Medicinrådet

Bilag til direkte indplacering af risankizumab i Medicinrådets evidensgennemgang vedrørende biologiske og målrettede syntetiske lægemidler til colitis ulcerosa

Vers. 1.0

Bilagsoversigt

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

July 31, 2025

Response to the Danish Medicines Council's assessment of Skyrizi for ulcerative colitis

AbbVie thanks for the asessemnt and the opportunity to review and comment on the evaluation of Skyrizi for treatment of ulcerative colitis. We agree with the overall conclusions of the assessment but want to add further context on the comparability of studies.

In the Skyrizi trials, responders from the induction study INSPIRE proceeded to the maintenance study COMMAND where they were re-randomized to risankizumab or placebo (PBO). Hence, COMMAND is termed a PBO withdrawal study meaning that all patients on PBO in maintenance are previous responders to active treatment with risankizumab in induction. The long half-life and retention of risankizumab in the tissues [1] results in all patients in the maintenance placebo arms experiencing prolonged benefits from the induction treatment resulting in artificially elevated placebo responses in the maintenance phase. As a result of this, the Skyrizi response in maintenance outcomes are reduced in an indirect comparison (ITC) that does not account for this.

Performing an ITC is always subject to uncertainty but, as acknowledged in the Danish Medicines Council assessment of Skyrizi for Crohn's disease [2] where the same effect is seen, accounting for the long half-life of risankizumab and the resulting drug retention is key for interpreting risankizumab clinical trial data correct.

[1] Pang Y, Khatri A, Suleiman AA, et al. Clinical Pharmacokinetics and Pharmacodynamics of Risankizumab in Psoriasis Patients. *Clin Pharmacokinet* 2020; 59: 311–326.

[2] Tillæg til Medicinrådets behandlingsvejledning vedrørende biologiske og målrettede syntetiske lægemidler til behandling af Crohns sygdom - Direkte indplacering af risankizumab til patienter med Crohns sygdom, https://filer.medicinraadet.dk/media/tuwjxug5/till%C3%A6g-til-medicinr%C3%A5dets-beh-vejl-vedr-biologiske-og-m%C3%A5lrettede-syntetiske-l%C3%A6gemidler-til-crohns-sygdom-version-1-0.pdf (2023).

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08.08.2025
DBS/LSC

Forhandlingsnotat

Dato for behandling i Medicinrådet	03.09.2025
Leverandør	AbbVie
Lægemiddel	Skyrizi (risankizumab)
Ansøgt indikation	Behandling af voksne patienter med moderat til svær aktiv colitis ulcerosa, der har udvist utilstrækkeligt respons, mistet respons eller var intolerante over for konventionel eller biologisk behandling
Indikationsudvidelse	Indikationsudvidelse – direkte indplacering i behandlingsvejledning.

Prisinformation

Amgros har forhandlet følgende pris på Skyrizi (risankizumab):

Tabel 1: Forhandlingsresultat

Lægemiddel	Styrke	Pakningsstørrelse	AIP (DKK)	SAIP (DKK)	Rabatprocent ift. AIP
Skyrizi	180 mg	1 stk. pen/sprøjte	18.211,10	[redacted]	[redacted]

Amgros har følgende aftalepriser på Skyrizi (risankizumab):

Tabel 2: Aftalepriser

Lægemiddel	Styrke	Pakningsstørrelse	AIP (DKK)	SAIP (DKK)	Rabatprocent ift. AIP
Skyrizi	600 mg	10 ml	17.913,19	[redacted]	[redacted]
Skyrizi	360 mg	1 stk. pen/sprøjte	17.913,19	[redacted]	[redacted]

Aftaleforhold

[redacted]

Konkurrencesituationen

[redacted]

Tabel 2 viser lægemiddeludgifter på udvalgte sammenlignelige lægemidler. Lægemiddeludgiften pr. patient er beregnet på 78 uger (18 måneders behandling) jf. det kliniske sammenligningsgrundlag i Medicinrådets opsummering af evidensgennemgang vedrørende biologiske og målrettede syntetiske lægemidler til colitis ulcerosa.

Tabel 3: Sammenligning af lægemiddeludgifter pr. patient

Lægemiddel	Styrke (pakningsstørrelse)	Dosering	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. behandling på 78 uger (SAIP, DKK)*
Amgevita (biosimilær, adalimumab)	40 mg, 2 stk. pen/sprøjte	**Induktion (s.c.):** 160 mg uge 0, 80 mg uge 2. **Vedligeholdelse (s.c.):**	[redacted]	[redacted]

		40 mg (SC) hver 2. uge.		
Simponi (golimumab)	100 mg, 1 stk. pen 50 mg, 1 stk. pen	**Induktion (s.c.):** 200 mg uge 0, 100 mg uge 2. **Vedligeholdelse (s.c.):** 50 mg (< 80 kg) hver 4. uge.	[redacted]	[redacted]
Zessly (infliximab)	100 mg, 3 stk. hætteglas	**Induktion (i.v.):** 5 mg/kg mg uge 0, 4 og 6. **Vedligeholdelse (i.v.):** 5 mg/kg mg hver 8. uge	[redacted]	[redacted]
Omvoh (mirikizumab)	300 mg, 1 stk. hætteglas 100 mg, 2 stk. pen	**Induktion (i.v.):** 300 mg uge 0, 4 og 8. **Vedligeholdelse (s.c.):** 200 mg hver 4. uge.	[redacted]	[redacted]
Skyrizi (risankizumab)	600 mg, 1 stk. hætteglas 180 mg, 1 stk. Pen	**Induktion (i.v.):** 1200 mg uge 0, 4 og 8. **Vedligeholdelse (s.c.):** 180 mg hver 8. uge fra uge 12.	[redacted]	[redacted]
Skyrizi (risankizumab)	600 mg, 1 stk. hætteglas 360 mg, 1 stk. pen	**Induktion (i.v.):** 1200 mg uge 0, 4 og 8. **Vedligeholdelse (s.c.):** 360 mg hver 8. uge fra uge 12.	[redacted]	[redacted]
Entyvio (vedolizumab)	300 mg, 1 stk. hætteglas 108 mg, 1 stk. pen/sprøjte	**Induktion (i.v.):** 300 mg uge 0 og 2 **Vedligeholdelse (s.c.):** 108 mg uge 6, og herefter 108 mg hver 2. uge.	[redacted]	[redacted]
Entyvio (vedolizumab)	300 mg, 1 stk. hætteglas	**Induktion (i.v.):** 300 mg uge 0, 2 og 6. **Vedligeholdelse (i.v.):**	[redacted]	[redacted]

		300 mg hver 8. uge.		
Stelara (ustekinumab)	130 mg, 1 stk. hætteglas 90 mg, 1 stk. sprøjte	**Induktion (i.v.):** 390 mg (55-85 kg) uge 0. **Vedligeholdelse (s.c.):** 90 mg i uge 8 og herefter hver 12. uge.	[redacted]	[redacted]

*jf. det kliniske sammenligningsgrundlag i Medicinrådets opsummering af evidensgennemgang vedrørende biologiske og målrettede syntetiske lægemidler til colitis ulcerosa
Note: Gennemsnitsvægt for en patient er estimeret til 75 kg

Status fra andre lande

Tabel 4: Status fra andre lande

Land	Status	Link
Norge	Ikke anbefalet	Link til anbefaling
England	Anbefalet	Link til anbefaling

Opsummering

[redacted]

Application for the assessment of Skyrizi by updating the guidelines for inflammatory bowel disease – ulcerative colitis

Contact information

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Abbreviations

AMS	adapted Mayo score
AT	advanced therapy
ATC	anatomical therapeutic chemical
BMSL	biologiske og målrettede syntetiske lægemidler
CI	confidence interval
DMC	Danish Medicines Council
EC	European Commission
EMA	European Medicines Agency
ESS	endoscopy subscore
FACIT-F	Functional Assessment of Chronic Illness Therapy-Fatigue
FCP	fecal calprotectin
FMS	full Mayo Score
HEMI	histological endoscopic improvement
HEMR	histological endoscopic remission
hs-CRP	high-sensitivity C-reactive protein
IBDQ	inflammatory bowel disease questionnaire
IL	interleukin
IMM	immunomodulator
IR	inadequate response
ITC	indirect treatment comparison
ITT	intention to treat
IV	intravenous
NA	not applicable
NCT	national clinical trial
NMA	network meta-analysis
NP	not presented
OBI	on-body injector
PBO	placebo
PK	pharmaco-kinetic
RBS	rectal bleeding subscore
RZB	risankizumab
SAE	serious adverse event
SC	subcutaneous
SD	standard deviation
SF-36	short form 36
SFS	stool frequency subscore
TNF	tumour necrosis factor
TNFi	TNF inhibitor
UC	ulcerative colitis

1. Regulatory information on the pharmaceutical

Overview of the pharmaceutical	
Proprietary name	Skyrizi
Generic name	Risankizumab
Therapeutic indication as defined by EMA	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 biological therapy.
Marketing authorization holder in Denmark	AbbVie Deutschland GmbH & Co. KG
ATC code	L04AC18
Combination therapy and/or co-medication	No
(Expected) Date of EC approval	July 25, 2024
Has the pharmaceutical received a conditional marketing authorization?	No
Accelerated assessment in the European Medicines Agency (EMA)	No
Orphan drug designation (include date)	No
Other therapeutic indications approved by EMA	Plaque psoriasis, psoriatic arthritis, Crohn's disease
Other indications that have been evaluated by the DMC (yes/no)	Yes, plaque psoriasis, psoriatic arthritis, Crohn's disease
Dispensing group	BEGR
Packaging – types, sizes/number of units and concentrations	Concentrate for infusion: vial of 600 mg risankizumab Solution for injection: Cartridges contains 180 mg or 360 mg risankizumab and 1 on-body injector [OBI]

