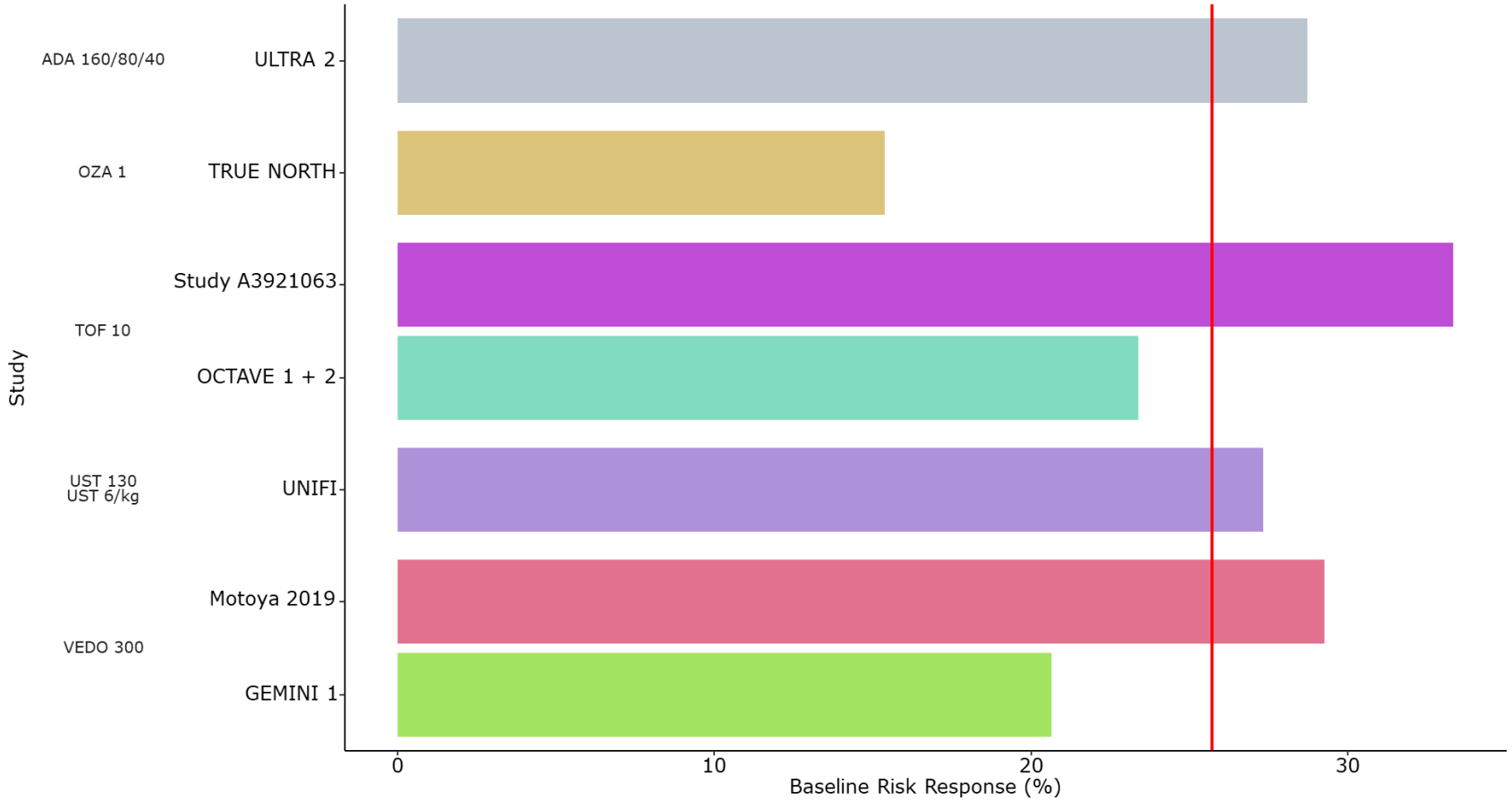
Figure N-4. Placebo response versus treatment effect for clinical response at induction in the bio-naïve population



Plot of treatment effects organised by treatment on the log odds scale versus placebo response. Baseline risk is equivalent to placebo response. Lines are only presented when ≥ 2 data points are available.

Abbreviations: ADA = adalimumab; GOL = golimumab; IFX = infliximab; OZA = ozanimod; PBO = placebo; TOF = tofacitinib; UST = ustekinumab; VEDO = vedolizumab.

Figure N-5. Placebo rates for clinical response at induction in the bio-experienced population



Note: red line represents the average placebo response across all trials. Baseline risk is equivalent to placebo response.

Abbreviations: ADA = adalimumab; GOL = golimumab; IFX = infliximab; OZA = ozanimod; PBO = placebo; TOF = tofacitinib; UST = ustekinumab; VEDO = vedolizumab.

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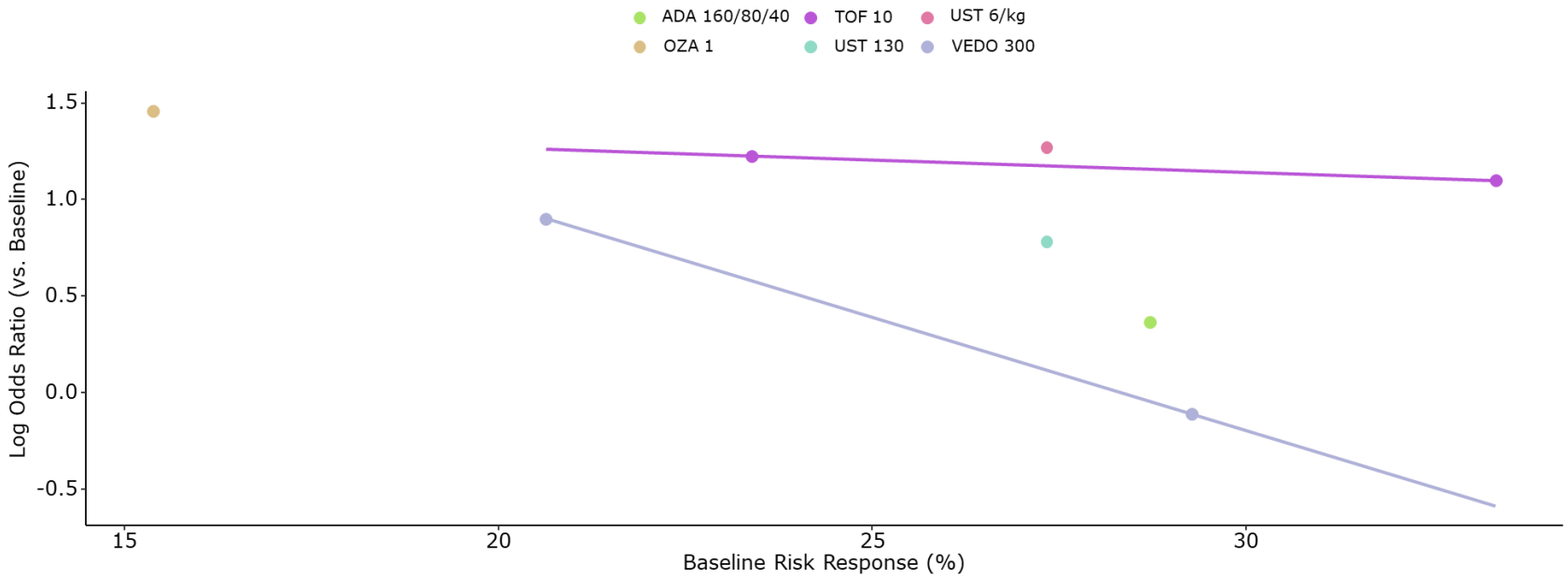
Figure N-6. Placebo response versus treatment effect for clinical response at induction in the bio-experienced population



Plot of treatment effects organised by treatment on the log odds scale versus placebo response. Baseline risk is equivalent to placebo response. Lines are only presented when ≥ 2 data points are available.

Abbreviations: ADA = adalimumab; GOL = golimumab; IFX = infliximab; OZA = ozanimod; PBO = placebo; TOF = tofacitinib; UST = ustekinumab; VEDO = vedolizumab.

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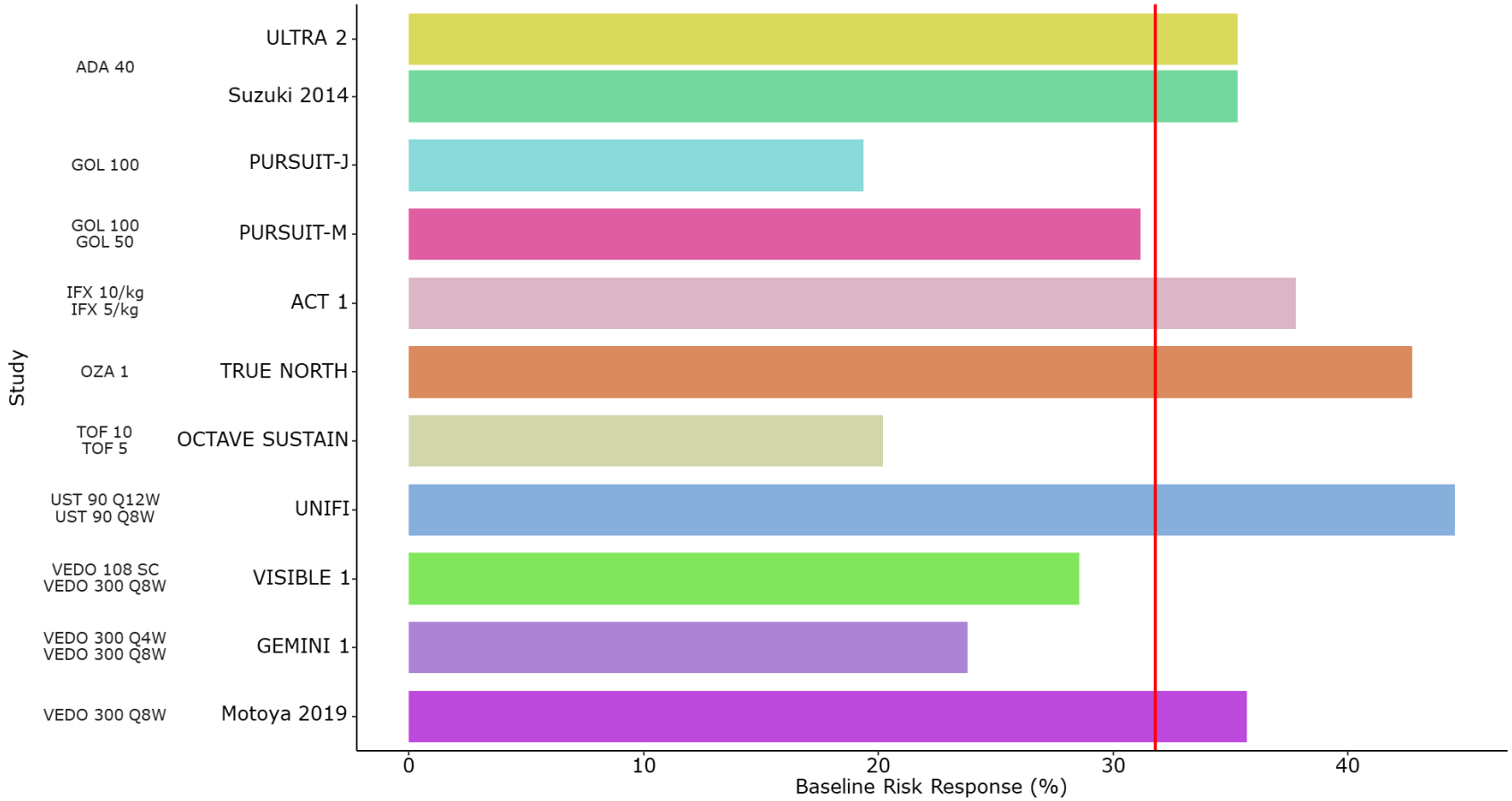
Figure N-7. Placebo rates for clinical response at maintenance in the overall population



Placebo rates presented for the base case, treat-through to re-randomised analyses. Treat-through data has been recalculated as per **Section 7.2.7 in the main dossier**.

Note: red line represents the average placebo response across all trials. Baseline risk is equivalent to placebo response.

Abbreviations: ADA = adalimumab; GOL = golimumab; IFX = infliximab; OZA = ozanimod; PBO = placebo; Q4W = every 4 weeks; Q8W = every 8 weeks; Q12W = every 12 weeks; SC = subcutaneous; TOF = tofacitinib; UST = ustekinumab; VEDO = vedolizumab.

