Medicinrådet

Bilag til direkte indplacering af mirikizumab i Medicinrådets evidensgennemgang vedrørende biologiske og målrettede syntetiske lægemidler til Crohns sygdom

Vers. 1.0

Bilagsoversigt

1. Forhandlingsnotat fra Amgros vedr. mirikizumab
2. Ansøgers endelige ansøgning vedr. mirikizumab

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08.08.2025

DBS/LSC

Forhandlingsnotat

Dato for behandling i Medicinrådet	03.09.2025
Leverandør	Eli Lilly
Lægemiddel	Omvoh (mirikizumab)
Ansøgt indikation	Behandling af voksne patienter med moderat til svær aktiv Crohns sygdom, som har haft utilstrækkelig respons på, mistet respons på eller intolerante over for enten konventionel behandling eller biologisk behandling.
Nyt lægemiddel / indikationsudvidelse	Indikationsudvidelse – direkte indplacering i behandlingsvejledning

Prisinformation

Amgros har forhandlet følgende aftalepris på Omvoh (mirikizumab). Amgros har kun forhandlet pris på den nye pakning til vedligeholdelsesbehandling i forbindelse med denne indikationsudvidelse:

Tabel 1: Forhandlingsresultat

Lægemiddel	Styrke (Pakningsstørrelse)	AIP (DKK)	Nuværende SAIP, (DKK)	Rabat ift. AIP
Omvoh **NY**	200 mg + 100 mg (1 + 1 stk.) pen	17.812,89	[redacted]	[redacted]

Amgros har følgende aftalepriser på Omvoh:

Tabel 1: Aftalepriser

Lægemiddel	Styrke (Paknings-størrelse)	AIP (DKK)	Nuværende SAIP, (DKK)	Rabat ift. AIP
Omvoh	100 mg, 2 stk. pen	11.875,26	[redacted]	[redacted]
Omvoh	300 mg, 1 stk. hætteglas	12.916,49	[redacted]	[redacted]

Aftaleforhold

[redacted]

Konkurrencesituationen

Denne direkte indplacering drejer sig om indplacering af Omvoh i de kliniske spørgsmål vedr. patienter:

- til behandling af voksne BMSL-naive patienter med moderat til svær aktiv Crohns sygdom
- til behandling af voksne BMSL-erfarne patienter med moderat til svær aktiv Crohns sygdom

[redacted]

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

Tabel 2: 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.):** 40 mg hver 2. uge.	[redacted]	[redacted]
Steqeyma (biosimilær, 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 uge 8 og herefter hver 12. uge.	[redacted]	[redacted]
Zessly (infliximab)	100 mg, 3 stk. hætteglas	**Induktion (i.v.):** 5 mg/kg uge 0, 2 og 6. **Vedligehold (i.v.):** 5 mg/kg hver 8. uge.	[redacted]	[redacted]
Omvoh (mirikizumab)	300 mg, 1 stk. hætteglas 200 mg + 100 mg (1+1 stk.) pen **NY**	**Induktion (i.v.):** 900 mg uge 0, 4 og 8. **Vedligeholdelse (s.c.):** 300 mg hver 4. uge.	[redacted]	[redacted]
Skyrizi (risankizumab)	600 mg, 1 stk. hætteglas 360 mg, 1 stk. pen	**Induktion (i.v.):** 600 mg uge 0, 4 og 8. **Vedligeholdelse (s.c.):** 360 mg hver 8. uge fra uge 12.	[redacted]	[redacted]
Entyvio (vedolizumab) *i.v. + s.c.*	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) *i.v.*	300 mg, 1 stk. hætteglas	**Induktion (i.v.):** 300 mg uge 0, 2 og 6. **Vedligeholdelse (i.v.):** 300 mg hver 8. uge.	[redacted]	[redacted]

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

Status fra andre lande

Tabel 1: 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 mirikizumab (Omvoh®) for the treatment of moderately to severely active Crohn's disease by updating the guideline for biologic and targeted synthetic drugs for the treatment of Crohn's disease

Color scheme for text highlighting

Color of highlighted text	Definition of highlighted text
	Confidential information