2. Summary table

Summary	
Therapeutic indication relevant for the assessment	Treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to, lost response to, or were intolerant to conventional therapy or a biologic therapy.
Dosage regiment and administration:	The recommended induction dose is 1200 mg administered by intravenous (IV) infusion at Week 0, Week 4, and Week 8. Starting at Week 12 and every 8 weeks thereafter, the recommended maintenance dose is based on individual patient presentation: • A dose of 180 mg administered by subcutaneous injection is recommended for patients with adequate improvement in disease activity after induction • A dose of 360 mg administered by subcutaneous injection is recommended for patients with inadequate improvement in disease activity after induction Maintenance dosing to be administered using an on-body injector (OBI).
Choice of comparator [if any]	No specified comparator.
Most important efficacy endpoints (Difference/gain compared to comparator)	Clinical remission in induction • Risankizumab 1200 mg IV: 20.3% [17.2; 23.4] • Placebo: 6.2% [3.6; 8.9] • Difference (adjusted): 14.0% [10.0; 18.0] Steroid free remission in maintenance • Risankizumab 180 mg: 39.6% [32.4; 46.8] • Risankizumab 360 mg: 37.1% [30.2; 44.0] • Withdrawal placebo: 25.1% [18.9; 31.4] • Difference 180 mg to withdrawal (adjusted): 15.8% [6.9; 24.8] • Difference 360 mg to withdrawal (adjusted): 13.7% [4.8; 22.7] Mucosal healing in maintenance • Risankizumab 180 mg: 50.7% [43.4; 58.1] • Risankizumab 360 mg: 48.2% [41.0; 55.4] • Withdrawal placebo: 31.7% [25.0; 38.4]

Summary	
	• Difference 180 mg to withdrawal (adjusted): 20.1% [10,6; 29.6] • Difference 360 mg to withdrawal (adjusted): 17.4% [7.9; 26.9]
Most important serious adverse events for the intervention and comparator	During induction, 10.2% of patients on placebo experienced a SAE with gastrointestinal disorders being the most common (5.9%), followed by infections and infestations (1.4%), and neoplasms (0.9%). Corresponding numbers for risankizumab 1200 mg were SAE 2.3% with infections and infestations being the most common (0.6%), followed by gastrointestinal disorders (0.5%), and injury, poisoning and procedural complications (0.5%). During maintenance, 8.2% of patients on placebo experienced a SAE with gastrointestinal disorders being the most common (3.1%), followed by infections and infestations (2.0%), and renal and urinary disorders (1.0%). Corresponding numbers for risankizumab 180 mg were SAE 5.2% with gastrointestinal disorders, hepatobiliary disorders, infections and infestations, and injury, poisoning and procedural complications being equally common (1.0%). Corresponding numbers for risankizumab 360 mg were SAE 5.1% with gastrointestinal disorders being the most common (2.1%), followed by neoplasm (1.0%), and injury, poisoning and procedural complications (1.0%).

3. The patient population, intervention and relevant outcomes

3.1 The medical condition, patient population, current treatment options and choice of comparator(s)

The medical condition

UC is a chronic, systemic, immune-mediated inflammatory bowel disease of the large intestine that causes continuous mucosal inflammation extending, to a variable extent, from the rectum to the more proximal colon. The hallmark symptoms of UC are frequent diarrhoea, rectal bleeding, abdominal pain, urgency, tenesmus, and faecal incontinence. Nocturnal defecation and fatigue are also frequently reported. In addition to these

symptoms, UC is associated with serious comorbidities that may require specialized care and coordination. This can include extra-intestinal manifestations, secondary immune-mediated inflammatory diseases, thrombosis, and long-term consequences including colorectal cancer. The clinical and economic burden of UC is substantial, with high rates of morbidity, health care costs, and loss of productivity.

In Denmark, UC prevalence is estimated to about 32,000 patients [1]. The Danish Medicines Council expert group estimate that about 2,100 UC patients per year are treated with advanced treatment (AT) [Danish BMSL [biologiske og målrettede syntetiske lægemidler] options. Furthermore, it is estimated that about 500 patients will start their first AT for UC per year while at least 300 AT experienced patients will restart or switch treatment every year.

Patient population

The relevant patient population for this evaluation is in line with risankizumab indication for UC: adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to, lost response to, or were intolerant to conventional therapy or a biologic therapy.

Current treatment guidelines

The Danish Medicine Council (DMC) have published treatment guidelines regarding the use of biological and targeted synthetic drugs for UC taking clinical efficacy and safety into account [2–4].

Separate guidelines are provided for patients with and without experience of advanced treatment (AT, BMSL [biologiske og målrettede syntetiske lægemidler]).

The general approach for treatment of UC includes an initial high dose induction treatment, aiming to achieve disease control and reach clinical response or clinical remission. This is followed by long term maintenance treatment, using lower doses, to maintain remission, reduce steroid use, and achieve mucosal healing. Some patients may require dose escalations in maintenance. In case of active disease, insufficient treatment effect, or relapsing disease despite immunomodulation, treatment with biologics or small molecule agents (BMSL [biologiske og målrettede syntetiske lægemidler]) can be required [4].

Recently, also filgotinib, upadacitinib, ozanimod, mirikizumab and etrasimod has been placed into the guidelines. The clinical recommendations are based on four key outcomes:

- Clinical remission after induction (week 6-8)
- Systemic steroid free remission during maintenance (week 52)
- Adverse events
- Mucosal healing after maintenance (week 52)

In a recent summary of the available evidence for treatment of UC, also change from baseline in IBDQ (Inflammatory Bowel Disease Questionnaire) was included [2].

For BMSL-naïve patients with moderate to severe active UC, golimumab, infliximab and vedolizumab (IV and SC) constitute the best treatment options, can be considered clinically equivalent and thus possible first choice. Adalimumab, golimumab, infliximab, ustekinumab and vedolizumab (IV and SC) are the best treatment options for bio-experienced patients with moderate to severe active ulcerative colitis, can be considered clinically equivalent and thus possible first choices.

Information relevant for the assessment not covered in the guidelines

In the risankizumab clinical trial program for UC, responders from the induction study INSPIRE proceeded to the maintenance study COMMAND where they were re-randomized to risankizumab (two different doses) or placebo (PBO). Hence, COMMAND is termed a PBO withdrawal study meaning that all patients on PBO in maintenance are previous responders to active treatment with risankizumab in induction. This design is analogous to the risankizumab trials in Crohn's disease.

This withdrawal is a key aspect of the study design and combined with the long half-life and retention of IL-23 inhibitors in the tissues [5] all patients in the maintenance placebo arms experience prolonged benefits from the induction treatment. As an effect of this, placebo responses in the maintenance phase of the risankizumab trial will be artificially elevated due to remaining effects of active treatment given in induction.

Performing an indirect treatment comparison (ITC) is always subject to uncertainty but, as acknowledged in the Danish Medicines Council assessment of Skyrizi for Crohn's disease [6], the long half-life of risankizumab and the resulting drug retention is key for interpreting risankizumab clinical trial data correct. This, combined with the withdrawal placebo design of the maintenance study COMMAND, leads to placebo responses in the maintenance phase of the risankizumab trial being artificially elevated due to remaining effects of active treatment given in induction. This aspect must be addressed in any ITC or network meta-analysis (NMA) aimed at evaluating comparative efficacy for risankizumab also in UC, so that retention will not introduce additional bias in the results when comparing to treatments with shorter retention. As an alternative option, this application includes also data from a patient population that responded to placebo in induction and were then continued on placebo in maintenance. Hence, this patient population will not show artificially elevated placebo responses and this analysis is thus termed *true placebo* to differentiate from *withdrawal placebo*.

3.2 The intervention

Overview of intervention	
Therapeutic indication relevant for the assessment	Treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to, lost response to, or were intolerant to conventional therapy or a biologic therapy.
Method of administration	Induction: intravenous administration Maintenance: subcutaneous administration using OBI
Dosing	The recommended induction dose is 1200 mg administered by intravenous (IV) infusion at Week 0, Week 4, and Week 8. Starting at Week 12 and every 8 weeks thereafter, the recommended maintenance dose is based on individual patient presentation: • A dose of 180 mg administered by subcutaneous injection is recommended for patients with adequate improvement in disease activity after induction • A dose of 360 mg administered by subcutaneous injection is recommended for patients with inadequate improvement in disease activity after induction Maintenance dosing to be administered using an on-body injector (OBI).
Should the pharmaceutical be administered with other medicines?	No
Treatment duration / criteria for end of treatment	No
Necessary monitoring, both during administration and during the treatment period	According to standard care for UC in Denmark.
Need for diagnostics or other tests (e.g. companion diagnostics). How are these included in the model?	N/A
Package size(s)	Concentrate for infusion: vial of 600 mg risankizumab Solution for injection: Cartridges contains 180 mg or 360 mg risankizumab and 1 on-body injector [OBI]

3.2.1 The intervention in relation to Danish clinical practice

Skyrizi is expected to be used as a treatment option for patients with moderate to severe active UC where conventional treatment or AT has been insufficient or is unsuitable. There are no new tests or methods required.