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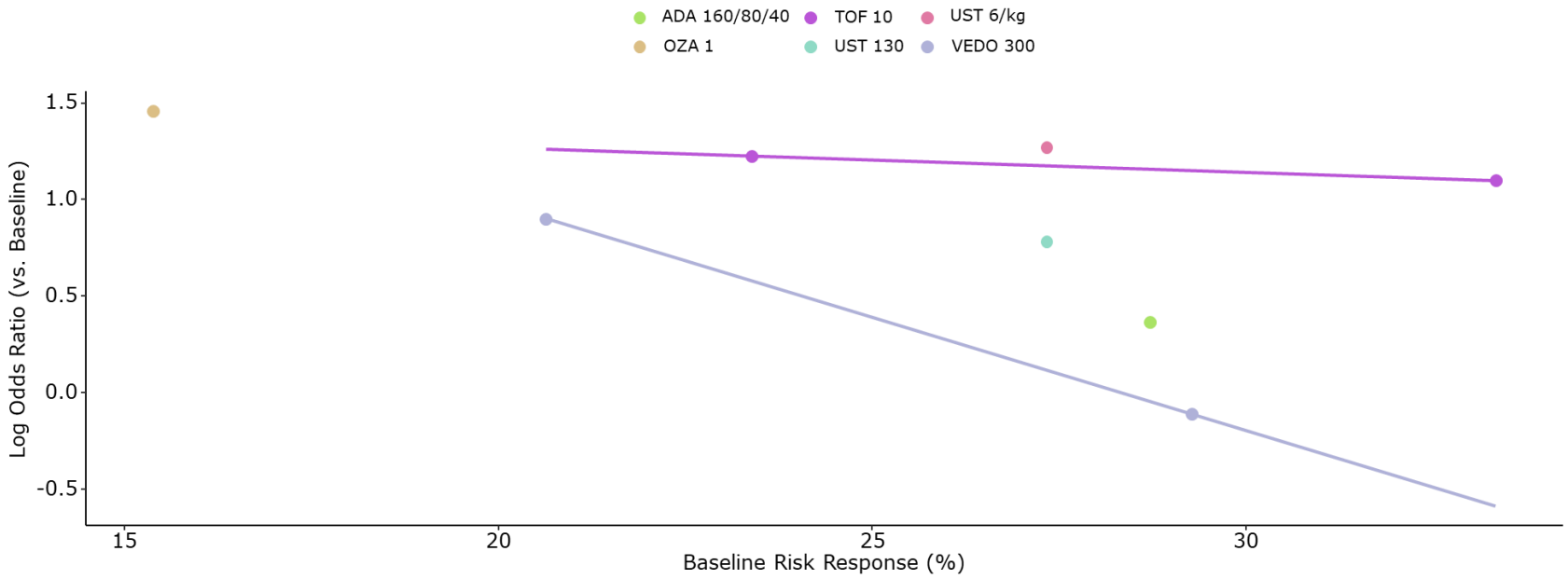
Figure N-8. Placebo response versus treatment effect for clinical response at maintenance in the overall population



Plot of treatment effects organised by treatment on the log odds scale versus placebo response. Baseline risk is equivalent to placebo response. Lines are only presented when ≥ 2 data points are available. Placebo rates presented for the base case, treat-through to re-randomised analyses. Treat-through data has been recalculated as per **Section 7.2.7 in the main dossier**.

Abbreviations: ADA = adalimumab; GOL = golimumab; IFX = infliximab; OZA = ozanimod; PBO = placebo; Q4W = every 4 weeks; Q8W = every 8 weeks; Q12W = every 12 weeks; SC = subcutaneous; TOF = tofacitinib; UST = ustekinumab; VEDO = vedolizumab.

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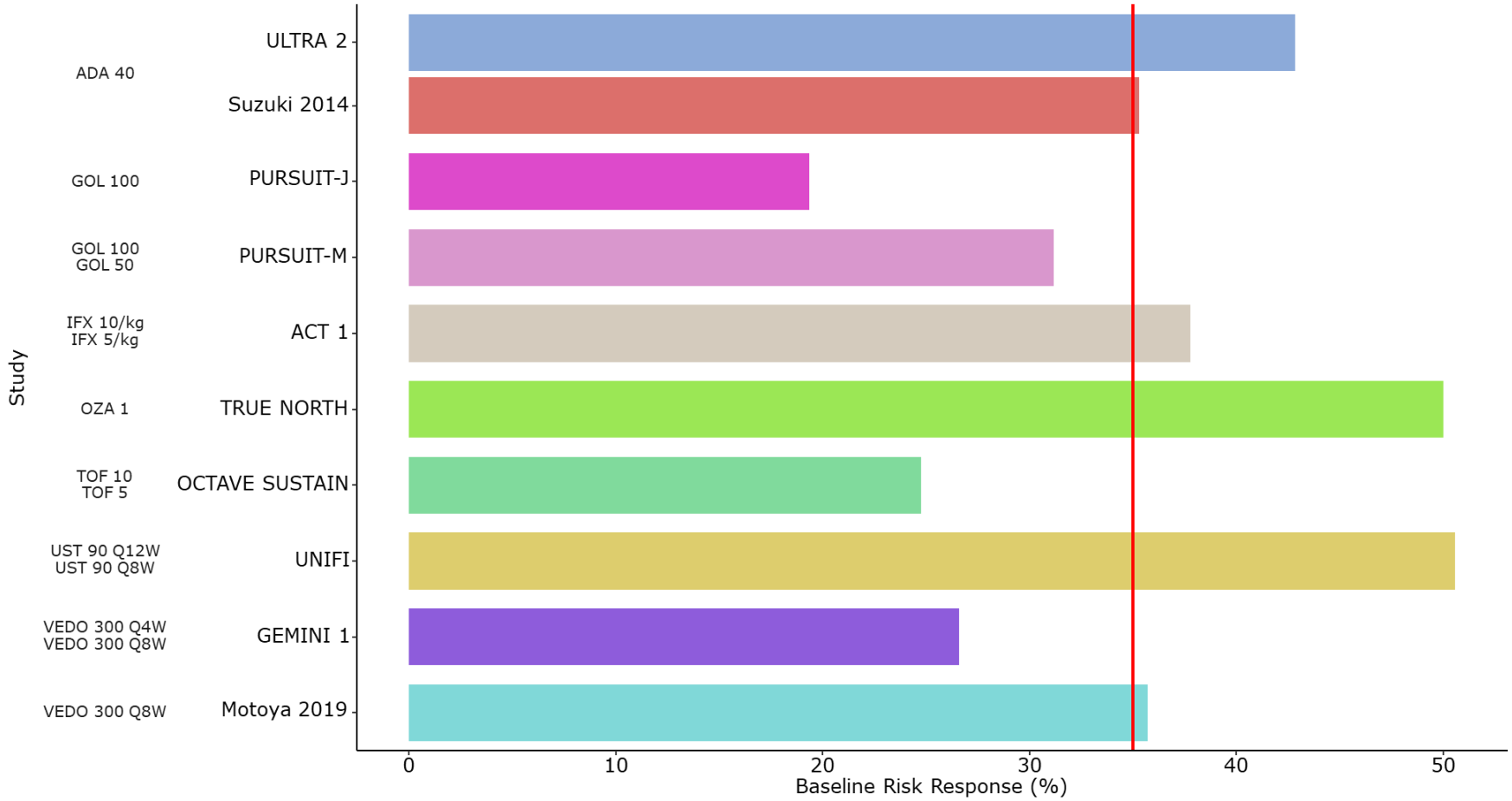
Figure N-9. Placebo rates for clinical response at maintenance in the bio-naïve population

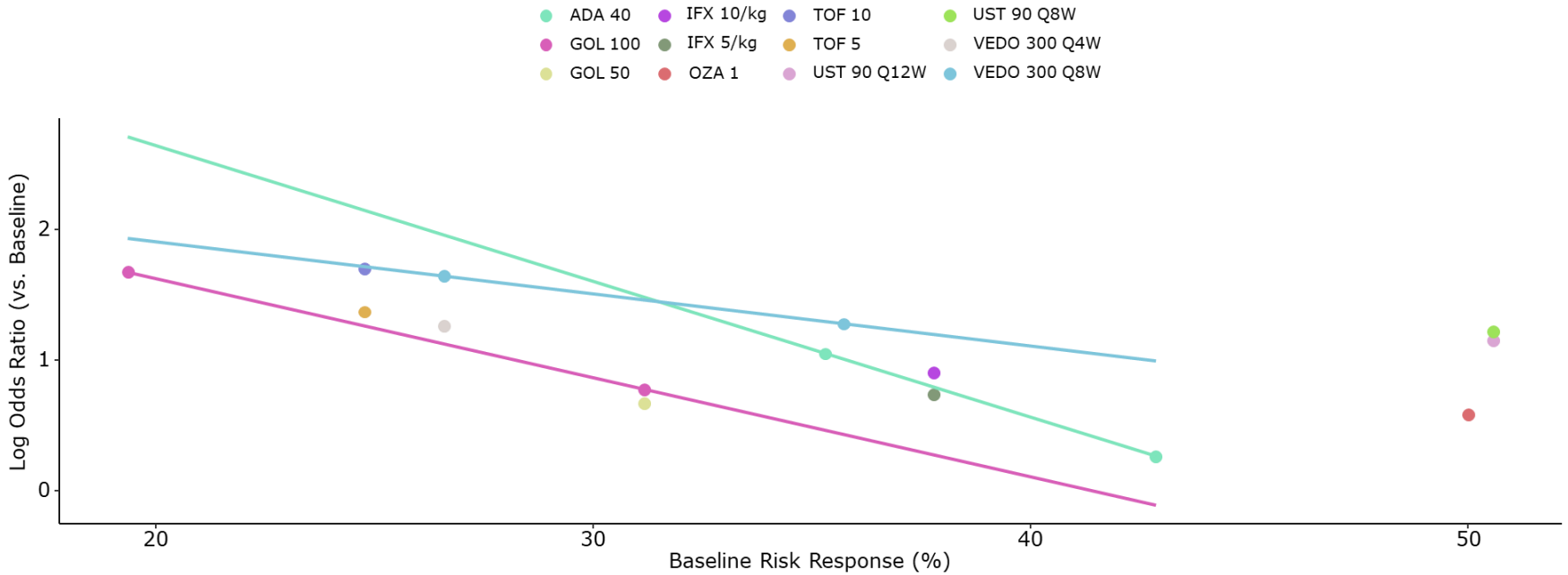


Placebo rates presented for the base case, treat-through to re-randomised analyses. Treat-through data has been recalculated as per **Section 7.2.7 in the main dossier**.

Note: red line represents the average placebo response across all trials. Baseline risk is equivalent to placebo response.

Abbreviations: ADA = adalimumab; GOL = golimumab; IFX = infliximab; OZA = ozanimod; PBO = placebo; Q4W = every 4 weeks; Q8W = every 8 weeks; Q12W = every 12 weeks; SC = subcutaneous; TOF = tofacitinib; UST = ustekinumab; VEDO = vedolizumab.

Figure N-10. Placebo response versus treatment effect for clinical response at maintenance in the bio-naïve population



Plot of treatment effects organised by treatment on the log odds scale versus placebo response. Baseline risk is equivalent to placebo response. Lines are only presented when ≥ 2 data points are available. Placebo rates presented for the base case, treat-through to re-randomised analyses. Treat-through data has been recalculated as per **Section 7.2.7 in the main dossier**.

Abbreviations: ADA = adalimumab; GOL = golimumab; IFX = infliximab; OZA = ozanimod; PBO = placebo; Q4W = every 4 weeks; Q8W = every 8 weeks; Q12W = every 12 weeks; SC = subcutaneous; TOF = tofacitinib; UST = ustekinumab; VEDO = vedolizumab.

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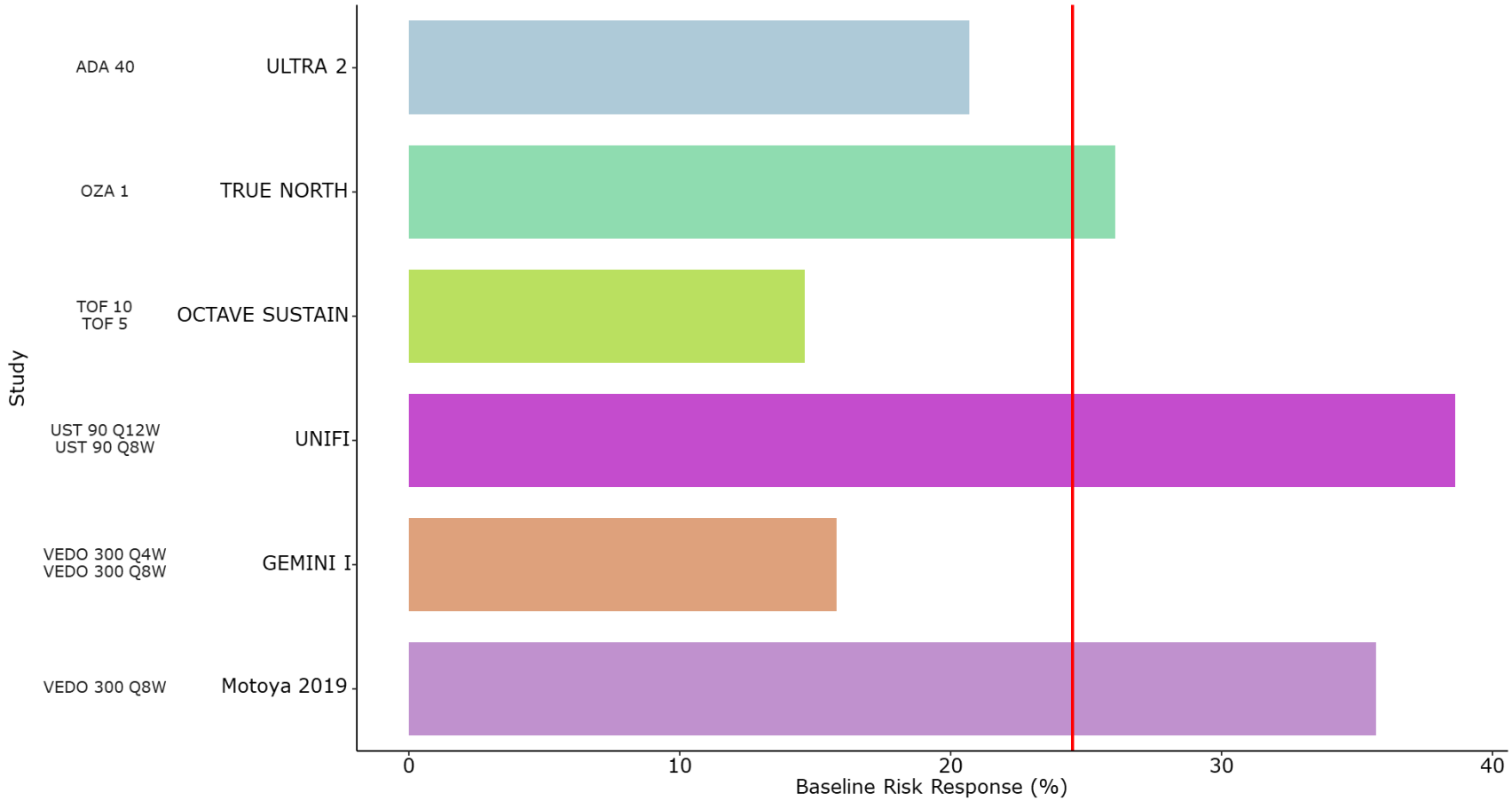
Figure N-11. Placebo rates for clinical response at maintenance in the bio-experienced population