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Abbreviations

Abbreviation	Definition
AP	Abdominal pain
BMI	Body mass index
BTSD	Biological and targeted synthetic drugs
CCF	Conventional Care Failure
CD	Crohn's disease
CI	Confidence interval
DMC	Danish Medicines Council
EMA	European Medicines Agency
IBDQ	Inflammatory Bowel Disease Questionnaire
IgG4	Immunoglobulin G4
IL	Interleukin
IV	Intravenous
NMA	Network Meta-Analysis
NRI	Non-responder imputation
N/A	Not applicable
PRO	Patient-reported outcomes
Q4W	Every 4 weeks
SAE	Serious adverse event
SC	Subcutaneous
SES-CD	Simple Endoscopic Score

SF	Stool frequency
TEAE	Treatment-emergent adverse event
TNF	Tumor necrosis factor

1. Regulatory information on the pharmaceutical

Overview of the pharmaceutical	
Proprietary name	Omvoh®
Generic name	Mirikizumab
Therapeutic indication as defined by EMA	Omvoh is indicated for the treatment of adult patients with moderately to severely active Crohn's disease (CD) who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a biologic treatment.
Marketing authorization holder in Denmark	Eli Lilly and Company
ATC code	L04AC24
Combination therapy and/or co-medication	No
Date of EC approval	21 February 2025
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	Omvoh is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a biologic treatment.
Other indications that have been evaluated by the DMC (yes/no)	The DMC has included Omvoh directly in the treatment guidelines for ulcerative colitis as of February 24, 2024.
Dispensing group	BEGR

Overview of the pharmaceutical	
Packaging – types, sizes/number of units and concentrations	Treatment induction pack: Omvoh® 300 mg, 1 vial (glass) – each vial contains 300 mg of mirikizumab in 15 mL (20 mg/mL) Treatment maintenance pack: 1 pack contains: Omvoh® 100 mg solution for injection 1 pre-filled pen of 1 mL *and* Omvoh® 200 mg solution for injection 1 pre-filled pen of 2 mL. See picture below. 

2. Summary table

Summary	
Therapeutic indication relevant for the assessment	No deviation
Dosage regiment and administration:	The induction dose is 900 mg (3 vials with 300 mg each) by intravenous infusion for ≥90 minutes at weeks 0, 4 and 8. The maintenance dose is 300 mg (i.e. one pre-filled pen with 100 mg/1 mL and one pre-filled pen with 200 mg/2 mL) by subcutaneous injection every 4 weeks after completion of induction dosing.
Choice of comparator	According to the DMC treatment guideline for biologic and targeted synthetic drugs (BTSD) for the treatment of CD, the appropriate comparators for this assessment consist of the following therapies, administered in accordance with the dosing schedules and administration protocols specified in the guideline: adalimumab, infliximab, ustekinumab, risankizumab, vedolizumab.
Most important efficacy endpoints (Difference/gain compared to comparator)	Clinical remission by Crohn's Disease Activity Index (CDAI) at week 12 Overall population: mirikizumab: 37.7%, placebo: 25.1%, Δ=12,4 (2.2, 22.7)*. Biologic failed: mirikizumab: 35.6%, placebo: 24.7%, Δ= 10.8(0.6,21.1)**. Not biologic failed: mirikizumab: 39.6%, placebo: 25.5%, Δ=14.1 (4.0,24.2)**. Clinical response by patient reported outcomes (PRO) week 12 and Corticosteroid-free from Week 40 to Week 52 and clinical remission by CDAI at week 52 Overall population: mirikizumab: 43.7%, placebo: 18.6%, Δ25.0= (15.2, 34.7)*. Biologic failed: mirikizumab: 40.6%, placebo: 12.4%, Δ=28.2 (19.5,36.9)**. Not biologic failed: mirikizumab: 46.6%, placebo: 24.5%, Δ=22.1 (12.0, 32.2)**. When comparing the CDAI response with and without PRO to placebo, the efficacy delta decreases when PRO at week 12 is included. This suggests that the efficacy of the combined endpoint may be considered conservative (data on file). Proportion of patients achieving a score ≥ 170 on the Inflammatory Bowel Disease Questionnaire (IBDQ). Overall: mirikizumab: 58.5%, placebo: 19.6; Δ=39.0 (32.2, 45.9)** Biologic failed: mirikizumab: 56.9%, placebo: 14.4; Δ=42.5 (33.4, 51.6)**