4. Overview of literature

The treatment guideline includes a network meta-analysis (NMA) so no systematic literature search was performed.

The relevant studies for risankizumab in UC are presented in Table 1 below with more detail in Appendix A.

Table 1 Relevant literature included in the assessment of efficacy and safety

Trial name, NCT identifier and reference (Full citation incl. reference number)*	Study design	Study duration	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Patient population (specify if a subpopulation in the relevant study)	Intervention	Comparator	Relevant for PICO nr. in treatment guideline	Outcomes and follow-up period
INSPIRE, NCT03398148, [7]	Phase 2 and Phase 3 multicentre, randomized, double-blind, placebo controlled study	12 weeks	Start: 07/03/18 Completion: 11/05/23	Diagnosis of UC for ≥3 months (confirmed by biopsy or investigator assessment) with demonstrated intolerance or inadequate response to aminosalicylates, oral locally acting steroids, systemic steroids (prednisone or equivalent), immunomodulators, and/or biologic therapies or tofacitinib. Moderately to severely active UC with an Adapted Mayo score of 5 to 9 points and endoscopic subscore of 2 to 3. Subgroup analysis of patients with or without previous experience of treatment with advance therapies (AT) where AT is defined as infliximab, adalimumab, golimumab, ustekinumab, vedolizumab, tofacitinib, filgotinib, upadacitinib, or ozanimod.	Risankizumab 1200 mg	Placebo	1 and 2	Clinical remission 12 weeks IBDQ remission 12 weeks IBDQ change from baseline 12 weeks

Trial name, NCT identifier and reference (Full citation incl. reference number)*	Study design	Study duration	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Patient population (specify if a subpopulation in the relevant study)	Intervention	Comparator	Relevant for PICO nr. in treatment guideline	Outcomes and follow-up period
COMMAND, NCT03398135, [7]	Phase 3 multicentre, randomized, double-blind, placebo-controlled maintenance and open-label extension study	52 weeks	Start: 28/08/18 Completion (estimated): 25/09/28	Patients enrolled in INSPIRE who responded to induction treatment with risankizumab defined as decrease from baseline of induction study of Adapted Mayo score ≥ 2 points and ≥ 30%, PLUS a decrease in rectal bleeding sub-score (RBS) ≥ 1 or an absolute RBS ≤ 1. Subgroup analysis of patients with or without previous experience (at induction start) of treatment with advance therapies (AT) where AT is defined as infliximab, adalimumab, golimumab, ustekinumab, vedolizumab, tofacitinib, filgotinib, upadacitinib, or ozanimod.	Risankizumab 180 mg Risankizumab 360 mg	Placebo	1 and 2	Steroid free clinical remission 52 weeks Serious adverse events 52 weeks Endoscopic improvement[1] 52 weeks IBDQ remission 52 weeks IBDQ change from baseline 52 weeks [1]Used for mucosal healing in guideline

* If there are several publications connected to a trial, include all publications used.

5. Clinical question 1

For clinical question 1, the Danish treatment guidelines [4] have assessed whether there are clinically significant differences between the medicines for BMSL naïve patients with moderate to severe ulcerative colitis. The risankizumab trials analyse subgroups of patients with or without experience to treatment with advanced therapies (AT, defined as infliximab, adalimumab, golimumab, ustekinumab, vedolizumab, tofacitinib, filgotinib, upadacitinib, or ozanimod). Results from AT naïve patients are considered relevant for analysis of BMSL naïve patients.

5.1 Efficacy of risankizumab compared to placebo for BMSL naïve patients

5.1.1 Relevant studies

Relevant studies are INSPIRE and COMMAND. Results from AT naïve patients are considered relevant for analysis of BMSL naïve patients.

5.1.2 Comparability of studies

The Medicines Council have previously performed an NMA for treatment of BMSL naïve patients with UC. The study designs of the Skyrizi UC trials are largely in line with recent comparator studies used in the previous NMA.

As discussed above, the maintenance study COMMAND is termed a PBO withdrawal study meaning that all patients on PBO in maintenance are previous responders to active treatment with risankizumab in induction. This withdrawal is a key aspect of the study design and combined with the long half-life and retention of IL-23 inhibitors in the tissues [5] all patients in the *maintenance placebo* arms experience prolonged benefits from the induction treatment. As an effect of this, placebo responses in the maintenance phase of the risankizumab trial will be artificially elevated due to remaining effects of active treatment given in induction, as acknowledged in the Medicines Council assessment of Skyrizi for Crohn's disease [6].

To address this, also data on file using *true placebo* is provided in this application.

5.1.3 Comparability of patients across studies and with Danish patients eligible for treatment

According to the treatment guidelines [4], patient characteristics for the included studies are comparable and also in accordance with the Danish patient population. The patient characteristics for the Skyrizi trials (Table 2 below) are comparable between the treatment arms and also in line with previous trials in UC.

Table 3 compare the active treatment arms for relevant treatment options in induction while Table 4 compares active treatment arms for relevant treatment options in maintenance. It should be noted that the Skyrizi trials have a high proportion of heavily pre-treated and treatment refractory patients.

Table 2 Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety

	INSPIRE		COMMAND		
	RZB1200	PBO	RZB180	RZB360	PBO
N	650	325	179	186	183
Male sex, n (%)	385 (59.2)	201 (61.8)	105 (58.7)	107 (57.5)	101 (55.2)
Age, mean (SD)	41.8 (13.5)	42.8 (14.3)	40.9 (14.7)	42.5 (12.9)	39.2 (14.2)
Disease duration, mean (SD), y	7.7 (6.9)	8.1 (7.0)	8.5 (7.4)	9.3 (7.1)	8.2 (7.2)
Adapted Mayo Score, mean (SD)	7.1 (1.2)	7.1 (1.3)	7.2 (1.2)	7.0 (1.3)	7.2 (1.2)
Immunosuppressants	108 (16.6)	53 (16.3)	35 (19.6)	32 (17.2)	37 (20.2)
Aminosalicylates	475 (73.1)	238 (73.2)	119 (66.5)	135 (72.6)	117 (63.9)
Corticosteroids	236 (36.3)	112 (34.5)	74 (41.3)	59 (31.7)	68 (37.2)
Inadequate response (IR) to AT	333 (51.2)	170 (52.3)	134 (74.9)	139 (74.7)	138 (75.4)
1 IR-AT	153 (23.5)	80 (24.6)	52 (29.1)	55 (29.6)	62 (33.9)
2 IR-AT	112 (17.2)	55 (16.9)	44 (24.6)	37 (19.9)	40 (21.9)
>2 IR-AT	68 (10.5)	35 (10.8)	38 (21.2)	47 (25.3)	36 (19.7)

Table 3 Baseline characteristics of patients in active treatment arms of relevant induction studies

	RZB1200	VED300	UST 6	MIRI300
N	650	746	322	868
Male sex, %	59%	58.0%	60.6%	61.1%
Age, mean	41.8	40.1	41.7	42.9
Caps on Prior IR	No cap	No cap (only 2 approved TNFs)	No cap (only 3 approved drugs)	Excluded > 3
Disease duration, Mean	7.7	6.8	8.2	7.2
Pancolitis/Extensive	51.4%	37.7%	47.5%	36.6%
FCP (mcg/g), median	1531	868	1506	1559
hs-CRP (mg/L), median	3.5	NP	4.8	4.1
Baseline steroid use	36.3%	37%	52%	40.4%
Baseline IMM use	16.6%	16.5%	27.6%	24.3%
No advanced therapies failure	48.8%	59%	48.4%	58.4%
Advanced therapy IR	51.2%	41%	51.6%	41.6%

	RZB1200	VED300	UST 6	MIRI300
TNF-IR	44.0%	41%	50.9%	37.4%
Vedo-IR	30.2%	NA	18.6%	18.3%
JAK-IR	9.3%	NA	NA	3.9%
1 therapy	23.5%	NP	NP	20.7%
2 therapies	17.2%	NP	NP	17.7%
>2 therapies	10.5%	NP	NP	3.1%
BL Mayo Score	7.1 AMS	8.6 FMS	8.9 FMS	6.5 AMS
Mod	57.9% - 5-7 AMS	NP	86% - 6-10 FMS	46.5% - 4-6 AMS
Sev	42.1% - 8-9 AMS[1]	NP	14% - 11-12 FMS	53.3% - 7-9 AMS[1]
Endoscopy Subscore = 3	68.0%	NP	NP	66.1%

AMS, adapted Mayo score; BL, baseline; FCP, fecal calprotectin; FMS, full Mayo score; hs-CRP, high-sensitivity C-reactive protein; IMM, immunomodulator; IR, inadequate response, NA, not applicable; NP, not presented.

[1] Severe disease is defined differently in risankizumab and mirikizumab studies.