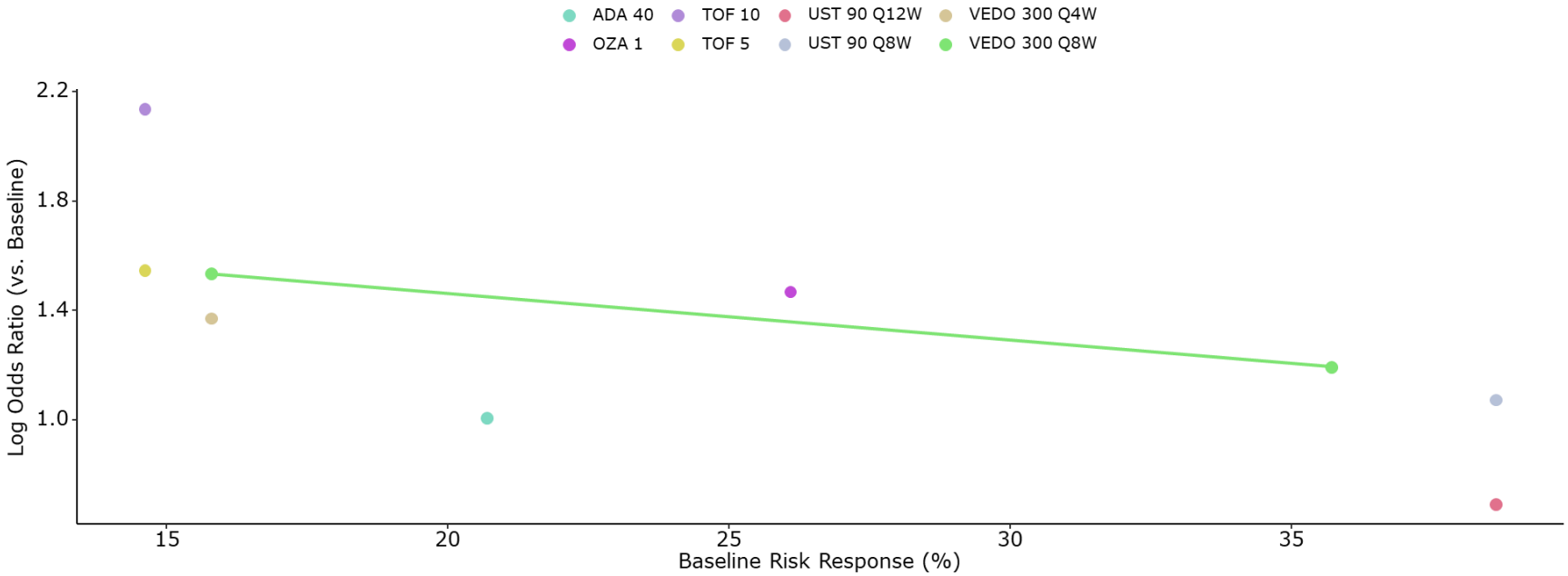


Placebo rates presented for the base case, treat-through to re-randomised analyses. Treat-through data has been recalculated as per **Section 7.2.7 in the main dossier**.

Note: red line represents the average placebo response across all trials. Baseline risk is equivalent to placebo response.

Abbreviations: ADA = adalimumab; GOL = golimumab; IFX = infliximab; OZA = ozanimod; PBO = placebo; Q4W = every 4 weeks; Q8W = every 8 weeks; Q12W = every 12 weeks; SC = subcutaneous; TOF = tofacitinib; UST = ustekinumab; VEDO = vedolizumab.

Figure N-12. Placebo response versus treatment effect for clinical response at maintenance in the bio-experienced population

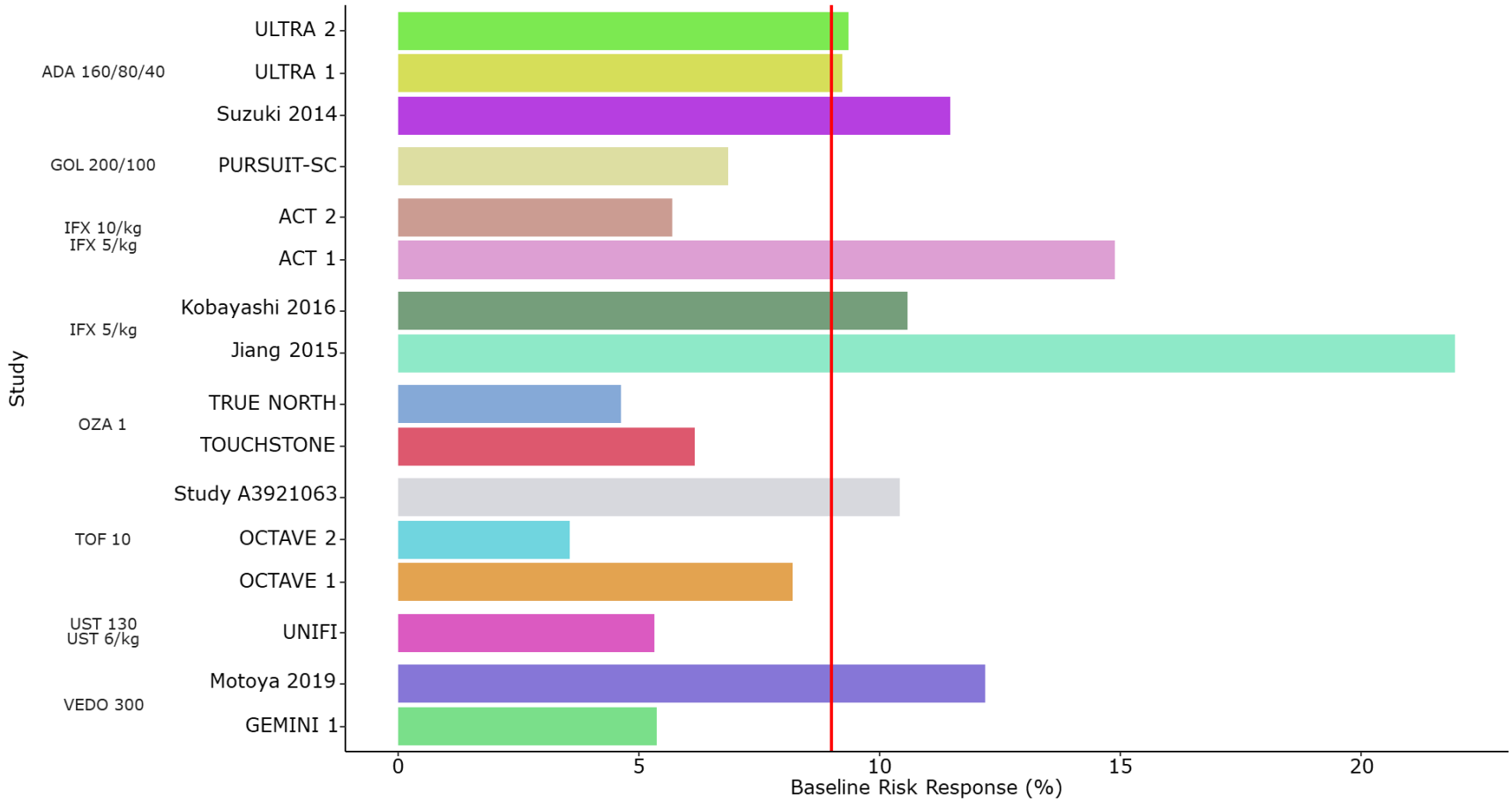


Plot of treatment effects organised by treatment on the log odds scale versus placebo response. Baseline risk is equivalent to placebo response. Lines are only presented when ≥ 2 data points are available. Placebo rates presented for the base case, treat-through to re-randomised analyses. Treat-through data has been recalculated as per **Section 7.2.7 in the main dossier**.

Abbreviations: ADA = adalimumab; GOL = golimumab; IFX = infliximab; OZA = ozanimod; PBO = placebo; Q4W = every 4 weeks; Q8W = every 8 weeks; Q12W = every 12 weeks; SC = subcutaneous; TOF = tofacitinib; UST = ustekinumab; VEDO = vedolizumab.

Appendix N.4.2 Clinical remission

Figure N-13. Placebo rates for clinical remission at induction in the overall population



Note: red line represents the average placebo response across all trials. Baseline risk is equivalent to placebo response.

Abbreviations: ADA = adalimumab; GOL = golimumab; IFX = infliximab; OZA = ozanimod; PBO = placebo; TOF = tofacitinib; UST = ustekinumab; VEDO = vedolizumab.

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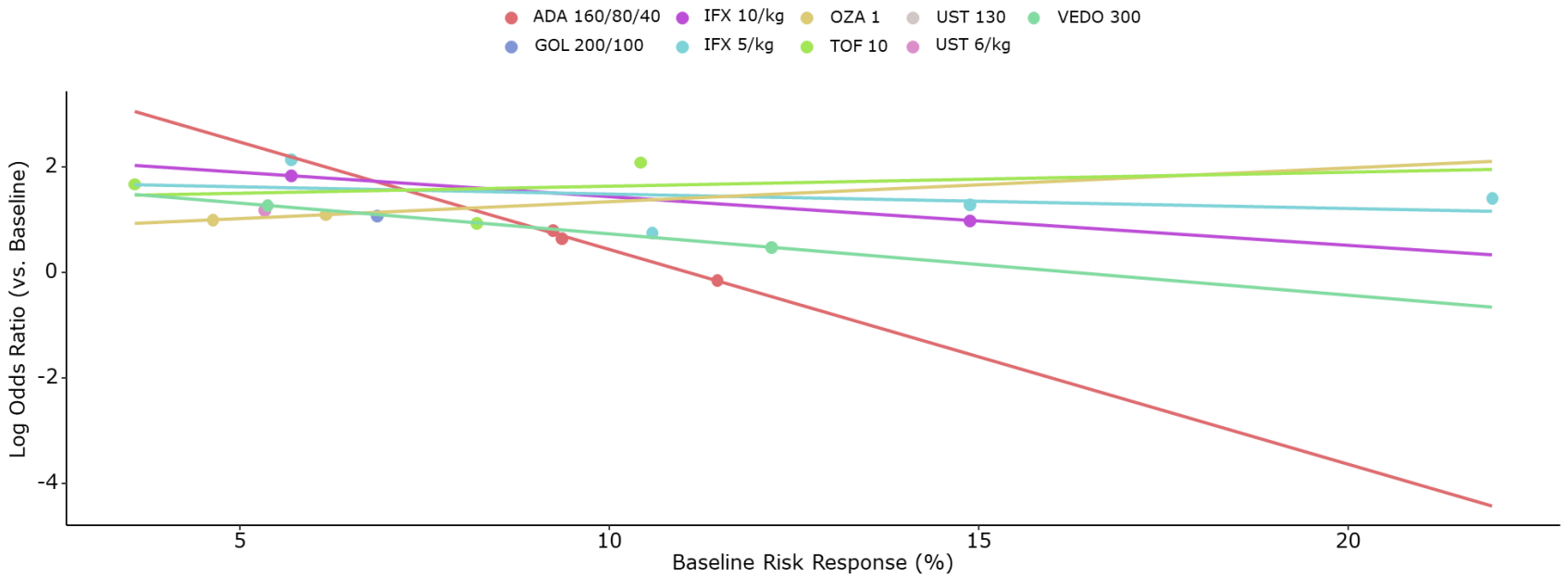
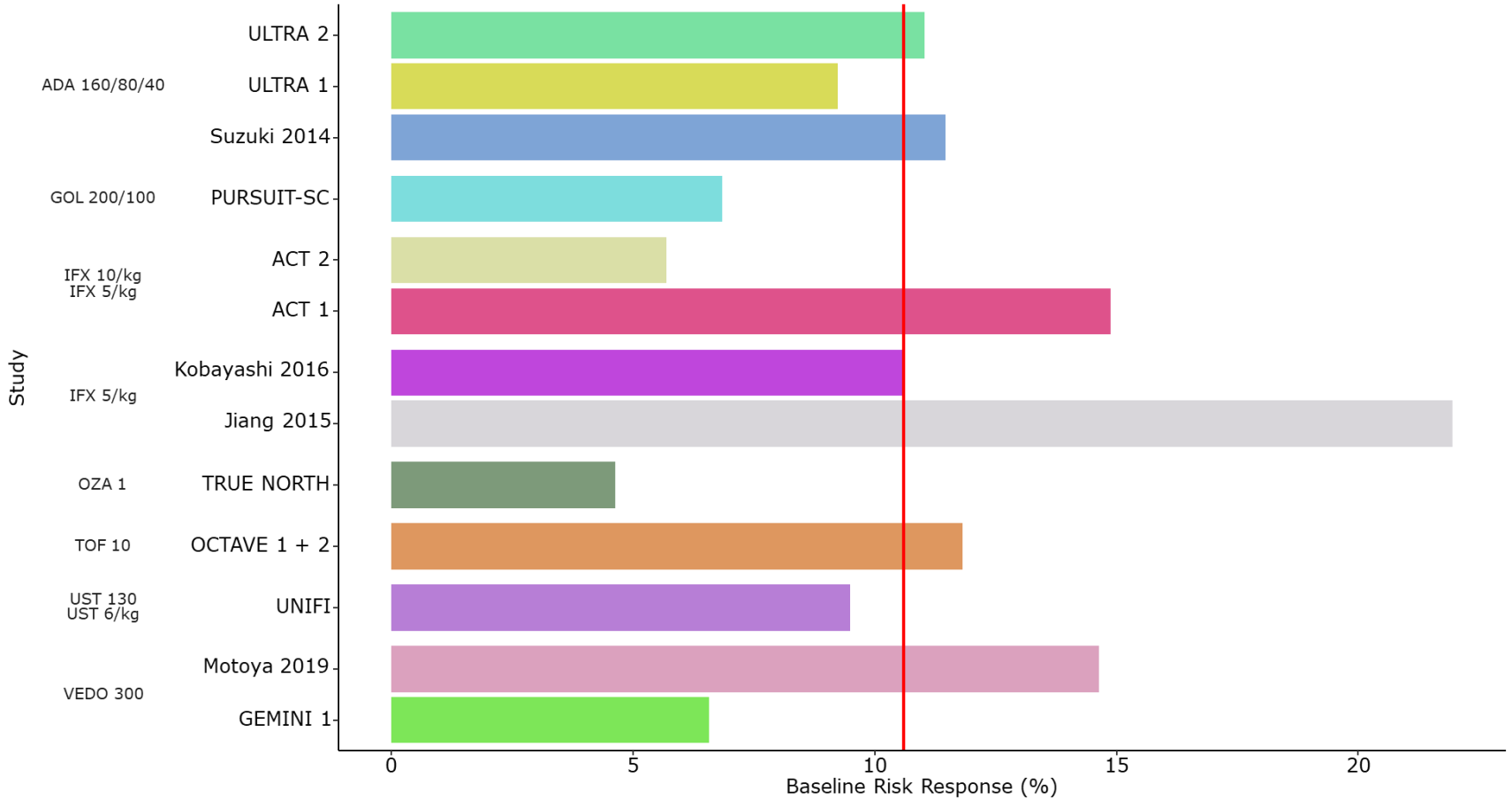
Figure N-14. Placebo response versus treatment effect for clinical remission at induction in the overall population



Plot of treatment effects organised by treatment on the log odds scale versus placebo response. Baseline risk is equivalent to placebo response. Lines are only presented when ≥ 2 data points are available.