Summary	
	Not biologic failed: mirikizumab: 60.1%, placebo:24.5; Δ=35.6; (25.5, 45.6)** Difference in change from baseline on IBDQ (response) Overall: mirikizumab: 69.3%, placebo:26.1%; Δ=43.2 (36.0, 50.4)** Biologic failed: mirikizumab: 68.0%, placebo; 18.6%; Δ=49.4 (39.9, 58.9)** Not biologic failed: mirikizumab: 70.5%, placebo: 33.3%; Δ=37.1 (26.6, 47.6)**
Most important serious adverse events for the intervention and comparator	Overall, the frequencies of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and discontinuations due to AEs were higher in the placebo group compared with the mirikizumab group. In the CD treatment regimen analysis set (which evaluated the whole VIVID-1 study period from Week 0 to 52), the system organ classes with SAEs reported in more than 1% of mirikizumab-treated participants were gastrointestinal disorders (5.4%) and infections and infestations (2.2%). Furthermore, most TEAEs were mild or moderate in severity. The most common TEAEs reported in mirikizumab-treated participants in the CD treatment regimen analysis were COVID-19 (16.5%), anaemia (6.7%), and headache (6.5%). For placebo the proportions for those same TEAEs were 13.7%, 6.6% and 4.3% respectively.

*99.5% CI, ** 95% CI

3. The patient population, intervention and relevant outcomes

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

The governing treatment guideline is the Danish Medicines Council (DMC) guideline and treatment recommendation regarding biological and targeted synthetic drugs (BTSD) for the treatment of Crohn's Disease (CD) (1, 2). The DMC treatment guideline divides the population into two groups according to exposure to BTSD. Naïve patients, who have not previously received treatment with BTSD, and patients previously treated with BTSD. This aligns with the indication that EMA has granted mirikizumab (Omvoh®, hereinafter referred to as per active ingredient); "*for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a biologic treatment*" (3).

According to the guideline, the appropriate comparators for this assessment consist of the following therapies, administered in accordance with the dosing schedules and administration protocols specified in the guideline: adalimumab, infliximab, ustekinumab, risankizumab, vedolizumab.

3.2 The intervention

Mirikizumab is a humanised immunoglobulin G4 (IgG4) isotype monoclonal antibody that binds with high affinity and specificity to the p19 subunit of human interleukin (IL-23) cytokine and inhibits its interaction with the IL-23 receptor (3). The recommended dosing of mirikizumab is induction with 900 mg intravenous (IV) infusion for ≥90 minutes at Weeks 0, 4, and 8 followed by maintenance with 300 mg subcutaneous (SC) injection every 4 weeks.

IL-23 is a regulatory cytokine that affects the differentiation, expansion, and survival of T cell subsets, (e.g., Th17 cells and Tc17 cells) and innate immune cell subsets, which represent sources of effector cytokines, including IL-17A, IL-17F and IL-22 that drive inflammatory disease. In humans, selective blockade of IL-23 was shown to normalize production of these cytokines (3). Mirikizumab is further described in the table below.

Table 1 Overview of the intervention

Overview of intervention	
Therapeutic indication relevant for the assessment	Mirikizumab is indicated for the treatment of adult patients with moderately to severely active CD who have had an inadequate response with, lost response to, or were

Overview of intervention	
	intolerant to either conventional therapy or biologic treatment.
Method of administration	Introduction dose is performed by IV infusion. The maintenance dose is SC injection.
Dosing	The induction dose is 900 mg (3 vials with 300 mg each) by IV infusion for ≥90 minutes at weeks 0, 4 and 8. The maintenance dose is 300 mg by SC injection every 4 weeks after completion of induction dosing.
Should the pharmaceutical be administered with other medicines?	No.
Treatment duration / criteria for end of treatment	Consideration should be given to discontinuing treatment in patients who have shown no evidence of therapeutic benefit by week 24.
Necessary monitoring, both during administration and during the treatment period	Mirikizumab is intended for use under the guidance and supervision of a physician experienced in the diagnosis and treatment of CD. After training in SC injection technique, a patient may self-inject with mirikizumab.
Need for diagnostics or other tests (e.g. companion diagnostics). How are these included in the model?	No need for product specific diagnostic tests.
Package size(s)	**Treatment induction pack:** Omvoh® 300 mg, 1 vial (glass) – each vial contains 300 mg of mirikizumab in 15 mL (20 mg/mL). **Treatment maintenance pack:** 1 pack contains: Omvoh® 100 mg solution for injection 1 pre-filled pen of 1 mL and Omvoh® 200 mg solution for injection 1 pre-filled pen of 2 mL.