Table 4 Baseline characteristics of patients in active treatment arms of relevant maintenance studies

	RZB180/360Q8W	VED300Q8W	UST90Q12W	MIRI200
N	179/186	122	176	365
Male sex, %	59%/58%	57.4%	53.4%	58.6%
Age, mean	40.9/42.5	41.0	39.5	43.4
Disease duration, mean	8.5/9.3	6.2	8.6	6.9
Pancolitis/extensive	53%/51%	43%	NP	36%
FCP (mcg/g) median	1605/1569	864	1258	1482
hs-CRP (mg/L), median	4.7/2.9	NP	3.3	3.8
Baseline steroid use	41.3%/31.7%	39%	48.3%	37.0%
No advanced therapies failure	25.1%/25.3%	65%	59.3%	64.9%
Advanced therapy IR	74.9%/74.7%	35%	40.7%	35.1%
TNF-IR	69%/69%	35%	40.7%	31%
Vedo-IR	38%/45%	NA	12.8%	13%

	RZB180/360Q8W	VED300Q8W	UST90Q12W	MIRI200
JAK-IR	12.8%/15%	NA	NA	2.2%
1 therapy	29.1%/29.6%	NP	NP	NP
2 therapies	24.6%/19.9%	NP	NP	NP
>2 therapies	21.2%/25.3%	NP	NP	NP
BL Mayo Score	7.2/7.0 AMS	8.4 FMS	8.9 FMS	6.5 AMS
Mod	57/58.6 - 5-7 AMS	NP	87.2% - 6-10 FMS	
Sev	43%/41%.4 - 8-9 AMS[1]	NP	12.8% - 11-12 FMS	50.4% AMS[1]
Endoscopy Subscore = 3	73.7%/66.1%	NP	NP	64.4%

AMS, adapted Mayo score; BL, baseline; FCP, fecal calprotectin; FMS, full Mayo score; hs-CRP, high-sensitivity C-reactive protein; IMM, immunomodulator; IR, inadequate response, NA, not applicable; NP, not presented.

[1] Severe disease is defined differently in risankizumab and mirikizumab studies.

5.2 Comparative analyses of efficacy and safety

5.2.1 Efficacy and safety – results per study

In the Skyrizi UC trials [7], the primary outcome was clinical remission (stool frequency score ≤1 and not greater than baseline, rectal bleeding score of 0, and endoscopic subscore ≤1 without friability) at week 12 for the induction trial and at week 52 for the maintenance trial.

Among the 975 patients analyzed in the induction trial (aged 42.1 [SD, 13.8] years; 586/973 [60.1%] were male; and 677 [69.6%] were white), the clinical remission rates at week 12 were 132/650 (20.3%) for 1200 mg of risankizumab and 20/325 (6.2%) for placebo (adjusted between-group difference, 14.0% [95% CI, 10.0%-18.0%], P < .001). Among the 548 patients analyzed in the maintenance trial (aged 40.9 [SD, 14.0] years; 313 [57.1%] were male; and 407 [74.3%] were white), the clinical remission rates at week 52 were 72/179 (40.2%) for 180 mg of risankizumab, 70/186 (37.6%) for 360 mg of risankizumab, and 46/183 (25.1%) for placebo (adjusted between-group difference for 180 mg of risankizumab vs placebo, 16.3% [97.5% CI, 6.1%-26.6%], P < .001; adjusted between-group difference for 360 mg of risankizumab vs placebo, 14.2% [97.5% CI, 4.0%-24.5%], P = 0.002). No new safety risks were detected in the treatment groups.

Compared with placebo, risankizumab improved clinical remission rates in an induction trial and in a maintenance trial for patients with moderately to severely active ulcerative colitis.

Relevant results for this clinical question are presented in Appendix B.

5.2.2 Please provide a qualitative description of safety data. Differences in definitions of outcomes between studies

In the previous NMA performed by the Medicines Council it was concluded that the definition of adverse events differed between the included studies. The assessment was performed using the frequency of serious adverse events (SAE) and a narrative description of the safety profile.

Relevant data for this clinical question are presented in Appendix B with a narrative description provided below.

For the overall patient population in the induction trial [7], the most frequently reported adverse events (using the Medical Dictionary for Regulatory Activities preferred terms) were COVID-19 (4.8%) and anemia (3.4%) in the risankizumab group and colitis ulcerative (10.2%) and anemia (6.5%) in the placebo group. The rate of serious adverse events was 2.3% for risankizumab compared with 10.2% for placebo. One treatment-emergent death occurred in the risankizumab group and was due to respiratory failure caused by COVID-19 pneumonia.

For the overall patient population in the maintenance trial [7], the most frequently reported adverse events among all treatment groups were colitis ulcerative (13.0% in the 180 mg of risankizumab group and 13.8% in the 360 mg of risankizumab group vs 14.8% in the placebo group) and COVID-19 (8.8% in the 180 mg group and 13.3% in the 360 mg group vs 11.7% for placebo). Colitis ulcerative refers to the worsening of the underlying disease, which was defined at the investigator's discretion. Serious adverse events were reported in 5.2% in the 180 mg group and 5.1% in the 360 mg group vs 8.2% in the placebo group.

One non–treatment-emergent death in the 360 mg of risankizumab group due to colon adenocarcinoma was reported, which existed prior to administration of the first dose of the study drug. Malignancies were reported in 2 patients undergoing treatment with risankizumab with both events determined to be unrelated to the study drug.

5.2.3 Method of synthesis

The treatment guideline includes an NMA, so this section is omitted.

5.2.4 Results from the comparative analysis

The treatment guideline includes an NMA, so this section is omitted.

6. Clinical question 2

For clinical question 2, the Danish treatment guidelines [4] have assessed whether there are clinically significant differences between the medicines for BMSL exposed patients with moderate to severe ulcerative colitis. The risankizumab trials analyse subgroups of patients with or without experience to treatment with advanced therapies (AT, defined as infliximab, adalimumab, golimumab, ustekinumab, vedolizumab, tofacitinib, filgotinib, upadacitinib, or ozanimod). Results from AT exposed patients are considered relevant for analysis of BMSL exposed patients.

6.1 Efficacy of risankizumab compared to placebo for BMSL exposed patients

6.1.1 Relevant studies

Relevant studies are INSPIRE and COMMAND. Results from AT exposed patients are considered relevant for analysis of BMSL exposed patients.

6.1.2 Comparability of studies

The Medicines Council have previously performed an NMA for treatment of BMSL naïve patients with UC. The study designs of the Skyrizi UC trials are largely in line with recent comparator studies used in the previous NMA.

As discussed above, the maintenance study COMMAND is termed a PBO withdrawal study meaning that all patients on PBO in maintenance are previous responders to active treatment with risankizumab in induction. This withdrawal is a key aspect of the study design and combined with the long half-life and retention of IL-23 inhibitors in the tissues [5] all patients in the maintenance placebo arms experience prolonged benefits from the induction treatment. As an effect of this, placebo responses in the maintenance phase of the risankizumab trial will be artificially elevated due to remaining effects of active treatment given in induction, as acknowledged in the Medicines Council assessment of Skyrizi for Crohn's disease [6].

To address this, also data using true placebo is provided in this application.

6.1.3 Comparability of patients across studies and with Danish patients eligible for treatment

According to the treatment guidelines [4], patient characteristics for the included studies are comparable and also in accordance with the Danish patient population. The patient characteristics for the Skyrizi trials (Table 2 above) are comparable between the treatment arms and also in line with previous trials in UC.

6.2 Comparative analyses of efficacy and safety

6.2.1 Efficacy and safety – results per study

In the Skyrizi UC trials [7], the primary outcome was clinical remission (stool frequency score ≤1 and not greater than baseline, rectal bleeding score of 0, and endoscopic subscore ≤1 without friability) at week 12 for the induction trial and at week 52 for the maintenance trial.

Among the 975 patients analyzed in the induction trial (aged 42.1 [SD, 13.8] years; 586/973 [60.1%] were male; and 677 [69.6%] were white), the clinical remission rates at week 12 were 132/650 (20.3%) for 1200 mg of risankizumab and 20/325 (6.2%) for placebo (adjusted between-group difference, 14.0% [95% CI, 10.0%-18.0%], P < .001). Among the 548 patients analyzed in the maintenance trial (aged 40.9 [SD, 14.0] years; 313 [57.1%] were male; and 407 [74.3%] were white), the clinical remission rates at week 52 were 72/179 (40.2%) for 180 mg of risankizumab, 70/186 (37.6%) for 360 mg of risankizumab, and 46/183 (25.1%) for placebo (adjusted between-group difference for 180 mg of risankizumab vs placebo, 16.3% [97.5% CI, 6.1%-26.6%], P < .001; adjusted between-group difference for 360 mg of risankizumab vs placebo, 14.2% [97.5% CI, 4.0%-24.5%], P = 0.002). No new safety risks were detected in the treatment groups.

Compared with placebo, risankizumab improved clinical remission rates in an induction trial and in a maintenance trial for patients with moderately to severely active ulcerative colitis.

Relevant results for this clinical question are presented in Appendix B.

6.2.2 Please provide a qualitative description of safety data. Differences in definitions of outcomes between studies

In the previous NMA performed by the Medicines Council it was concluded that the definition of adverse events differed between the included studies. The assessment was performed using the frequency of serious adverse events (SAE) and a narrative description of the safety profile.

Relevant data for this clinical question are presented in Appendix B with a narrative description provided below.

For the overall patient population in the induction trial [7], the most frequently reported adverse events (using the Medical Dictionary for Regulatory Activities preferred terms) were COVID-19 (4.8%) and anemia (3.4%) in the risankizumab group and colitis ulcerative (10.2%) and anemia (6.5%) in the placebo group. The rate of serious adverse events was 2.3% for risankizumab compared with 10.2% for placebo. One treatment-emergent death occurred in the risankizumab group and was due to respiratory failure caused by COVID-19 pneumonia.