Abbreviations: ADA = adalimumab; GOL = golimumab; IFX = infliximab; OZA = ozanimod; PBO = placebo; TOF = tofacitinib; UST = ustekinumab; VEDO = vedolizumab.

Figure N-15. Placebo rates for clinical remission at induction in the bio-naïve population



Note: red line represents the average placebo response across all trials. Baseline risk is equivalent to placebo response.

Abbreviations: ADA = adalimumab; GOL = golimumab; IFX = infliximab; OZA = ozanimod; PBO = placebo; TOF = tofacitinib; UST = ustekinumab; VEDO = vedolizumab.

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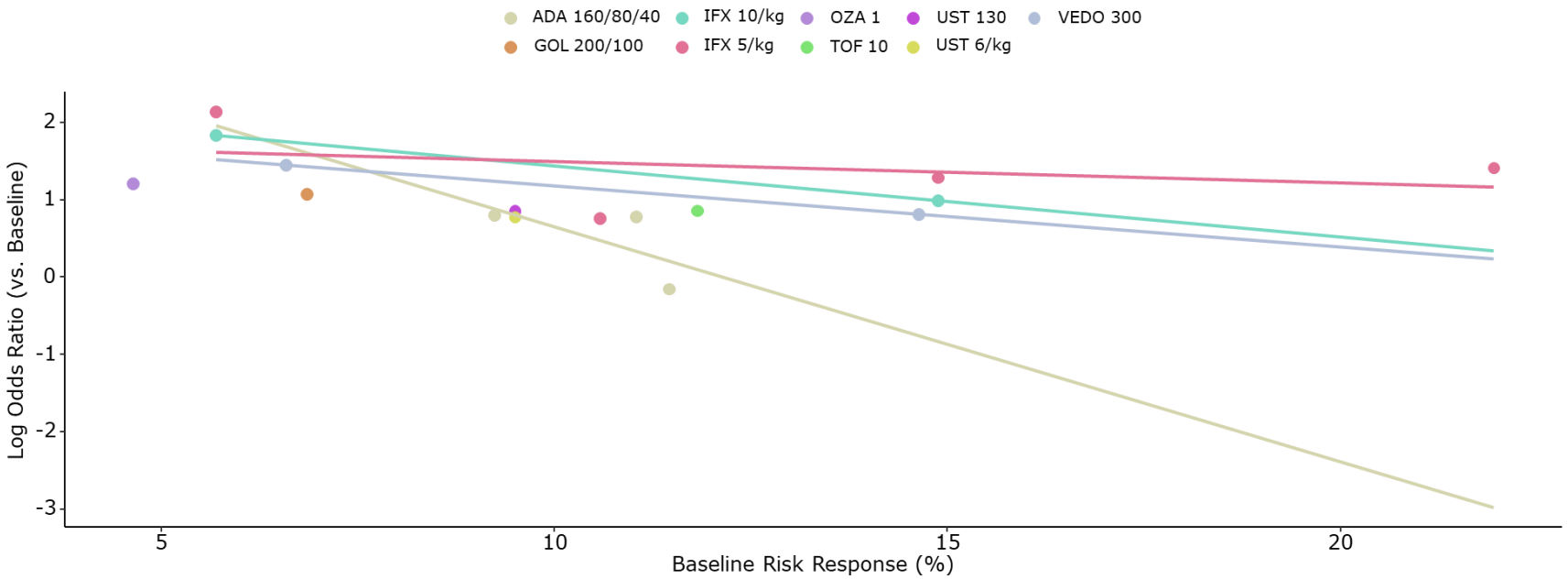
Figure N-16. Placebo response versus treatment effect for clinical remission at induction in the bio-naïve population



Plot of treatment effects organised by treatment on the log odds scale versus placebo response. Baseline risk is equivalent to placebo response. Lines are only presented when ≥ 2 data points are available.

Abbreviations: ADA = adalimumab; GOL = golimumab; IFX = infliximab; OZA = ozanimod; PBO = placebo; TOF = tofacitinib; UST = ustekinumab; VEDO = vedolizumab.

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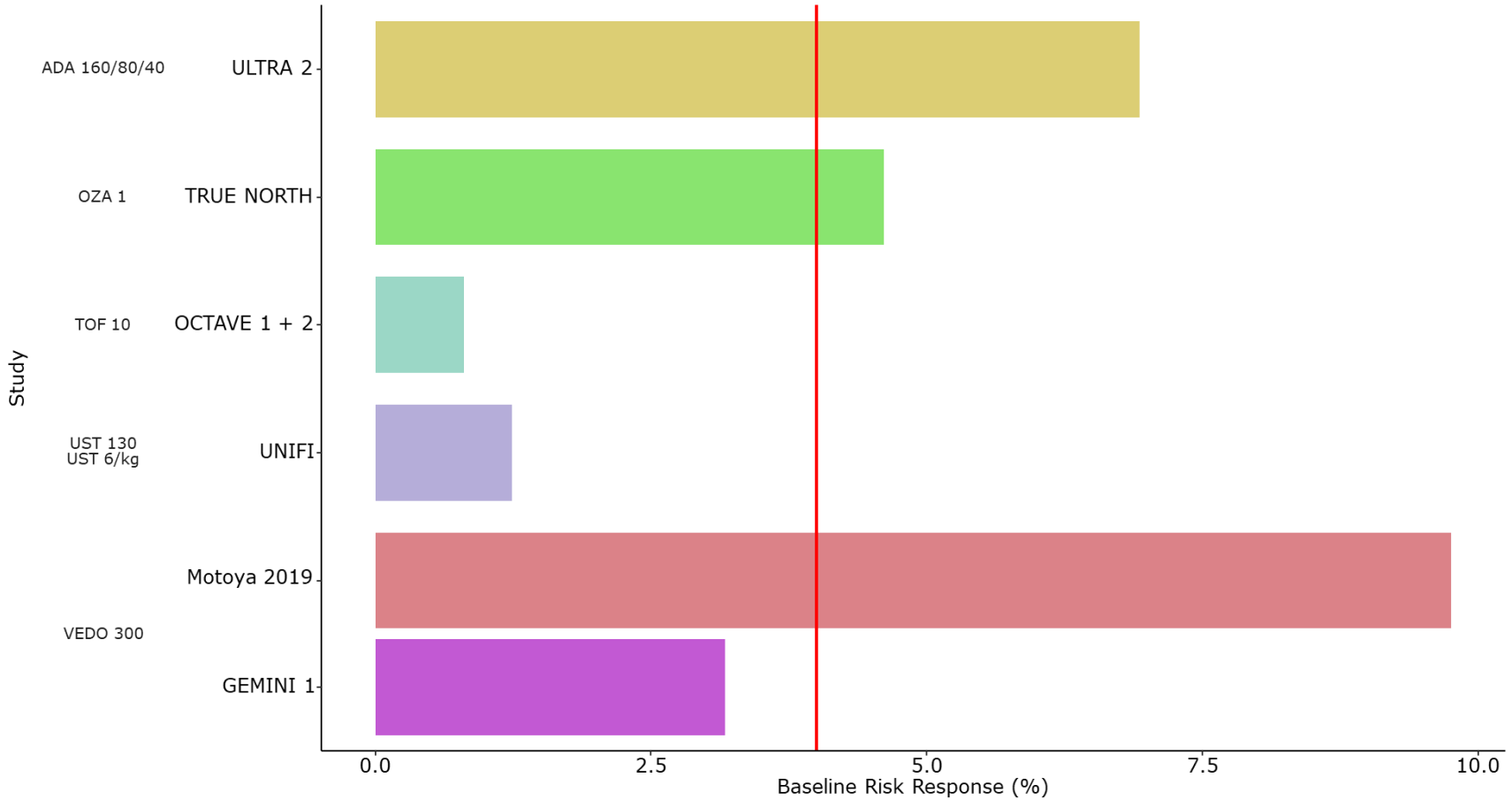
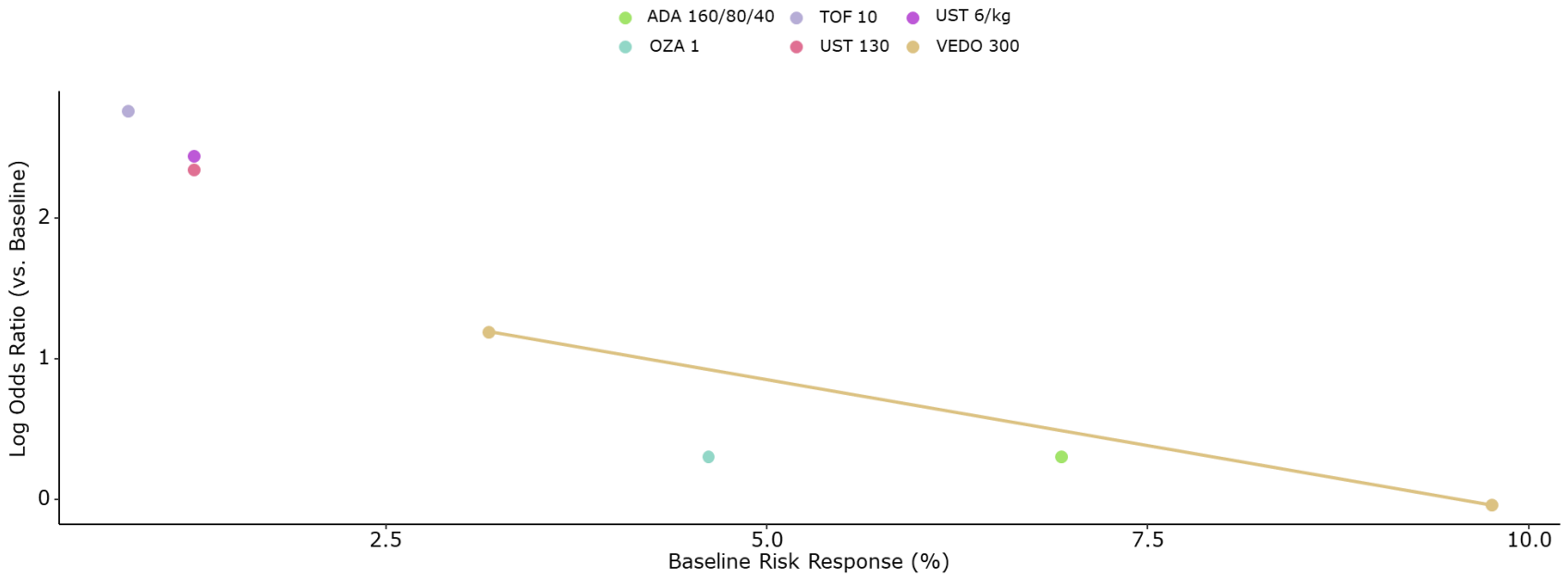
Figure N-17. Placebo rates for clinical remission at induction in the bio-experienced population



Note: red line represents the average placebo response across all trials. Baseline risk is equivalent to placebo response.

Abbreviations: ADA = adalimumab; GOL = golimumab; IFX = infliximab; OZA = ozanimod; PBO = placebo; TOF = tofacitinib; UST = ustekinumab; VEDO = vedolizumab.