3.2.1 The intervention in relation to Danish clinical practice

Mirikizumab is expected to be used by both BTSD-naïve and BTSD-experienced patients with moderately to severely CD. The introduction of mirikizumab provides an additional treatment option to the existing ones.

Mirikizumab is expected to fulfill the DMC treatment guideline criteria for treatment of BTSD-naïve patients with moderately to severely active CD and be recommended by the DMC as a treatment alternative in line with adalimumab, infliximab, ustekinumab, risankinumab, vedolizumab (SC) and vedolizumab (IV).

For BTSD-experienced CD patients, mirikizumab is expected to fulfill the DMC treatment guideline criteria and be recommended as a treatment alternative in line with adalimumab, infliximab, ustekinumab, risankinumab, vedolizumab (SC) and vedolizumab (IV).

No additional diagnostic or testing is expected.

4. Overview of literature

Not applicable as the current treatment guideline includes a network meta-analysis (NMA), and according to DMC guidance a systematic literature search can in such case be omitted.

The main pivotal trial for mirikizumab (VIVID-1 (I6T-MC-AMAM)) (4) is presented in Table 2. Baseline characteristics and results observed in the trial in context of how these compare with the studies included in the DMC treatment guideline are presented in section 5 and 6, respectively. VIVID-1 was designed to look at the total population, however whenever possible, the subgroup data for the BTSD-naïve (section 5) and BTSD-experienced (section 6) populations will be presented.

Please note, VIVID-1 consisted of two comparator arms; placebo and ustekinumab (6 mg/kg IV at week 0 and 90 mg SC Q8W starting at Week 8). However, the focus of this application is the comparison versus placebo whereas a short description of ustekinumab comparison is presented in section 5.2.1.

Table 2 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
VIVID-1 NCT03926130 Efficacy and safety of mirikizumab in patients with moderately-to-severely active Crohn's disease: a phase 3, multicentre, randomised, double-blind, placebo-controlled and active-controlled, treat-through study.	Phase III, multicentre, randomised, double-blind, double-dummy, parallel group, active- and placebo-controlled, treat-through study.	12 weeks of randomized induction period followed by a maintenance phase (weeks 12-52). Patients in treatment remained in the induction group during the maintenance phase; placebo-treated responders continued to receive placebo as maintenance therapy while non-responders received blinded mirikizumab.	Start: 23/07/2019 Completion: 23/08/23 Data cut-off: 52 weeks Future data cut-offs: N/A	Patients with a confirmed diagnosis of moderately to severely active CD or fistulizing CD and inadequate response, loss of response, or intolerance to at least one corticosteroid, immunomodulator, or approved biologic therapy for CD.	mirikizumab (900 mg IV Q4W at Weeks 0, 4, and 8)	Placebo and ustekinumab (~6 mg/kg IV at Week 0 and 90 mg SC Q8W starting at Week 8)	1 and 2	Percentage of patients achieving clinical remission at week 12 Percentage of patients achieving clinical response at week 12 and corticosteroid-free clinical remission at week 52 Percentage of patients achieving clinical response at week 12 and endoscopic remission at week 52 Proportion of patients experiencing one or more SAE (up to 52 Weeks) Change from Baseline in IBDQ Total Score at week 52

Abbreviations: CD, Crohn's disease; IBDQ, Inflammatory Bowel Disease Questionnaire; N/A, not applicable; Q4W/Q8W, Every 4/8 weeks; SAE, serious adverse event

5. Clinical question 1

5.1 Efficacy of mirikizumab compared to best available treatment for BTSD-naïve adult patients with moderately to severely active CD

5.1.1 Relevant studies

A total of 14 randomized controlled studies and 16 articles from the literature search have been included in the DMC guideline. In addition, the expert committee has chosen to include 2 articles based on 2 randomized studies. The studies were published from 1997-2018 and include randomized controlled, double-blind and single-blind studies, primarily phase 2 and 3 studies. The patient populations in the included studies are overall comparable and consistent with the Danish patient population, as stated in the DMC guideline (1). In addition, EMA's product summaries were accessed when describing known and serious side effects.