For the overall patient population in the maintenance trial [7], the most frequently reported adverse events among all treatment groups were colitis ulcerative (13.0% in the 180 mg of risankizumab group and 13.8% in the 360 mg of risankizumab group vs 14.8% in the placebo group) and COVID-19 (8.8% in the 180 mg group and 13.3% in the 360 mg group vs 11.7% for placebo). Colitis ulcerative refers to the worsening of the underlying disease, which was defined at the investigator's discretion. Serious adverse events were reported in 5.2% in the 180 mg group and 5.1% in the 360 mg group vs 8.2% in the placebo group.

One non–treatment-emergent death in the 360 mg of risankizumab group due to colon adenocarcinoma was reported, which existed prior to administration of the first dose of the study drug. Malignancies were reported in 2 patients undergoing treatment with risankizumab with both events determined to be unrelated to the study drug.

6.2.3 Method of synthesis

The treatment guideline includes an NMA, so this section is omitted.

6.2.4 Results from the comparative analysis

The treatment guideline includes an NMA, so this section is omitted.

7. Summary

UC is a chronic, systemic, immune-mediated inflammatory bowel disease of the large intestine that causes continuous mucosal inflammation extending, to a variable extent, from the rectum to the more proximal colon. The clinical and economic burden of UC is substantial, with high rates of morbidity, health care costs, and loss of productivity.

The global risankizumab UC program evaluates over 1,500 patients with moderately to severely active UC across two pivotal studies, INSPIRE (induction) and COMMAND (maintenance and long-term extension). Clinical responders from the induction trial continued to the maintenance study where they were re-randomized to receive placebo or one of two doses of risankizumab (180 mg or 360 mg). The patients re-randomized to placebo in maintenance received risankizumab treatment in induction and this group is therefore referred to as withdrawal placebo. When administered, risankizumab has a long half-life resulting in artificially elevated response levels for the placebo withdrawal arm which needs to be taken into account when interpreting the results.

In addition, the patients included in the Skyrizi UC trials were heavily pre-treated and the most treatment refractory patients included in clinical trials for UC.

Results from the phase 3 trials for risankizumab demonstrated statistically significantly higher rates compared to placebo of clinical remission, clinical response, and endoscopic improvement. The patients with moderately to severely active UC treated with risankizumab also experienced statistically significantly reduced symptoms of disease activity, including abdominal pain, bowel urgency, and tenesmus, as well as improved HRQoL.

This application includes relevant data needed for direct placement of Skyrizi into the Danish treatment guidelines for UC.

8. References

[1] Agrawal M, Christensen HS, Bøgsted M, et al. The rising burden of inflammatory bowel disease in Denmark over two decades: a nationwide cohort study. *Gastroenterology* 2022; 163: 1547-1554.e5.

[2] Opsummering af Medicinrådets evidensgennemgang vedrørende biologiske og målrettede syntetiske lægemidler til colitis ulcerosa, https://filer.medicinraadet.dk/media/iaihxrpj/opsummering-af-medicinradets-evidensgennemgang-vedr-laegemidler-til-colitis-ulcerosa-vers-2-0.pdf (2024).

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[4] Medicinrådets behandlingsvejledning vedrørende biologiske og målrettede syntetiske lægemidler til colitis ulcerosa, https://medicinraadet.dk/media/0odjhdea/medicinr%C3%A5dets-behandlingsvejledning-vedr-l%C3%A6gemidler-til-colitis-ulcerosa-vers-1-1_adlegacy.pdf (2021).

[5] Pang Y, Khatri A, Suleiman AA, et al. Clinical Pharmacokinetics and Pharmacodynamics of Risankizumab in Psoriasis Patients. *Clin Pharmacokinet* 2020; 59: 311–326.

[6] Tillæg til Medicinrådets behandlingsvejledning vedrørende biologiske og målrettede syntetiske lægemidler til behandling af Crohns sygdom - Direkte indplacering af risankizumab til patienter med Crohns sygdom, https://filer.medicinraadet.dk/media/tuwjxug5/till%C3%A6g-til-medicinr%C3%A5dets-beh-vejl-vedr-biologiske-og-m%C3%A5lrettede-syntetiske-l%C3%A6gemidler-til-crohns-sygdom-version-1-0.pdf (2023).

[7] Louis E, Schreiber S, Panaccione R, et al. Risankizumab for Ulcerative Colitis: Two Randomized Clinical Trials. *JAMA* 2024; 332: 881–897.

Appendix A. Main characteristics of studies included

Table 5 Main characteristic of studies included

Trial name: INSPIRE	**NCT number:03398148**
Objective	To evaluate the efficacy and safety of risankizumab compared to placebo in inducing clinical remission in subjects with moderately to severely active UC.
Publications – title, author, journal, year	Risankizumab for Ulcerative Colitis: Two Randomized Clinical Trials, Louis, E. et al. JAMA, 2024
Study type and design	Phase 2 and Phase 3 Multicentre, Randomized, Double-Blind, Placebo Controlled study. 975 patients were allocated to risankizumab 1200 mg IV dose or placebo in a randomization ratio of 2:1. The sample size was reassessed after analysing the combined PK, safety, and efficacy results from the Phase 2b study. It was determined to provide adequate powers for the primary endpoint and selected ranked secondary endpoints. The study is completed.
Sample size (n)	975
Main inclusion criteria	• Male or female aged >=18 to <= 80 years at the Baseline Visit. Where locally permissible, subjects 16 to < 18 years of age who meet the definition of Tanner stage 5 for development at the Baseline Visit • Confirmed diagnosis of ulcerative colitis (UC) for at least 3 months prior to Baseline • Active UC as assessed by Adapted Mayo Score and Endoscopic Subscore • Demonstrated intolerance or inadequate response to conventional therapy and tofacitinib (not a biologic) and one or more biologic therapies • Females must be postmenopausal for more than 1 year or surgically sterile or practicing specific forms of birth control
Main exclusion criteria	• Participant with a current diagnosis of Crohn's disease (CD), inflammatory bowel disease-unclassified (IBD-U) or a history of radiation colitis or ischemic colitis. • Participant receiving prohibited medications and treatment. • Extent of inflammatory disease limited to the rectum as assessed by screening endoscopy.

Trial name: INSPIRE	NCT number:03398148
	• Participant with currently known complications of UC (e.g., megacolon). • No known active Coronavirus Disease - 2019 (COVID-19) infection
Intervention	Risankizumab 1200mg IV at week 0, 4, and 8 (n=650).
Comparator(s)	Placebo IV at week 0, 4, and 8 (n=325).
Follow-up time	12 weeks
Primary, secondary and exploratory endpoints	• **Endpoints included in this application:** • Proportion of patients with clinical remission per Adapted Mayo Score [AMS] (stool frequency sub-score (SFS) <= 1, and not greater than baseline, rectal bleeding sub-score (RBS) = 0, and endoscopic sub-score (ESS) <= 1 without the evidence of friability) at week 12. • Change from baseline to week 12 in inflammatory bowel disease questionnaire (IBDQ) total score. • **Other endpoints:** • Proportion of patients with endoscopic improvement (ESS of 0 or 1 without the evidence of friability) at week 12 • Proportion of patients achieving clinical response per AMS (decrease in AMS >= 2 points and >= 30% from baseline, plus a decrease in RBS >= 1 or an absolute RBS <= 1) at week 12 • Proportion of patients with histological endoscopic improvement (HEMI) of the mucosa (ESS of 0 or 1 without evidence of friability and Geboes score ≤ 3.1) at week 12 • Proportion of patients with endoscopic remission (ESS = 0) at week 12 • Proportion of patients achieving clinical response per partial AMS (decrease from baseline ≥ 1 point and ≥ 30% a decrease in RBS ≥ 1 or an absolute RBS ≤ 1) at week 4 • Proportion of patients who reported no bowel urgency at week 12 • Proportion of patients who reported no abdominal pain at week 12 • Proportion of patients achieving histological endoscopic remission (HEMR) of the mucosa (ESS of 0 and Geboes score < 2.0) at week 12 • Change from baseline to week 12 in functional assessment of chronic illness therapy-fatigue (FACIT-F)

Trial name: INSPIRE	NCT number:03398148
	• Proportion of patients with UC-related hospitalizations through week 12 • Proportion of patients who reported no nocturnal bowel movements at week 12 • Proportion of patients who reported no tenesmus at week 12 • Change from baseline to week 12 in number of faecal incontinence episodes per week • Change from baseline to week 12 in number of days per week with sleep interrupted due to UC symptoms • Proportion of patients achieving clinical remission per Full Mayo Score [FMS] (FMS ≤2 with no sub-score >1) at week 12 in patients with FMS of 6 to 12 at baseline • Proportion of patients achieving clinical response per AMS at week 12 in patients with pancolitis at baseline • Change from baseline to week 12 in short form-36 (SF-36)
Method of analysis	The primary efficacy analysis population for INSPIRE study was the intent-to-treat (ITT) analysis set, which included all randomized patients who received at least one dose of study drug during the 12 Week induction. Patients who were randomized and received at least one dose of risankizumab during extended treatment were analyzed separately for exploratory purposes. Safety analysis was based on the safety analysis set, which included all patients who received at least one dose of study drug during the 12 Week induction. Patients who received at least one dose of risankizumab during extended treatment after Week 12 were analyzed separately for exploratory purposes.
Subgroup analyses	Specific subgroups of interest included patients stratified based on prior advanced therapy inadequate responder status (AT-IR versus non-AT-IR).
Other relevant information	For this application, also the proportion of patients with IBDQ remission (Total Score >= 170) was included.