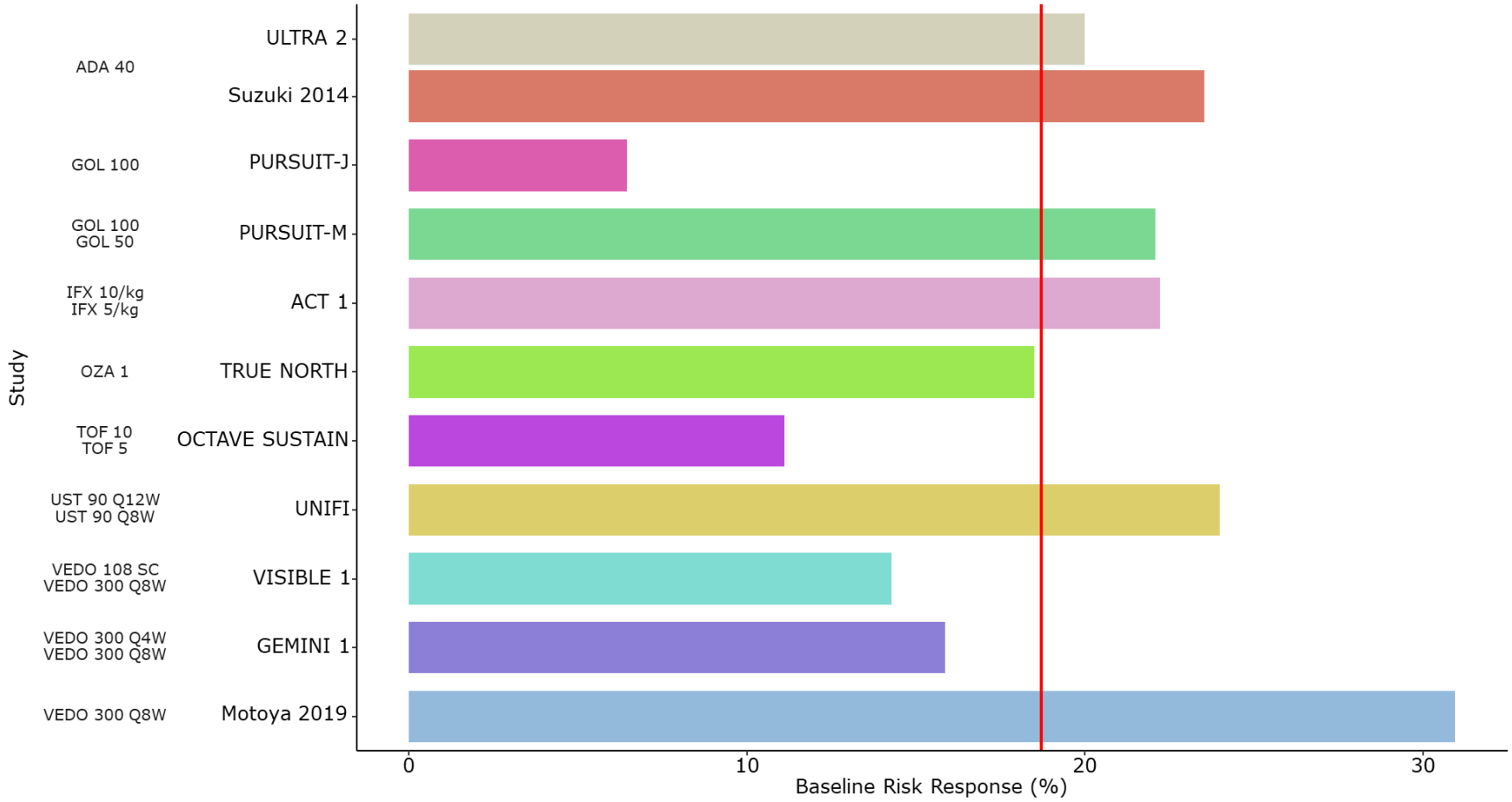
Figure N-18. Placebo response versus treatment effect for clinical remission at induction in the bio-experienced population



Plot of treatment effects organised by treatment on the log odds scale versus placebo response. Baseline risk is equivalent to placebo response. Lines are only presented when ≥ 2 data points are available.

Abbreviations: ADA = adalimumab; GOL = golimumab; IFX = infliximab; OZA = ozanimod; PBO = placebo; TOF = tofacitinib; UST = ustekinumab; VEDO = vedolizumab.

Figure N-19. Placebo rates for clinical remission at maintenance in the overall population



Placebo rates presented for the base case, treat-through to re-randomised analyses. Treat-through data has been recalculated as per **Section 7.2.7 in the main dossier**.

Note: red line represents the average placebo response across all trials. Baseline risk is equivalent to placebo response.

Abbreviations: ADA = adalimumab; GOL = golimumab; IFX = infliximab; OZA = ozanimod; PBO = placebo; Q4W = every 4 weeks; Q8W = every 8 weeks; Q12W = every 12 weeks; SC = subcutaneous; TOF = tofacitinib; UST = ustekinumab; VEDO = vedolizumab.

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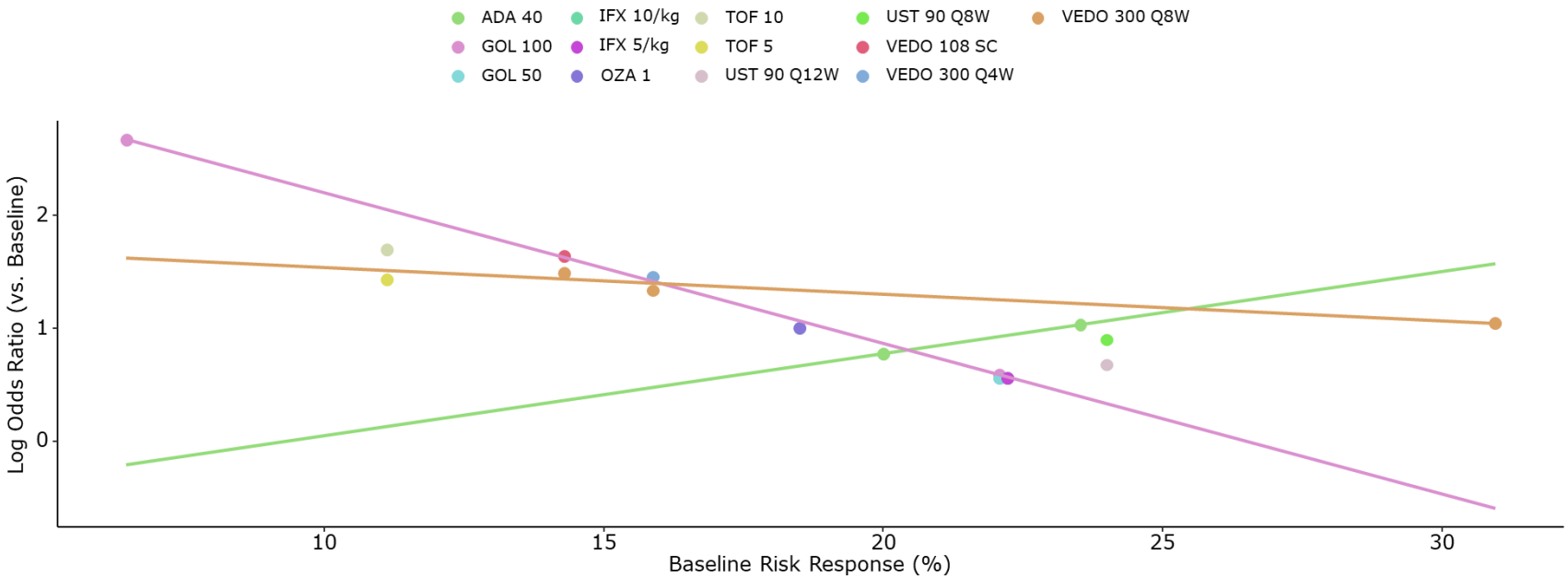
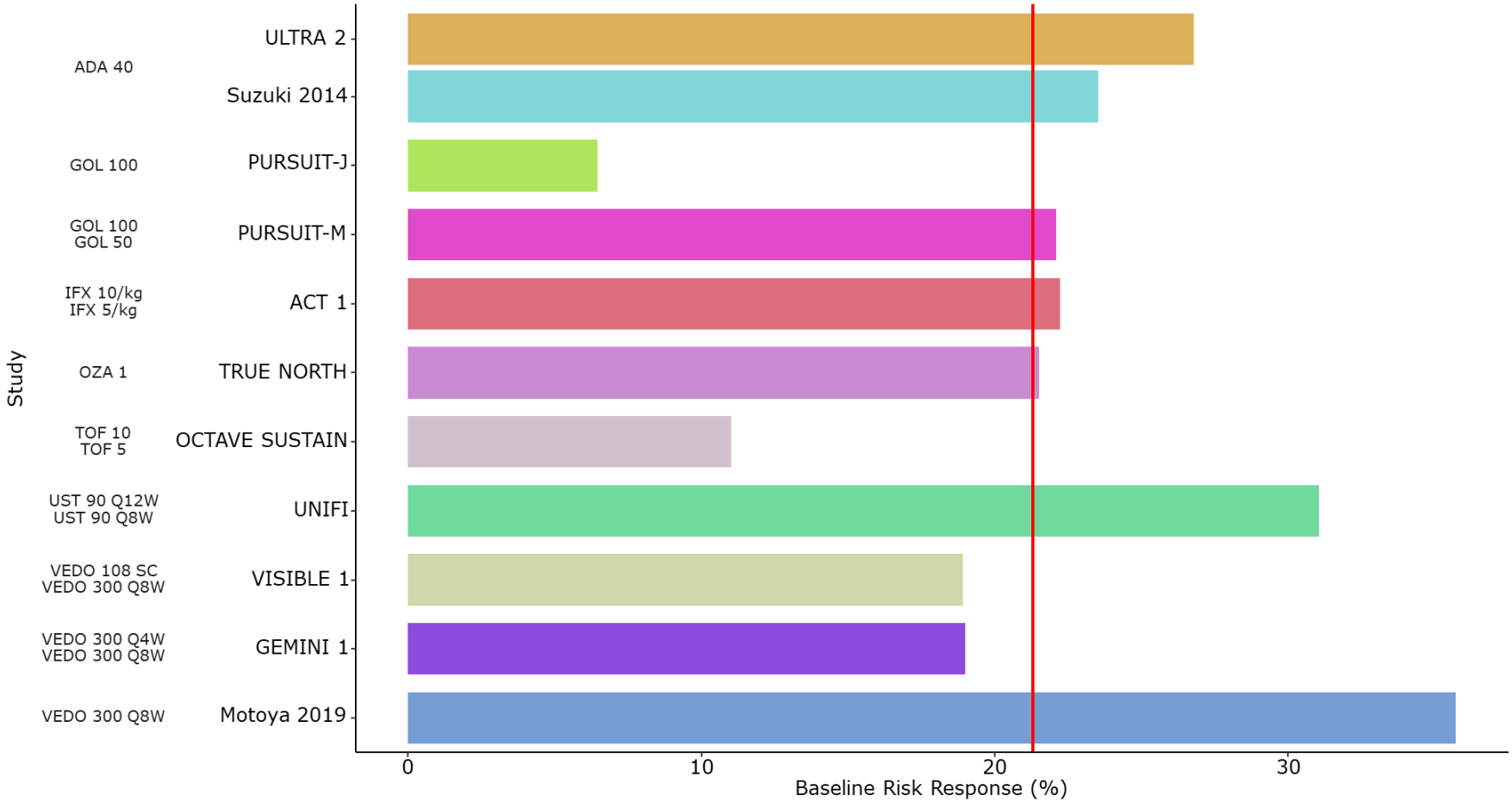
Figure N-20. Placebo response versus treatment effect for clinical remission at maintenance in the overall population



Plot of treatment effects organised by treatment on the log odds scale versus placebo response. Baseline risk is equivalent to placebo response. Lines are only presented when ≥ 2 data points are available. Placebo rates presented for the base case, treat-through to re-randomised analyses. Treat-through data has been recalculated as per **Section 7.2.7 in the main dossier**.

Abbreviations: ADA = adalimumab; GOL = golimumab; IFX = infliximab; OZA = ozanimod; PBO = placebo; Q4W = every 4 weeks; Q8W = every 8 weeks; Q12W = every 12 weeks; SC = subcutaneous; TOF = tofacitinib; UST = ustekinumab; VEDO = vedolizumab.

Figure N-21. Placebo rates for clinical remission at maintenance in the bio-naïve population



Placebo rates presented for the base case, treat-through to re-randomised analyses. Treat-through data has been recalculated as per **Section 7.2.7 in the main dossier**

Note: red line represents the average placebo response across all trials. Baseline risk is equivalent to placebo response.

Abbreviations: ADA = adalimumab; GOL = golimumab; IFX = infliximab; OZA = ozanimod; PBO = placebo; Q4W = every 4 weeks; Q8W = every 8 weeks; Q12W = every 12 weeks; SC = subcutaneous; TOF = tofacitinib; UST = ustekinumab; VEDO = vedolizumab.

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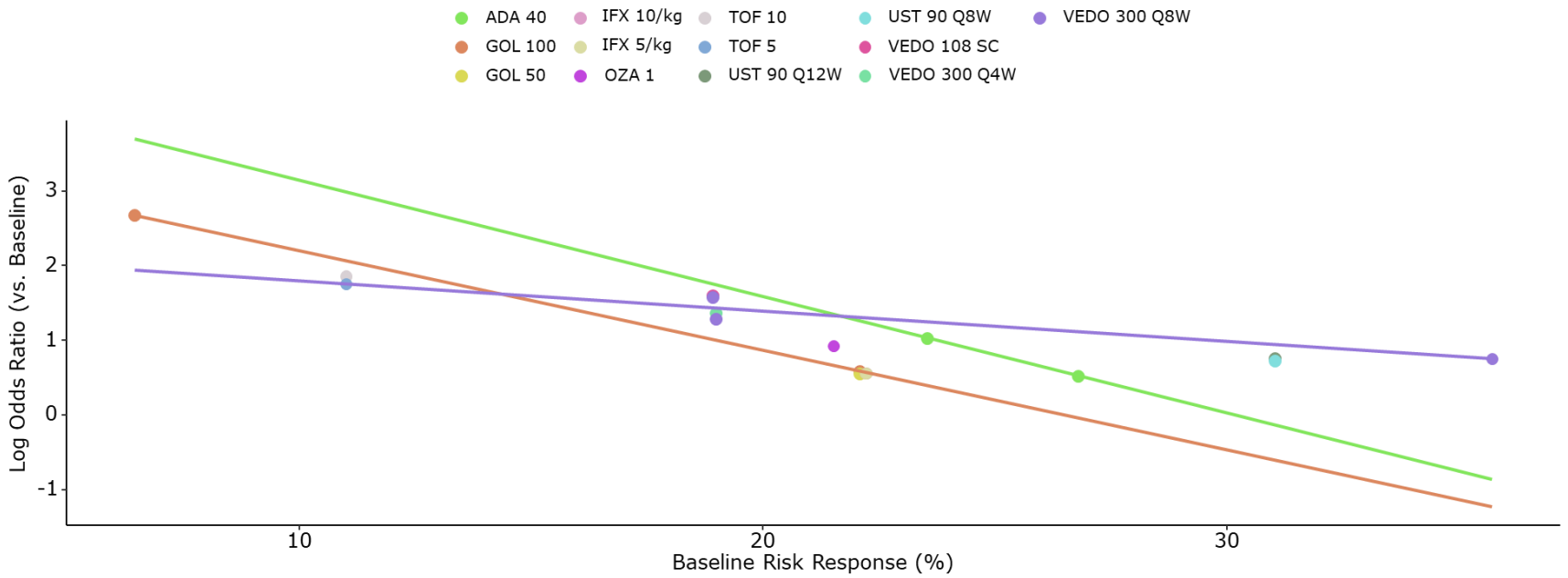
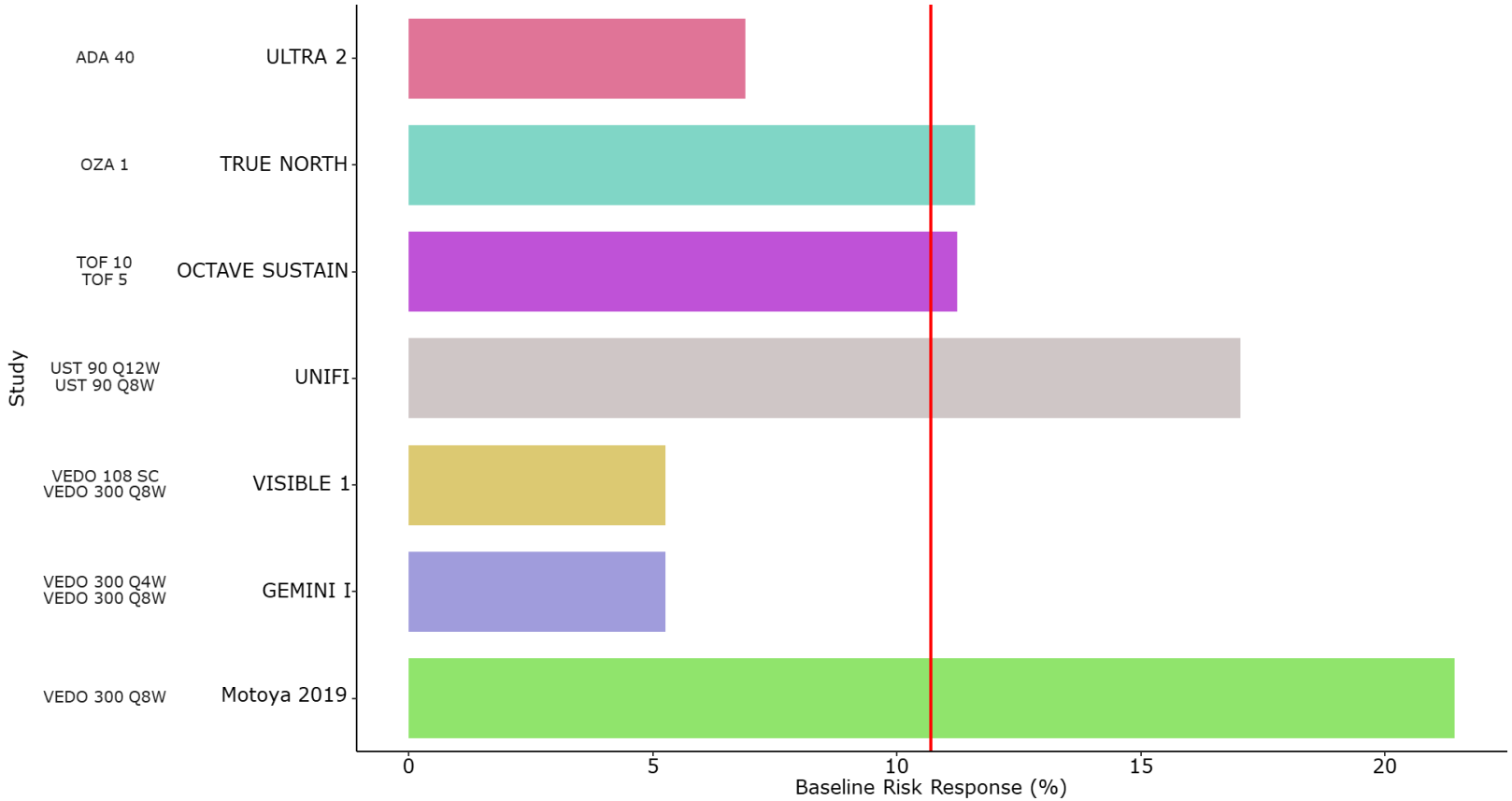
Figure N-22. Placebo response versus treatment effect for clinical remission at maintenance in the bio-naïve population



Plot of treatment effects organised by treatment on the log odds scale versus placebo response. Baseline risk is equivalent to placebo response. Lines are only presented when ≥ 2 data points are available. Placebo rates presented for the base case, treat-through to re-randomised analyses. Treat-through data has been recalculated as per **Section 7.2.7 in the main dossier**.

Abbreviations: ADA = adalimumab; GOL = golimumab; IFX = infliximab; OZA = ozanimod; PBO = placebo; Q4W = every 4 weeks; Q8W = every 8 weeks; Q12W = every 12 weeks; SC = subcutaneous; TOF = tofacitinib; UST = ustekinumab; VEDO = vedolizumab.

Figure N-23. Placebo rates for clinical remission at maintenance in the bio-experienced population



Placebo rates presented for the base case, treat-through to re-randomised analyses. Treat-through data has been recalculated as per **Section 7.2.7 in the main dossier**.

Note: red line represents the average placebo response across all trials. Baseline risk is equivalent to placebo response.

Abbreviations: ADA = adalimumab; GOL = golimumab; IFX = infliximab; OZA = ozanimod; PBO = placebo; Q4W = every 4 weeks; Q8W = every 8 weeks; Q12W = every 12 weeks; SC = subcutaneous; TOF = tofacitinib; UST = ustekinumab; VEDO = vedolizumab.

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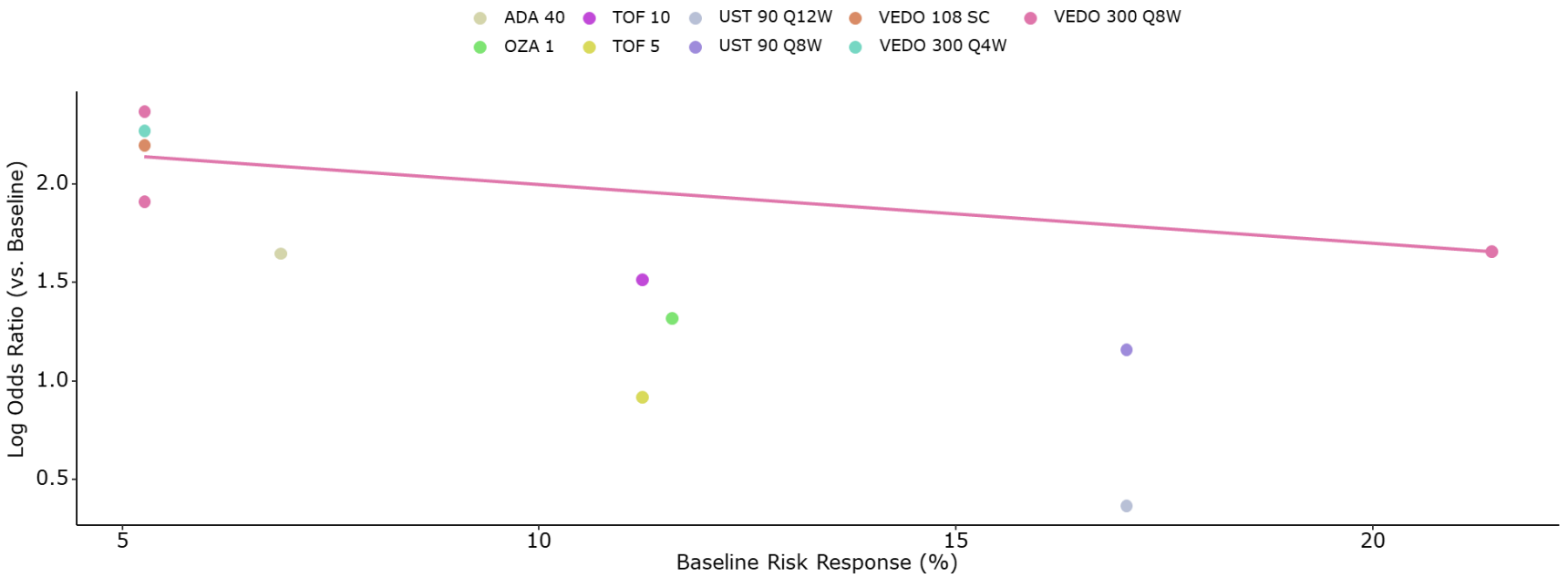
Figure N-24. Placebo response versus treatment effect for clinical remission at maintenance in the bio-experienced population



Plot of treatment effects organised by treatment on the log odds scale versus placebo response. Baseline risk is equivalent to placebo response. Lines are only presented when ≥ 2 data points are available. Placebo rates presented for the base case, treat-through to re-randomised analyses. Treat-through data has been recalculated as per **Section 7.2.7 in the main dossier**.

Abbreviations: ADA = adalimumab; GOL = golimumab; IFX = infliximab; OZA = ozanimod; PBO = placebo; Q4W = every 4 weeks; Q8W = every 8 weeks; Q12W = every 12 weeks; SC = subcutaneous; TOF = tofacitinib; UST = ustekinumab; VEDO = vedolizumab

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Appendix N.5 Alignment with previous NMAs in UC

Table N-5. Studies included in current and previous NMAs

Primary agent(s)	Trials	Trial type	Ozanimod NMA	NICE submissions				ICER	CADTH submissions
				UST	TOF	VEDO	ADA/IFX/GOL		UST
OZA	True North	Both induction and maintenance	Yes (Bio-Naïve, Bio-Experienced)	No	No	No	No	No	No
	TOUCHSTONE	Both induction and maintenance	Yes (Overall only)	No	No	No	No	No	No
ADA	ULTRA 1	Induction only	Yes (Bio-Naïve)	Yes (Bio-Naïve)	Yes (Bio-Naïve)	Yes (Bio-Naïve)	Yes (Bio-Naïve)	Yes (Bio-Naïve)	Yes (Bio-Naïve, Bio-Experienced)
	ULTRA 2	Both induction and maintenance	Yes (Bio-Naïve, Bio-Experienced)	Yes (Bio-Naïve, Bio-Experienced)	Yes (Bio-Naïve, Bio-Experienced)	Yes (Bio-Naïve, Bio-Experienced)	Yes (Bio-Naïve, Bio-Experienced)	Yes (Bio-Naïve, Bio-Experienced)	Yes (Bio-Naïve, Bio-Experienced)
	Suzuki 2014	Both induction and maintenance	Yes (Bio-Naïve)	Sensitivity Analysis (Bio-Naïve)	Yes (Bio-Naïve)	Yes (Bio-Naïve)	Sensitivity Analysis (Bio-Naïve)	Yes (Bio-Naïve)	Sensitivity Analysis (Bio-Naïve)
GOL	PURSUIT-SC	Induction only	Yes (Bio-Naïve)	Yes (Bio-Naïve)	Yes (Bio-Naïve)	Yes (Bio-Naïve)	Yes (Bio-Naïve)	Yes (Bio-Naïve)	Yes (Bio-Naïve)
	PURSUIT M	Maintenance only	Yes (Bio-Naïve)	Yes (Bio-Naïve)	Yes (Bio-Naïve)	Yes (Bio-Naïve)	Yes (Bio-Naïve)	Yes (Bio-Naïve)	Yes (Bio-Naïve)
	PURSUIT J	Both induction and maintenance	Yes (Bio-Naïve)	Yes (Bio-Naïve)	Yes (Bio-Naïve)	No	No	Yes (Bio-Naïve)	Sensitivity Analysis (Bio-Naïve)
IFX	ACT 1	Both induction and maintenance	Yes (Bio-Naïve)	Yes (Bio-Naïve)	Yes (Bio-Naïve)	Yes (Bio-Naïve)	Yes (Bio-Naïve)	Yes (Bio-Naïve)	Yes (Bio-Naïve)

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Primary agent(s)	Trials	Trial type	Ozanimod NMA	NICE submissions				ICER	CADTH submissions
				UST	TOF	VEDO	ADA/IFX/GOL		UST
	ACT 2	Both induction and maintenance	Yes (Bio-Naïve)	Yes (Bio-Naïve)	Yes (Bio-Naïve)	Yes (Bio-Naïve)	Yes (Bio-Naïve)	Yes (Bio-Naïve)	Yes (Bio-Naïve)
	Kobayashi 2016	Both induction and maintenance	Yes (Bio-Naïve)	No	Yes (Bio-Naïve)	No	No	Yes (Bio-Naïve)	Sensitivity Analysis (Bio-Naïve)
	Jiang 2015	Both induction and maintenance	Yes (Bio-Naïve)	Sensitivity Analysis (Bio-Naïve)	Yes (Bio-Naïve)	No	No	Yes (Bio-Naïve)	Sensitivity Analysis (Bio-Naïve)
	NCT01551290	Both induction and maintenance	No	No	No	No	No	Yes (Bio-Naïve)	No
	Jarnerot 2005	Induction only	No	No	No	No	No	No	No
	Probert 2003	Induction only	No	Yes (Bio-Naïve)	No	No	No	No	Yes (Bio-Naïve)
TOF	OCTAVE 1	Induction only	Yes (Bio-Naïve, Bio-Experienced)	Yes (Bio-Naïve, Bio-Experienced)	Yes (Bio-Naïve, Bio-Experienced)	No	No	Yes (Bio-Naïve, Bio-Experienced)	Yes (Bio-Naïve, Bio-Experienced)
	OCTAVE 2	Induction only	Yes (Bio-Naïve, Bio-Experienced)	Yes (Bio-Naïve, Bio-Experienced)	Yes (Bio-Naïve, Bio-Experienced)	No	No	Yes (Bio-Naïve, Bio-Experienced)	Yes (Bio-Naïve, Bio-Experienced)
	OCTAVE SUSTAIN	Maintenance only	Yes (Bio-Naïve, Bio-Experienced)	Yes (Bio-Naïve, Bio-Experienced)	Yes (Bio-Naïve, Bio-Experienced)	No	No	Yes (Bio-Naïve, Bio-Experienced)	Yes (Bio-Naïve, Bio-Experienced)
	Study A3921063	Induction only	Yes (Bio-Naïve, Bio-Experienced)	No	Yes (Bio-Naïve, Bio-Experienced)	No	No	No	Yes (Bio-Naïve, Bio-Experienced)