Trial name: COMMAND	NCT number:03398135
Objective	To evaluate the efficacy and safety of risankizumab versus placebo as maintenance therapy in patients with moderately to severely active UC who responded to risankizumab induction in INSPIRE.
Publications – title, author, journal, year	Risankizumab for Ulcerative Colitis: Two Randomized Clinical Trials, Louis, E. et al. JAMA, 2024
Study type and design	Phase 3 maintenance study (Figure 10) comprising a randomized, double-blind, placebo-controlled maintenance study and an open-label long-term extension (LTE) study.
Sample size (n)	548
Main inclusion criteria	• Achieved clinical response, defined as decrease in AMS ≥ 2 points and ≥ 30% from baseline, PLUS a decrease in RBS ≥ 1 or an absolute RBS ≤ 1 at the last visit of INSPIRE. For patients with missing final endoscopy for INSPIRE due to COVID-19 pandemic, clinical response is defined as a decrease in Partial Adapted Mayo Score ≥ 1 point and ≥ 30% from baseline, PLUS a decrease in RBS ≥1 or an absolute RBS ≤1 at the last visit of INSPIRE.
Main exclusion criteria	• Patients considered by the investigator, for any reason, to be unsuitable candidates for the study. • Patients should not be enrolled in COMMAND if high grade colonic dysplasia or colon cancer is discovered at the endoscopy performed at the final visit of INSPIRE. • Subject who has a known hypersensitivity to risankizumab or the excipients of any of the study drugs or the ingredients of Chinese hamster ovary OR had an adverse event during INSPIRE that in the Investigator's judgment makes the patient unsuitable for this study. • Confirmed positive urine pregnancy test at the Final Visit of INSPIRE. • Subject is not in compliance with prior and concomitant medication requirements throughout INSPIRE. • Subject with any active or chronic recurring infections based on the Investigator's assessment makes the patient an unsuitable candidate for the study. • Have a known history of lymphoproliferative disease, including lymphoma, or signs and symptoms suggestive of possible lymphoproliferative disease, such as lymphadenopathy and/or splenomegaly.
Intervention	Risankizumab 180 mg subcutaneous (SC) every 8 weeks (n=179). Risankizumab 360 mg subcutaneous (SC) every 8 weeks (n=186).

Trial name: COMMAND	NCT number:03398135
Comparator(s)	Withdrawal placebo subcutaneous (SC) every 8 weeks (n=183)
Follow-up time	52 weeks
Primary, secondary and exploratory endpoints	**Endpoints included in this application:** • Proportion of patients with endoscopic improvement (ESS of 0 or 1 without the evidence of friability) at Week 52. • Proportion of patients achieving clinical remission per AMS at Week 52 with no cortico-steroid use for 90 days • Change from Baseline (of induction) to Week 52 in Inflammatory Bowel Disease Questionnaire (IBDQ) total score. **Other endpoints:** • Proportion of patients with clinical remission per Adapted Mayo Score [AMS] (stool frequency sub-score (SFS) <= 1, and not greater than baseline, rectal bleeding sub-score (RBS) = 0, and endoscopic sub-score (ESS) <= 1 without the evidence of friability) at week 52 • Proportion of patients with histological endoscopic improvement (HEMI) of the mucosa (ESS of 0 or 1 without evidence of friability and Geboes score ≤ 3.1) at week 52. • Proportion of patients with endoscopic remission (ESS = 0) at Week 52. • Proportion of patients with clinical remission per AMS at Week 52 in patients with clinical remission at Week 0 (of maintenance). • Proportion of patients who reported no bowel urgency at Week 52. • Proportion of patients who reported no abdominal pain at Week 52. • Proportion of patients with histological endoscopic remission (HEMR) of the mucosa (ESS of 0 and Geboes score < 2.0) at Week 52. • Proportion of patients with endoscopic improvement at Week 52 in patients with endoscopic improvement at Week 0 (of maintenance). • Proportion of patients with clinical response per AMS (decrease in AMS >= 2 points and >= 30% from baseline, plus a decrease in RBS >= 1 or an absolute RBS <= 1) at Week 52. • Change from Baseline (of induction) to Week 52 in FACIT-F. • Proportion of patients who reported no nocturnal bowel movements at Week 52.

Trial name: COMMAND	NCT number:03398135
	• Proportion of patients who reported no tenesmus at Week 52. • Change from Baseline (of induction) to Week 52 in number of faecal incontinence episodes per Week. • Change from Baseline (of induction) to Week 52 in number of days over a Week with sleep interrupted due to UC symptoms. • Proportion of patients with UC-related hospitalizations through Week 52. • Proportion of patients achieving clinical remission per FMS (FMS ≤2 with no sub-score >1) at Week 52 in patients with a FMS of 6 to 12 at Baseline (of induction). • Proportion of patients who discontinued corticosteroid use at Week 52 in patients taking steroids at baseline (of induction). • Proportion of patients who discontinued corticosteroid use, remained corticosteroid free for 90 days and achieved clinical remission at Week 52 in patients taking steroids at Baseline (of induction). • Proportion of patients with UC-related surgeries through Week 52. • Proportion of patients with clinical response per AMS at Week 52 in patients with pancolitis at baseline. • Change from Week 0 to Week 52 in Short Form-36 (SF-36)
Method of analysis	The ITT analysis set for the pivotal maintenance trial includes all patients who achieved clinical response based on the Adapted Mayo Score utilizing the endoscopy sub-score provided by the central reader. The safety analysis sets include all patients who received at least one dose of study drug.
Subgroup analyses	Specific subgroups of interest included patients stratified based on prior advanced therapy inadequate responder status (AT-IR versus non-AT-IR).
Other relevant information	For this application, also the proportion of patients with IBDQ remission (Total Score >= 170) was included. In addition to the withdrawal placebo patients described above, a subgroup of patients who responded to IV placebo in induction were continued on placebo in maintenance (see section 3.2) As discussed above, this true placebo group should be used to make an unbiased comparison between risankizumab and other treatments with shorter retention.

Appendix B. Efficacy results per study

Results per study

Tabel 6 Results per study

Results of INSPIRE (NCT03398148), AT naïve patients, 12 weeks											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Clinical remission	RZB 1200 mg	293	88 (30.0) 24.8; 35.3	21.1	14.2; 28.1		3.4	1.9; 5.9		95% CI for response rate is the synthetic result based on Student's t-distribution from PROC MIANALYZE procedure if there are missing data due to logistic restrictions (COVID-19 or geo-political restrictions) or is based on the normal approximation to the binomial distribution if there are no missing data due to logistic restrictions (COVID-19 or geo-political restrictions). The 95% CIs for adjusted difference and adjusted RR are	
	PBO	147	13 (8.8) 4.3; 13.4								

Results of INSPIRE (NCT03398148), AT naïve patients, 12 weeks											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
										calculated according to the Cochran-Mantel-Haenszel (CMH) test adjusted for strata (Advanced Therapy-IR status (yes vs no), baseline steroid use (yes vs no), and baseline Adapted Mayo score (<= 7 vs > 7)) for the comparison of two treatment groups.	
Change from baseline in IBDQ total score	RZB 1200 mg	282	49.0 (44.7; 53.3)	19.0	12.1; 26.0		N/A			The LS mean, 95% CI and SE are the synthetic result based on ANCOVA including baseline value, stratification factors (baseline steroid use (yes vs no), and baseline Adapted Mayo score (<= 7 vs > 7)) and treatment in the model from PROC MIANALYZE procedure. Any subject(s) with missing baseline stratification factors to be used in stratified statistical	
	PBO	140	30.0 (24.1; 36.0)								

Results of INSPIRE (NCT03398148), AT naïve patients, 12 weeks											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
										analysis models, had their strata assigned per the IRT strata at randomization to perform the stratified analysis.	
IBDQ remission	RZB 1200 mg	293	183 (62.5) 56.9; 68.0	19.6	9.9; 29,3		1.5	1.2; 1.8		95% CI for response rate is the synthetic result based on Student's t-distribution from PROC MIANALYZE procedure if there are missing data due to logistic restrictions (COVID-19 or geo-political restrictions) or is based on the normal approximation to the binomial distribution if there are no missing data due to logistic restrictions (COVID-19 or geo-political restrictions). The 95% CI for adjusted difference and adjusted RR are calculated according to the Cochran-Mantel-Haenszel	
	PBO	147	63 (42.9) 34.9; 50.9								

Results of INSPIRE (NCT03398148), AT naïve patients, 12 weeks											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
										(CMH) test adjusted for strata (Advanced Therapy-IR status (yes vs no), baseline steroid use (yes vs no), and baseline Adapted Mayo score (<= 7 vs > 7)) for the comparison of two treatment groups.	