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Primary agent(s)	Trials	Trial type	Ozanimod NMA	NICE submissions				ICER	CADTH submissions
				UST	TOF	VEDO	ADA/IFX/GOL		UST
UST	UNIFI	Both induction and maintenance	Yes (Bio-Naïve, Bio-Experienced)	Yes (Bio-Naïve, Bio-Experienced)	No	No	No	Yes (Bio-Naïve, Bio-Experienced)	Yes (Bio-Naïve, Bio-Experienced)
VEDO	GEMINI 1	Both induction and maintenance	Yes (Bio-Naïve, Bio-Experienced)	Yes (Bio-Naïve, Bio-Experienced)	Yes (Bio-Naïve, Bio-Experienced)	Yes (Bio-Naïve, Bio-Experienced)	No	Yes (Bio-Naïve, Bio-Experienced)	Yes (Bio-Naïve, Bio-Experienced)
	Motoya 2019	Both induction and maintenance	Yes (Bio-Naïve, Bio-Experienced)	No	No	No	No	Yes (Bio-Naïve, Bio-Experienced)	Sensitivity Analysis (Bio-Naïve, Bio-Experienced)
	VISIBLE 1	Both induction and maintenance	Yes (Bio-Naïve, Bio-Experienced)	No	No	No	No	Yes (Bio-Naïve, Bio-Experienced)	No
	Feagan 2005	Induction only	No	No	No	No	No	No	No
IFX vs. ADA	Mshimesh 2017	Not available*	No	No	Yes (Bio-Naïve)	No	No	No	No
IFX + AZA	UC-SUCCESS	Induction only	Sensitivity analysis (Bio-Naïve)	No	Safety Analysis (Bio-Naïve)	No	No	No	No
ADA vs. VEDO	VARSITY	Both induction and maintenance	Yes (Bio-Naïve, Bio-Experienced)	Yes (Bio-Naïve, Bio-Experienced)	No	No	No	Yes (Bio-Naïve, Bio-Experienced)	Yes (Bio-Naïve, Bio-Experienced)

*Publication retracted

Abbreviations: ADA = adalimumab; AZA = azathioprine; CADTH = Canadian Agency for Drugs and Technologies in Health; GOL = golimumab; ICER = Institute for Clinical and Economic Review; IFX = infliximab; NICE = National Institute for Health and Care Excellence; NMA = network meta-analysis; OZA = ozanimod; TOF = tofacitinib; UST = ustekinumab; VEDO = vedolizumab.

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Appendix N.6 Heterogeneity highlighted in previous NMAs

Table N-6. Summary of heterogeneity highlighted and addressed in current and previous major NMAs in UC

Source of potential heterogeneity	Ozanimod for UC NMA	Ustekinumab NICE technology appraisal [TA633]	Ustekinumab CADTH submission	Tofacitinib NICE technology appraisal [TA547]	Vedolizumab NICE technology appraisal [TA342]	ICER UC evidence report
Trial eligibility criteria	Not identified as a major source of heterogeneity	Not identified as a major source of heterogeneity	Not identified as a major source of heterogeneity	Not identified as a major source of heterogeneity	Not identified as a major source of heterogeneity	Not identified as a major source of heterogeneity
Trial designs	Identified as a major source of heterogeneity, adjusted for in the maintenance period using a treat-through to re-randomised design	Identified as a major source of heterogeneity, adjusted for in the maintenance period using a re-randomised to treat-through design	Identified as a major source of heterogeneity, adjusted for in the maintenance period using a re-randomised to treat-through design	Identified as a major source of heterogeneity, adjusted for in the maintenance period using a treat-through to re-randomised design	Identified as a major source of heterogeneity, adjusted treat-through trials assuming induction responders were the same as maintenance responders as sensitivity	Identified as a major source of heterogeneity, adjusted for in the maintenance period using a treat-through to re-randomised design
Patient characteristics	Moderate differences in corticosteroid use and other patient characteristics with True North and other trials; treatment effect modifier assessment suggests some risk of biasing induction NMA but little risk of biasing maintenance NMA; indirectly explored through placebo response adjustment	Considered similar with regards to age, gender, weight, and UC disease characteristics; economic explored sensitivity analyses evaluating influence of patient characteristics; no treatment effect modifier or meta-regression performed	Duration of disease, age, weight, proportion of males, CRP, and Mayo Score at baseline deemed to be comparable across trials	Analyses of heterogeneity did not suggest any significant differences in treatment effect between subgroups in OCTAVE trials; ERG noted heterogeneity on prior TNF, disease duration, extent of disease, IBDQ, lab measurements as levels as potential effect modifiers that differed across trials	Heterogeneity assessment revealed alignment of patient characteristics between trials, except for prior TNF exposure which was identified as a major characteristic that might affect patient outcome; subgroup analyses performed accordingly	Noted some differences in patient characteristics regarding disease severity, duration, use of conventional therapy; indirectly accounted for through placebo response adjustment
Biologic population definitions	Heterogenous due to differences in definitions of biologic (i.e. TNF, or TNF and UST and VEDO) as well as definitions of	Heterogenous due to differences in definitions of biologic (i.e. TNF, or TNF and VEDO) as well as definitions of experienced	Heterogenous due to differences in definitions of biologic (i.e. TNF, or TNF and VEDO) as well as definitions of experienced	Heterogenous due to differences in definitions of experienced and naïve (e.g., exposed or failure)	Heterogeneous due to differences in definitions of experienced and naïve (e.g. exposed or failure)	Heterogenous due to differences in definitions of biologic (i.e. TNF, or TNF and UST and VEDO) as well as definitions of

Source of potential heterogeneity	Ozanimod for UC NMA	Ustekinumab NICE technology appraisal [TA633]	Ustekinumab CADTH submission	Tofacitinib NICE technology appraisal [TA547]	Vedolizumab NICE technology appraisal [TA342]	ICER UC evidence report
	experienced and naïve (e.g., exposed or failure)	and naïve (e.g., exposed or failure)	and naïve (e.g., exposed or failure)			experienced and naïve (e.g., exposed or failure)
Outcome definitions	Post hoc analysis conducted to obtain 4-component response and remission data from True North to align with other trials; excluded trials that did not define response and remission outcomes based on Mayo Score; some heterogeneity due to use a central endoscopy score in True North & OCTAVE	Leveraged "global" definition of response and remission in NMA as it aligned with other trials; ERG noted that definitions are likely similar enough such that all trials can be included in NMA	Highlighted heterogeneity due to clinical remission being defined differently for OCTAVE and Probert 2003 and mucosal healing equating to endoscopic improvement in certain cases	Leveraged definitions of clinical response and remission that aligned with other trials for OCTAVE trials (i.e., did not require RBS = 0); explored central and local endoscopy reads from OCTAVE	Leveraged definitions of clinical response and remission that aligned with other trials; no discussion on outcome definition heterogeneity	Some heterogeneity highlighted through stricter definition of remission in OCTAVE trials in addition to use of central endoscopy reading, while other trials used local scoring; use of worst rank method for Mayo Scores in ADA trials
Placebo response	Varied across trials and was observed to have a relationship with treatment effects; placebo adjustment explored as a sensitivity	Not adjusted for, discussed as a potential source of heterogeneity	Not highlighted as a potential source of heterogeneity	Not adjusted for, discussed as a potential source of heterogeneity	Not adjusted for, stated as a potential source of heterogeneity cause by differences in patient characteristics between trials	Varied across trials and was observed to have a relationship with treatment effects; placebo adjustment leveraged in biologic-naïve analyses

Abbreviations: ADA = adalimumab; ICER = Institute for Clinical and Economic Review; NICE = National Institute for Health and Care Excellence; NMA = network meta-analysis; RBS = rectal bleeding score; TNF = tumour necrosis factor; UC = ulcerative colitis; UST = ustekinumab; VEDO = vedolizumab.

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Appendix N.7 NMA data extraction tables

Appendix N.7.1 Clinical efficacy

Appendix N.7.1.1 Induction

Table N-7. Efficacy data for clinical remission after induction therapy (weeks 6-12)

Drug	Study	Follow-up time, weeks	Intervention	Bio-naive		Bio-experienced	
				n/N	%	n/N	%
Ozanimod	TRUE NORTH [10]	10	Ozanimod 1 mg	66/299	22.1	13/130	10.0
			Placebo	10/151	6.6	3/65	4.6
	TOUCHSTONE [11]	8	Ozanimod 1 mg			NA	NA
			Placebo			NA	NA
Adalimumab	ULTRA 2 [12]	8	Adalimumab 160/80/40 mg	NA	NA	9/98	9.2
			Placebo	NA	NA	7/101	6.9
Golimumab	PURSUIT-SC [13]	6	Golimumab 200/100 mg	45/253	17.8	NA	NA
			Placebo	16/251	6.4	NA	NA
	PURSUIT-M [14]	6	Golimumab 50 mg	NA	NA	NA	NA
			Golimumab 100 mg	NA	NA	NA	NA
			Placebo	NA	NA	NA	NA
	PURSUIT-J [15]	6	Golimumab 100 mg	NA	NA	NA	NA
			Placebo	NA	NA	NA	NA
Infliximab	ACT 1 [16]	8	Infliximab 5/kg	47/121	38.8	NA	NA
			Placebo	18/121	14.9	NA	NA
	ACT 2 [16]	8	Infliximab 5/kg	41/121	33.9	NA	NA
			Placebo	7/123	5.7	NA	NA
	Jiang 2015[17]	8	Infliximab 5/kg	22/41	53.7	NA	NA
			Placebo	9/41	21.9	NA	NA
	Kobayashi 2016[18]	8	Infliximab 5/kg	21/104	20.2	NA	NA
			Placebo	11/104	10.6	NA	NA
Vedolizumab	GEMINI 1 [19]	6	Vedolizumab 300 mg	30/130	23.1	8/95	8.4
			Placebo	5/76	6.6	3/73	4.1
	VISIBLE 1 [20]	6	Vedolizumab 300 mg	NA	NA	NA	NA
			Vedolizumab 108 mg	NA	NA	NA	NA
			Placebo	NA	NA	NA	NA
	Motoya 2019 [21]	10	Vedolizumab 300 mg	22/79	27.8	8/85	9.4

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Drug	Study	Follow-up time, weeks	Intervention	Bio-naive		Bio-experienced	
				n/N	%	n/N	%
			Placebo	6/41	14.6	4/41	9.8
Ustekinumab	UNIFI [22]	8	Ustekinumab 6 mg/kg	NA	NA	23/175	13.1
			Ustekinumab 90 mg Q12W	NA	NA	NA	NA
			Placebo	NA	NA	2/168	1.2

NA = not applicable; Q12W = every 12 weeks.

Table N-8. Efficacy data for clinical response after induction therapy (weeks 6-12)

Drug	Study	Follow-up time, weeks	Intervention	Bio-naive		Bio-experienced	
				n/N	%	n/N	%
Ozanimod	TRUE NORTH [10]	10	Ozanimod 1 mg	157/299	52.5	48/130	36.9
			Placebo	44/151	29.1	12/65	18.5
	TOUCHSTONE [11]	8	Ozanimod 1 mg	NA	NA	NA	NA
			Placebo	NA	NA	NA	NA
Adalimumab	ULTRA 2 [12]	8	Adalimumab 160/80/40 mg	NA	NA	36/98	36.7
			Placebo	NA	NA	29/101	28.7
Golimumab	PURSUIT-SC [13]	6	Golimumab 200/100 mg	129/253	51.0	NA	NA
			Placebo	76/251	30.3	NA	NA
	PURSUIT-M [14]	6	Golimumab 50 mg	NA	NA	NA	NA
			Golimumab 100 mg	NA	NA	NA	NA
			Placebo	NA	NA	NA	NA
	PURSUIT-J [15]	6	Golimumab 100 mg	NA	NA	NA	NA
			Placebo	NA	NA	NA	NA
Infliximab	ACT 1 [16]	8	Infliximab 5/kg	84/121	69.4	NA	NA

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Drug	Study	Follow-up time, weeks	Intervention	Bio-naive		Bio-experienced	
				n/N	%	n/N	%
			Placebo	45/121	37.2	NA	NA
	ACT 2 [16]	8	Infliximab 5/kg	78/121	64.5	NA	NA
			Placebo	36/123	29.3	NA	NA
	Jiang 2015[17]	8	Infliximab 5/kg	32/41	78.1	NA	NA
			Placebo	15/41	36.6	NA	NA
	Kobayashi 2016[18]	8	Infliximab 5/kg	57/104	54.8	NA	NA
			Placebo	37/104	35.6	NA	NA
Vedolizumab	GEMINI 1 [19]	6	Vedolizumab 300 mg	69/130	53.1	37/95	38.9
			Placebo	20/76	26.3	18/73	24.7
	VISIBLE 1 [20]	6	Vedolizumab 300 mg	NA	NA	NA	NA
			Vedolizumab 108 mg	NA	NA	NA	NA
			Placebo	NA	NA	NA	NA
	Motoya 2019 [21]	10	Vedolizumab 300 mg	42/79	53.2	23/85	27.1
			Placebo	15/41	36.6	12/41	29.3
Ustekinumab	UNIFI [22]	8	Ustekinumab 6 mg/kg	NA	NA	98/147	66.7
			Ustekinumab 90 mg Q12W	NA	NA	NA	NA
			Placebo	NA	NA	54/151	35.8

NA = not applicable; Q12W = every 12 weeks.