Results of INSPIRE (NCT03398148), AT exposed patients, 12 weeks											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Clinical remission	RZB 1200 mg	357	44 (12.3) 8.9; 15.7	8.3	3.8; 12.8		3.1	1.4; 6.8		95% CI for difference and RR calculated using normal approximation to the binomial distribution. The calculations are based on non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19 or non-responder imputation only if there are no missing data due to COVID-19. No p-value was calculated for subgroup analysis.	
	PBO	178	7 (4.1) 1.1; 7.0								
Change from baseline in IBDQ	RZB 1200 mg	337	37.7 (33.7; 41.7)	18.4	11.4; 25.3		N/A			The LS mean, 95% CI and SE are the synthetic result based on ANCOVA including baseline value, stratification factors (baseline steroid use (yes vs no), and	
	PBO	170	19.3 (13.6; 25.1)								

Results of INSPIRE (NCT03398148), AT exposed patients, 12 weeks											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
total score										baseline Adapted Mayo score (<= 7 vs > 7)) and treatment in the model from PROC MIANALYZE procedure. Any subject(s) with missing baseline stratification factors to be used in stratified statistical analysis models, had their strata assigned per the IRT strata at randomization to perform the stratified analysis.	
IBDQ remission	RZB 1200 mg	357	164 (45.9) 40.7; 51.0	16.6	8.2; 25.1		1.6	1.2; 2.0		95% CI for response rate is the synthetic result based on Student's t-distribution from PROC MIANALYZE procedure if there are missing data due to logistic restrictions (COVID-19 or geo-political restrictions) or	
	PBO	178	52 (29.2) 22.5; 35.9								

Results of INSPIRE (NCT03398148), AT exposed patients, 12 weeks											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
										is based on the normal approximation to the binomial distribution if there are no missing data due to logistic restrictions (COVID-19 or geo-political restrictions). The 95% CIs for adjusted difference and adjusted RR are calculated according to the Cochran-Mantel-Haenszel (CMH) test adjusted for strata (Advanced Therapy-IR status (yes vs no), baseline steroid use (yes vs no), and baseline Adapted Mayo score (<= 7 vs > 7)) for the comparison of two treatment groups.	

Results of INSPIRE (NCT03398148), overall patients, 12 weeks											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
SAE	RZB 1200 mg	651	15 (2.3)	-7.9	-11.4; -4-4		0.2	0.1; 0.4		The 95% CI for the rate difference is based on normal approximation to binominal distribution.	
	PBO	324	33 (10.2)								

Results of COMMAND (NCT03398135), AT naïve patients, 52 weeks, true placebo											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Endoscopic improvement (mucosal healing)	RZB180	41	25 (60.5) 45.4; 75.6	35.5	14.2; 56.8		2.4	1.3; 4.6		95% CI for response rate is the synthetic result based on Student's t-distribution from PROC MIANALYZE procedure if there are missing data due to logistic restrictions (COVID-19 or the geo-political conflict in Ukraine and surrounding impacted regions) or is based on the normal approximation to the binomial distribution if there are no missing data due to logistic restrictions (COVID-19 or the geo-political conflict in Ukraine and surrounding impacted regions).	
	RZB360	41	31 (74.6) 61.1; 88.2	49.6	29.4; 69.8		3.0	1.6; 5.6			
	True PBO	32	8 (25.0) 10.0; 40.0								
Steroid free remission	RZB180	41	21 (50.7) 35.3; 66.2	25.7	4.2; 47.3		2.0	1.0; 4.0			
	RZB360	41	24 (58.5) 43.5; 73.6	33.5	12.3; 54.8		2.3	1.2; 4.5			
	True PBO	32	8 (25.0) 10.0; 40.0								

Results of COMMAND (NCT03398135), AT naïve patients, 52 weeks, true placebo											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Change from baseline in IBDQ total score	RZB180	39	59.8 (48.9; 70.7)	32.1	12.4; 51.9		N/A			The LS mean, 95% CI and SE are the synthetic result based on Mixed-Effect Model Repeat Measurement with Baseline, Week 0, treatment, visit, treatment-by-visit interaction in the model from PROC MIANALYZE procedure.	
	RZB360	39	53.6 (42.3; 64.8)	25.9	6.1; 45.7		N/A				
	True PBO	29	27.7 (11.8; 43.5)								
IBDQ remission	RZB180	41	31 (75.6) 62.5; 88.8	41.2	20.2; 62.3		2.2	1.3; 3.7		95% CI for response rate is the synthetic result based on Student's t-distribution from PROC MIANALYZE procedure if there are	
	RZB360	41	28 (67.9) 53.5; 82.3	33.5	11.6; 55.4		2.0	1.2; 3.3			

Results of COMMAND (NCT03398135), AT naïve patients, 52 weeks, true placebo											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
	True PBO	32	11 (34.4) 17.9; 50.8							missing data due to logistic restrictions (COVID-19 or the geo-political conflict in Ukraine and surrounding impacted regions) or is based on the normal approximation to the binomial distribution if there are no missing data due to logistic restrictions (COVID-19 or the geo-political conflict in Ukraine and surrounding impacted regions).	

Results of COMMAND (NCT03398135), AT naïve patients, 52 weeks, withdrawal placebo											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Endoscopic improvement (mucosal healing)	RZB180	41	25 (60.7) 45.7; 75.8	28.3	7.0; 49.6		1.9	1.1; 3.2		95% CI for response rate is the synthetic result based on Student's t-distribution from PROC MIANALYZE procedure if there are missing data due to logistic restrictions (COVID-19 or the geo-political conflict in Ukraine and surrounding impacted regions) or is based on the normal approximation to the binomial distribution if there are no missing data due to logistic restrictions (COVID-19 or the geo-political conflict in Ukraine and surrounding impacted regions).	
	RZB360	41	31 (75.1) 61.7; 88.5	42.7	22.5; 62.8		2.3	1.4; 3.8			
	PBO	37	12 (32.4) 17.3; 47.5								
Steroid free remission	RZB180	41	21 (51.0) 35.6; 66.3	23.9	2.9; 45.0		1.9	1.0; 3.5			
	RZB360	41	24 (58.5) 43.5; 73.6	31.5	10.7; 52.3		2.2	1.2; 3.9			
	PBO	37	10 (27.0) 12.7; 41.3								

Results of COMMAND (NCT03398135), AT naïve patients, 52 weeks, withdrawal placebo											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Change from baseline in IBDQ total score	RZB180	39	57.0 (46.8; 67.1)	18.9	2.6; 35.2		N/A			The LS mean, 95% CI and SE are the synthetic result based on Mixed-Effect Model Repeat Measurement with Baseline, Week 0, treatment, visit, treatment-by-visit interaction in the model from PROC MIANALYZE procedure.	
	RZB360	39	52.4 (41.4; 63.4)	14.3	-1.7; 30.2		N/A				
	PBO	36	38.1 (25.6; 50.6)								
IBDQ remission	RZB180	41	31 (75.6) 62.5; 88.8	10.7	-9.5; 31.0		1.2	0.9; 1.6		95% CI for response rate is the synthetic result based on Student's t-distribution from PROC MIANALYZE procedure if there are	
	RZB360	41	28 (67.9) 53.0; 82.0	2.6	-18.5; 23.8		1.0	0.8; 1.4			

Results of COMMAND (NCT03398135), AT naïve patients, 52 weeks, withdrawal placebo											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
	PBO	37	24 (64.9) 49.5; 80.2							missing data due to logistic restrictions (COVID-19 or the geo-political conflict in Ukraine and surrounding impacted regions) or is based on the normal approximation to the binomial distribution if there are no missing data due to logistic restrictions (COVID-19 or the geo-political conflict in Ukraine and surrounding impacted regions).	

Results of COMMAND (NCT03398135), AT exposed patients, 52 weeks, true placebo											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Endoscopic improvement (mucosal healing)	RZB180	138	66 (47.8) 39.5; 56.2	34.7	21.1; 48.3		3.6	1.6; 8.4		95% CI for response rate is the synthetic result based on Student's t-distribution from PROC MIANALYZE procedure if there are missing data due to logistic restrictions (COVID-19 or the geo-political conflict in Ukraine and surrounding impacted regions) or is based on the normal approximation to the binomial distribution if there are no missing data due to logistic restrictions (COVID-19 or the geo-political conflict in Ukraine	
	RZB360	145	59 (40.7) 32.7; 48.7	27.5	14.1; 40.9		3.1	1.3; 7.2			
	True PBO	38	5 (13.2) 2.4; 23.9								
Steroid free remission	RZB180	138	50 (36.2) 28.2; 44.3	25.7	13.1; 38.3		3.4	1.3; 8.9			
	RZB360	145	45 (31.0) 23.5; 38.6	20.5	8.2; 32.8		2.9	1.1; 7.7			
	True PBO	38	4 (10.5) 0.8; 20.3								

Results of COMMAND (NCT03398135), AT exposed patients, 52 weeks, true placebo											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
										and surrounding impacted regions).	
Change from baseline in IBDQ total score	RZB180	129	48.4 (40.4; 56.3)	5.4	-12.9; 23.8		N/A			The LS mean, 95% CI and SE are the synthetic result based on Mixed-Effect Model Repeat Measurement with Baseline, Week 0, treatment, visit, treatment-by-visit interaction in the model from PROC MIANALYZE procedure.	
	RZB360	129	47.2 (39.0; 55.4)	4.3	-13.9; 22.5		N/A				
	True PBO	33	42.9 (26.4; 59.4)								
IBDQ remission	RZB180	138	76 (55.1) 46.8; 63.4	15.6	-2.0; 33.2		1.4	0.9; 2.1		95% CI for response rate is the synthetic result based	

Results of COMMAND (NCT03398135), AT exposed patients, 52 weeks, true placebo											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
	RZB360	145	73 (50.3) 42.2; 58.5	10.9	-6.7; 28.4		1.3	0.8; 2.0		on Student's t-distribution from PROC MIANALYZE procedure if there are missing data due to logistic restrictions (COVID-19 or the geo-political conflict in Ukraine and surrounding impacted regions) or is based on the normal approximation to the binomial distribution if there are no missing data due to logistic restrictions (COVID-19 or the geo-political conflict in Ukraine and surrounding impacted regions).	
	True PBO	38	15 (39.5) 23.9; 55.0								

Results of COMMAND (NCT03398135), AT exposed patients, 52 weeks, withdrawal placebo											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Endoscopic improvement (mucosal healing)	RZB180	138	66 (47.8) 39.5; 56.2	16.3	5.1; 27.6		1.5	1.1; 2.0		95% CI for response rate is the synthetic result based on Student's t-distribution from PROC MIANALYZE procedure if there are missing data due to logistic restrictions (COVID-19 or the geo-political conflict in Ukraine and surrounding impacted regions) or is based on the normal approximation to the binomial distribution if there are no missing data due to logistic restrictions (COVID-19 or the geo-political conflict in Ukraine and surrounding impacted regions).	
	RZB360	145	59 (47.8) 32.7; 48.7	9.2	-1.8; 20.2		1.3	0.9; 1.8			
	PBO	146	46 (31.5) 24.0; 39.0								
Steroid free remission	RZB180	138	50 (36.2) 28.2; 44.3	11.6	0.9; 22.2		1.5	1.0; 2.1			
	RZB360	145	45 (31.0) 23.5; 38.6	6.4	-3.9; 16.7		1.3	0.9; 1.8			
	PBO	146	36 (24.7) 17.7; 31.6								

Results of COMMAND (NCT03398135), AT exposed patients, 52 weeks, withdrawal placebo											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Change from baseline in IBDQ total score	RZB180	129	48.6 (39.8; 57.5)	16.7	5.5; 27.9		N/A			The LS mean, 95% CI and SE are the synthetic result based on Mixed-Effect Model Repeat Measurement with Baseline, Week 0, treatment, visit, treatment-by-visit interaction in the model from PROC MIANALYZE procedure.	
	RZB360	129	47.5 (38.2; 56.7)	15.5	3.2; 27.9		N/A				
	PBO	136	31.9 (23.1; 40.8)								
IBDQ remission	RZB180	138	76 (55.1) 46.8; 63.4	18.1	6,7; 29.5		1.5	1.1; 1.9		95% CI for response rate is the synthetic result based on Student's t-distribution from PROC MIANALYZE procedure if there are	
	RZB360	145	73 (50.3) 42.2; 58.5	13.4	2.1; 24.7		1.4	1.0; 1.8			

Results of COMMAND (NCT03398135), AT exposed patients, 52 weeks, withdrawal placebo											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
	PBO	146	54 (37.0) 42.2; 58.5							missing data due to logistic restrictions (COVID-19 or the geo-political conflict in Ukraine and surrounding impacted regions) or is based on the normal approximation to the binomial distribution if there are no missing data due to logistic restrictions (COVID-19 or the geo-political conflict in Ukraine and surrounding impacted regions).	

Results of COMMAND (NCT03398135), overall patients, 52 weeks, withdrawal placebo											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
SAE	RZB180	193	10 (5.2)	-3.0	-7.9; 2.0		0.6	0.3; 1.4		The 95% CI for treatment difference is based on the normal approximation.	
	RZB360	195	10 (5.1)	-3.0	-8.0; 1.9		0.6	0.3; 1.4			
	PBO	196	16 (8.2)								
Steroid free remission	RZB180	179	71 (39.6) 32.4; 46.8	15.8	6.9; 24.8	0.0012	1.6	1.2; 2.2	<0.005	95% CI for response rate is the synthetic result based on Student's t-distribution from PROC MIANALYZE procedure if there are missing data due to logistic restrictions (COVID-19 or the geo-political conflict in Ukraine and surrounding impacted regions) or is based on the normal approximation to the binomial distribution if there are no missing data due to logistic restrictions	
	RZB360	186	69 (37.1) 30.2; 44.0	13.7	4.8; 22.7	0.0046	1.6	1.1; 2.1	<0.005		
	PBO	183	46 (25.1) 18.9; 31.4								

Results of COMMAND (NCT03398135), overall patients, 52 weeks, withdrawal placebo											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
										(COVID-19 or the geo-political conflict in Ukraine and surrounding impacted regions). The 95% CI for adjusted difference, adjusted RR and the associated p-value of adjusted RR are calculated according to the Cochran-Mantel-Haenszel test adjusted for strata (induction Baseline Advanced Therapy-IR status (yes vs no), clinical remission status per Adapted Mayo score at Week 0 (per central read) (yes vs no) and last IV risankizumab induction dose (600 mg vs 1200 mg vs 1800 mg)) for the	

Results of COMMAND (NCT03398135), overall patients, 52 weeks, withdrawal placebo											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
										comparison of two treatment groups. If zero frequency occurred, the zero count will be replaced by 0.1 to prevent dividing by zero. The calculations are based on non-responder imputation incorporating multiple imputation to handle missing data due to logistic restrictions (COVID-19 or the geo-political conflict in Ukraine and surrounding impacted regions) or non-responder imputation only if there are no missing data due to logistic restrictions (COVID-19 or the geo-political conflict in Ukraine	

Results of COMMAND (NCT03398135), overall patients, 52 weeks, withdrawal placebo											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
										and surrounding impacted regions).	
Change from baseline in IBDQ total score	RZB180	168	52.6 (44.9; 60.2)	17.5	8.0; 27.1	0.0003	N/A			The LS mean, 95% CI and SE are the synthetic result based on Mixed-Effect Model Repeat Measurement with Baseline, Week 0, treatment, visit, treatment-by-visit interaction and strata (induction Baseline Advanced Therapy-IR status (yes vs no), clinical remission status per Adapted Mayo score at Week 0 (per central read) (yes vs no) and last IV risankizumab induction dose (600 mg vs 1200 mg vs 1800 mg)) in the model	
	RZB360	168	50.3 (42.2; 58.4)	15.2	5.2; 25.3	0.0031	N/A				
	PBO	172	35.0 (27.2; 42.9)								

Results of COMMAND (NCT03398135), overall patients, 52 weeks, withdrawal placebo											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
										from PROC MIANALYZE procedure.	

Results of COMMAND (NCT03398135), overall patients, 52 weeks, true placebo											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Steroid free remission	RZB180	179	71 (39.6) 32.4; 46.8	22.4	11.0; 33.8	0.0001	2.3	1.3; 4.0	<0.001	95% CI for response rate is the synthetic result based on Student's t-distribution from PROC MIANALYZE procedure if there are missing data due to logistic restrictions (COVID-19 or the geo-political conflict in Ukraine and surrounding impacted regions) or is based on the normal approximation to the binomial distribution if there are no missing data due to logistic restrictions (COVID-19 or the geo-political conflict in Ukraine and surrounding impacted regions).	
	RZB360	186	69 (37.1) 30.2; 44.0	20.0	8.7; 31.2	0.0005	2.2	1.3; 3.7	<0.001		
	True PBO	70	12 (17.1) 8.3; 26.0								

Results of COMMAND (NCT03398135), overall patients, 52 weeks, true placebo											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
										The 95% CI for adjusted difference, adjusted RR and the associated p-value of adjusted RR are calculated according to the Cochran-Mantel-Haenszel test adjusted for strata (induction Baseline Advanced Therapy-IR status (yes vs no), clinical remission status per Adapted Mayo score at Week 0 (per central read) (yes vs no) and last IV risankizumab induction dose (600 mg vs 1200 mg vs 1800 mg)) for the comparison of two treatment groups. If zero frequency occurred, the zero count will be replaced	

Results of COMMAND (NCT03398135), overall patients, 52 weeks, true placebo											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
										by 0.1 to prevent dividing by zero. The calculations are based on non-responder imputation incorporating multiple imputation to handle missing data due to logistic restrictions (COVID-19 or the geo-political conflict in Ukraine and surrounding impacted regions) or non-responder imputation only if there are no missing data due to logistic restrictions (COVID-19 or the geo-political conflict in Ukraine and surrounding impacted regions).	
Change from baseline in	RZB180	168	51.0 (44.4; 57.5)	13.9	0.0; 27.6	0.0491	N/A			The LS mean, 95% CI and SE are the synthetic result	

Results of COMMAND (NCT03398135), overall patients, 52 weeks, true placebo											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
IBDQ total score	RZB360	168	48.3 (41.6; 55.0)	11.2	-2.8; 25.2	0.1172	N/A			based on Mixed-Effect Model Repeat Measurement with Baseline, Week 0, treatment, visit, treatment-by-visit interaction and strata (induction Baseline Advanced Therapy-IR status (yes vs no), clinical remission status per Adapted Mayo score at Week 0 (per central read) (yes vs no) and last IV risankizumab induction dose (600 mg vs 1200 mg vs 1800 mg)) in the model from PROC MIANALYZE procedure.	
	True PBO	62	37.1 (25.0; 49.2)								

Appendix C. Comparative analysis of efficacy

This section is not relevant, no comparative analysis submitted.

Appendix D. Literature searches for the clinical assessment

This section is not relevant, no literature search was performed.

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