Table N-9. Efficacy data for endoscopic improvement after induction therapy (weeks 6-12)

Drug	Study	Follow-up time, weeks	Intervention	Bio-naive		Bio-experienced	
				n/N	%	n/N	%
Ozanimod	TRUE NORTH [10]	10	Ozanimod 1 mg	97/299	32.4	20/130	15.4
			Placebo	19/151	12.6	7/65	10.8
	TOUCHSTONE [11]	8	Ozanimod 1 mg			NA	NA
			Placebo			NA	NA
Adalimumab	ULTRA 2 [12]	8	Adalimumab 160/80/40 mg	NA	NA	28/98	28.6

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Drug	Study	Follow-up time, weeks	Intervention	Bio-naive		Bio-experienced	
				n/N	%	n/N	%
			Placebo	NA	NA	27/101	26.7
Golimumab	PURSUIT-SC [13]	6	Golimumab 200/100 mg	107/253	42.3	NA	NA
			Placebo	72/251	28.7	NA	NA
	PURSUIT-M [14]	6	Golimumab 50 mg	NA	NA	NA	NA
			Golimumab 100 mg	NA	NA	NA	NA
			Placebo	NA	NA	NA	NA
	PURSUIT-J [15]	6	Golimumab 100 mg	NA	NA	NA	NA
			Placebo	NA	NA	NA	NA
Infliximab	ACT 1 [16]	8	Infliximab 5/kg	75/121	62.0	NA	NA
			Placebo	41/121	33.9	NA	NA
	ACT 2 [16]	8	Infliximab 5/kg	73/121	60.3	NA	NA
			Placebo	38/123	30.9	NA	NA
	Jiang 2015[17]	8	Infliximab 5/kg	24/41	58.5	NA	NA
			Placebo	10/41	24.4	NA	NA
	Kobayashi 2016[18]	8	Infliximab 5/kg	48/104	46.2	NA	NA
			Placebo	29/104	27.9	NA	NA
Vedolizumab	GEMINI 1 [19]	6	Vedolizumab 300 mg	64/130	49.2	28/95	29.5
			Placebo	19/76	25.0	18/73	24.7
	VISIBLE 1 [20]	6	Vedolizumab 300 mg	NA	NA	NA	NA
			Vedolizumab 108 mg	NA	NA	NA	NA
			Placebo	NA	NA	NA	NA
	Motoya 2019 [21]	10	Vedolizumab 300 mg	38/79	48.1	22/85	25.9
			Placebo	13/41	31.7	12/41	29.3
Ustekinumab	UNIFI [22]	8	Ustekinumab 6 mg/kg	NA	NA	38/175	21.7
			Ustekinumab 90 mg Q12W	NA	NA	NA	NA
			Placebo	NA	NA	12/168	7.1

NA = not applicable; Q12W = every 12 weeks.

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Appendix N.7.1.2 Maintenance

Table N-10. Efficacy data for clinical remission after maintenance therapy (weeks 44-60)

Drug	Study	Follow-up time, weeks	Intervention	Bio-naive		Bio-experienced	
				n/N	%	n/N	%
Ozanimod	TRUE NORTH [10]	52	Ozanimod 1 mg	63/154	40.9	22/76	28.9
			Placebo	35/158	22.2	7/69	10.1
	TOUCHSTONE [11]	32	Ozanimod 1 mg	NA	NA	NA	NA
			Placebo	NA	NA	NA	NA
Adalimumab	ULTRA 2 [12]	44	Adalimumab 160/80/40 mg	NA	NA	10/98	10.2
			Placebo	NA	NA	3/101	3.0
Golimumab	PURSUIT-SC [13]	60	Golimumab 200/100 mg	NA	NA	NA	NA
			Placebo	NA	NA	NA	NA
	PURSUIT-M [14]	60	Golimumab 50 mg	50/151	33.1	NA	NA
			Golimumab 100 mg	51/151	33.8	NA	NA
			Placebo	34/154	22.1	NA	NA
	PURSUIT-J [15]	60	Golimumab 100 mg	16/32	50.0	NA	NA
			Placebo	2/31	6.5	NA	NA
Infliximab	ACT 1 [16]	54	Infliximab 5/kg	42/121	34.7	NA	NA
			Placebo	20/121	16.5	NA	NA
	ACT 2 [16]	30	Infliximab 5/kg	NA	NA	NA	NA
			Placebo	NA	NA	NA	NA
	Jiang 2015[17]	30	Infliximab 5/kg	NA	NA	NA	NA
			Placebo	NA	NA	NA	NA
	Kobayashi 2016[18]	38	Infliximab 5/kg	NA	NA	NA	NA
			Placebo	NA	NA	NA	NA
Vedolizumab	GEMINI 1 [19]	52	Vedolizumab 300 mg	33/72	45.8	18/50	36.0
			Placebo	15/79	19.0	5/47	10.6
	VISIBLE 1 [20]	52	Vedolizumab 300 mg	17/32	53.1	6/22	27.3
			Vedolizumab 108 mg	36/67	53.7	13/39	33.3
			Placebo	7/37	18.9	1/19	5.3
	Motoya 2019 [21]	60	Vedolizumab 300 mg	13/24	54.2	10/17	58.8
			Placebo	10/28	35.7	3/14	21.4
Ustekinumab	UNIFI [22]	52	Ustekinumab 6 mg/kg	NA	NA	NA	NA
			Ustekinumab 90 Q12W	NA	NA	21/77	27.3
			Placebo	NA	NA	15/91	16.5

NA = not applicable; Q12W = every 12 weeks.

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Table N-11. Efficacy data for clinical response after maintenance therapy (weeks 44-60)

Drug	Study	Follow-up time, weeks	Intervention	Bio-naive		Bio-experienced	
				n/N	%	n/N	%
Ozanimod	TRUE NORTH [10]	52	Ozanimod 1 mg	96/154	62.3	42/76	55.3
			Placebo	76/158	48.1	17/69	24.6
	TOUCHSTONE [11]	32	Ozanimod 1 mg	NA	NA	NA	NA
			Placebo	NA	NA	NA	NA
Adalimumab	ULTRA 2 [12]	44	Adalimumab 160/80/40 mg	NA	NA	20/98	20.4
			Placebo	NA	NA	10/101	9.9
Golimumab	PURSUIT-SC [13]	60	Golimumab 200/100 mg	NA	NA	NA	NA
			Placebo	NA	NA	NA	NA
	PURSUIT-M [14]	60	Golimumab 50 mg	71/151	47.0	NA	NA
			Golimumab 100 mg	75/151	49.7	NA	NA
			Placebo	48/154	31.2	NA	NA
	PURSUIT-J [15]	60	Golimumab 100 mg	18/32	56.3	NA	NA
			Placebo	6/31	19.40	NA	NA
Infliximab	ACT 1 [16]	54	Infliximab 5/kg	55/121	45.5	NA	NA
			Placebo	24/121	19.8	NA	NA
	ACT 2 [16]	30	Infliximab 5/kg	NA	NA	NA	NA
			Placebo	NA	NA	NA	NA
	Jiang 2015[17]	30	Infliximab 5/kg	NA	NA	NA	NA
			Placebo	NA	NA	NA	NA
	Kobayashi 2016[18]	38	Infliximab 5/kg	NA	NA	NA	NA
			Placebo	NA	NA	NA	NA
Vedolizumab	GEMINI 1 [19]	52	Vedolizumab 300 mg	47/72	65.3	22/50	44.0
			Placebo	21/79	26.6	9/47	19.1
	VISIBLE 1 [20]	52	Vedolizumab 300 mg	NA	NA	NA	NA
			Vedolizumab 108 mg	NA	NA	NA	NA
			Placebo	NA	NA	NA	NA
	Motoya 2019 [21]	60	Vedolizumab 300 mg	16/24	66.7	11/17	64.7
			Placebo	10/28	35.7	5/14	35.7
Ustekinumab	UNIFI [22]	52	Ustekinumab 6 mg/kg	NA	NA	NA	NA
			Ustekinumab 90 mg Q12W	NA	NA	44/77	57.1
			Placebo	NA	NA	34/91	37.4

NA = not applicable

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Table N-12. Efficacy data for endoscopic improvement after maintenance therapy (weeks 44-60)

Drug	Study	Follow-up time, weeks	Intervention	Bio-naïve		Bio-experienced	
				n/N	%	n/N	%
Ozanimod	TRUE NORTH [10]	52	Ozanimod 1 mg	77/154	50.0	28/76	36.8
			Placebo	48/158	30.4	12/69	17.4
	TOUCHSTONE [11]	32	Ozanimod 1 mg	NA	NA	NA	NA
			Placebo	NA	NA	NA	NA
Adalimumab	ULTRA 2 [12]	44	Adalimumab 160/80/40 mg	NA	NA	NA	NA
			Placebo	NA	NA	NA	NA
Golimumab	PURSUIT-SC [13]	60	Golimumab 200/100	NA	NA	NA	NA
			Placebo	NA	NA	NA	NA
	PURSUIT-M [14]	60	Golimumab 50 mg	66/151	43.7	NA	NA
			Golimumab 100 mg	70/151	46.4	NA	NA
			Placebo	44/154	28.6	NA	NA
	PURSUIT-J [15]	60	Golimumab 100 mg	20/32	63	NA	NA
			Placebo	5/31	16	NA	NA
Infliximab	ACT 1 [16]	54	Infliximab 5/kg	NA	NA	NA	NA
			Placebo	NA	NA	NA	NA
	ACT 2 [16]	30	Infliximab 5/kg	NA	NA	NA	NA
			Placebo	NA	NA	NA	NA
	Jiang 2015[17]	30	Infliximab 5/kg	NA	NA	NA	NA
			Placebo	NA	NA	NA	NA
	Kobayashi 2016[18]	38	Infliximab 5/kg	NA	NA	NA	NA
			Placebo	NA	NA	NA	NA
Vedolizumab	GEMINI 1 [19]	52	Vedolizumab 300 mg	43/72	59.7	20/50	40.0
			Placebo	19/79	24.1	6/47	12.8
	VISIBLE 1 [20]	52	Vedolizumab 300 mg	NA	NA	NA	NA
			Vedolizumab 108 mg	NA	NA	NA	NA
			Placebo	NA	NA	NA	NA
	Motoya 2019 [21]	60	Vedolizumab 300 mg	15/24	62.5	11/17	64.7
			Placebo	10/28	35.7	4/14	28.6
Ustekinumab	UNIFI [22]	52	Ustekinumab 6 mg/kg	NA	NA	NA	NA
			Ustekinumab 90 mg Q12W	NA	NA	23/77	29.9
			Placebo	NA	NA	20/91	22.0

NA = not applicable; Q12W = every 12 weeks.

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Appendix N.7.2 Safety data

Table N-13. Serious adverse events data for combined treatment phases in the overall population

Drug, NCT number, study name and reference	Timepoint	Follow-up time, weeks[a]	Intervention	Mixed population	
				Proportion of patients	Proportion of patients[b], % [95% CI]
Infliximab *NCT00036439* ACT 1 Rutgeerts (2005)[16]	Mixed	54	Infliximab	26/121	21.5 [14.2, 28.8]
			Placebo	31/121	25.6 [17.8, 33.4]
Infliximab *NCT00096655* ACT 2 Rutgeerts (2005)[16]	Mixed	30	Infliximab	13/121	10.7 [5.2, 16.3]
			Placebo	24/123	19.5 [12.5, 26.5]
Infliximab *NA* NA Jiang (2015)[17]	Mixed	30	Infliximab	4/41	7.3 [0.0, 15.3]
			Placebo	3/41	9.8 [0.7, 18.8]
Infliximab *NA* NA Kobayashi (2016)[18]	Mixed	38	Infliximab	18/104	17.3 [10.0, 24.6]
			Placebo	19/104	18.3 [10.8, 25.7]
Vedolizumab *NCT00790933* GEMINI 1 Feagan (2013)[19]	Induction	6	Vedolizumab	25/746	3.4 [2.1, 4.6]
			Placebo	10/149	6.7 [2.7-10.7]
	Maintenance	52	Vedolizumab	10/122	8.2 [3.3-13.1]
			Placebo	20/126	15.9 [9.5-22.3]
Vedolizumab *NCT02039505* NA Motoya 2019[21]	Induction	10	Vedolizumab	10/164	6.1 [2.4-9.8]
			Placebo	4/82	4.9 [0.2-9.5]
	Maintenance	60	Vedolizumab	4/41	9.8 [0.7-18.8]
			Placebo	3/42	7.1 [0.0-14.9]
Vedolizumab *NCT02611830* VISIBLE 1 Sandborn (2020)[20]	Maintenance	68	Vedolizumab (IV)	7/54	13.0 [4.0-21.9]
			Vedolizumab (SC)	10/106	9.4 [3.9-15.0]
			Placebo	6/56	10.7 [2.6-18.8]
Golimumab *NCT01863771* PURSUIT-J Hibi (2017)[15]	Maintenance	60	Golimumab	1/32	3.1 [0.0-9.2]
			Placebo	4/31	12.9 [1.1-24.7]
Golimumab *NCT00488631* PURSUIT-M Sandborn (2014)[14]	Maintenance	60	Golimumab	35/308	11.4 [7.8-14.9]
			Placebo	12/156	7.7 [3.5-11.9]
Golimumab	Induction	6	Golimumab	9/331	2.7, [1.0-4.5]

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Drug, NCT number, study name and reference	Timepoint	Follow-up time, weeks[a]	Intervention	Mixed population	
				Proportion of patients	Proportion of patients[b], % [95% CI]
NCT00487539 PURSUIT-SC Sandborn (2014)[13]			Placebo	20/330	6.1 [3.5-8.6]
Ustekinumab *NCT02407236* UNIFI Sands (2019)[22]	Induction	8	Ustekinumab	11/320	3.4 [1.4-9.7]
			Placebo	22/319	6.9 [4.1-9.7]
	Maintenance	52	Ustekinumab	13/172	7.6 [3.6-11.5]
			Placebo	17/175	9.7 [5.3-14.1]
Ozanimod *NCT01647516* TOUCHSTONE Sandborn (2016)[11]	Mixed	32	Ozanimod	3/67	4.5 [0.0-9.4]
			Placebo	6/65	9.2 [2.2-16.3]
Ozanimod *NCT02435992* True North NA (2020)[10]	Induction	10	Ozanimod	17/429	4.0 [2.1-5.8]
			Placebo	7/216	3.2 [0.9-5.6]
	Maintenance	52	Ozanimod	12/230	5.2 [2.3-8.1]
			Placebo	18/227	7.9 [4.4-11.4]
Adalimumab *NCT00408629* ULTRA 2 Sandborn (2012)[12]	Mixed	52	Adalimumab	15/247	12.1 [8.1-16.0]
			Placebo	21/246	12.3 [8.3-16.3]

CI = confidence interval.

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