In this section, data for total population and BTSD-naïve subgroup data is presented. The treatment guideline bases the comparison for PICO 1 on the outcomes outlined below in Table 3.

Table 3 Overview of outcomes included for PICO 1 in the DMC treatment guideline for CD

Outcome	Outcome measure
Clinical remission after induction therapy (weeks 6-8)	Proportion of patients with total CDAI-score ≤150.
Systemic steroid-free remission with maintenance therapy (week 52)	Proportion of systemic steroid-free patients having a total CDAI-score ≤150 at week 52
Adverse events*	Proportion of patients experiencing one or more SAEs. Qualitative review of adverse reaction profile.
Endoscopic/imaging remission during maintenance treatment (week 52)	Proportion of patients achieving endoscopic/ diagnostic imaging remission
Quality of life*	Proportion of patients achieving a score ≥ 170 on the IBDQ. Difference in change from baseline on IBDQ.

* For these endpoints, data with the longest possible follow-up time is desired

Abbreviations: CDAI, Crohn's Disease Activity Index; IBDQ, Inflammatory Bowel Disease Questionnaire; SAE, Serious Adverse Event

Source: Medicinrådet 2021 (1)

5.1.2 Comparability of studies

VIVID-1 was a randomised, double-blind, double-dummy, parallel-group, active-, and placebo-controlled, treat-through study including a 12-week blinded induction period (weeks 0 to 12) followed by a 40-week blinded maintenance period (weeks 12 to 52). Eligible patients had a confirmed diagnosis of moderately to severely active CD or fistulizing CD and inadequate response, loss of response, or intolerance to at least one corticosteroid, immunomodulator, or approved biologic therapy for CD.

In the 12-week induction period, study participants were randomized in a 6:3:2 ratio to receive mirikizumab 900 mg IV Q4W, ustekinumab 6 mg/kg IV at week 0 and 90 mg SC Q8W starting at Week 8, or placebo.

Regardless of treatment response to induction therapy, participants in the mirikizumab and ustekinumab groups continued to receive the same medication in the maintenance period. Placebo-treated responders continued to receive placebo as maintenance and non-responders received blinded mirikizumab 900 mg IV Q4W for three doses followed by 300 mg SC Q4W.

Study participants who completed VIVID-1 were eligible to enter the ongoing, open-label, long-term extension trial, VIVID-2 (Not included in this application).

Throughout the study, stable doses (for ≥2 weeks prior to screening endoscopy) of oral 5-ASA and oral corticosteroids (prednisone ≤30 mg/day or equivalent or budesonide ≤9 mg/day) were permitted, as were stable doses (for ≥8 weeks prior to screening endoscopy) or immunomodulators including azathioprine, 6-mercaptopurine, and methotrexate. At week 12, participants taking corticosteroids who achieved clinical response as assessed by patient reported outcomes (PRO) were required to initiate steroid tapering as per the study protocol.

The VIVID-1 study is overall comparable to the studies included in the DMC treatment guideline in terms of treatment length, population stratifications, and study design. Differences between VIVID-1 and the included studies are described below. The length of the induction period ranges from 4-10 weeks (5-10) in most studies included in DMC's guideline compared to 12 weeks for VIVID-1. However, induction data up to 12 weeks can be evaluated according to DMC (1).

The length of the maintenance period in many of the studies included in the DMCs treatment guideline ranges from 28-54 (6, 7, 11-13). In comparison, the VIVID-1 study employs a 40-week maintenance period from week 12 to week 52.

Two clinical trial designs are included in the treatment guideline: treat-through and re-randomization. In treat-through trials, patients are randomized at baseline, with outcomes measured after both induction and maintenance treatment phases. In re-randomized responder trials, patients proceed to the maintenance phase only if they respond to the induction treatment. Induction phase responders are then re-randomized to either the intervention or a placebo/active comparator at maintenance doses.

The DMC treatment guideline incorporates treat-through induction studies for adalimumab (5, 7), vedolizumab (8), infliximab (10), and ustekinumab (11) and re-randomized maintenance studies for infliximab(14), adalimumab (15), vedolizumab (6), and ustekinumab (16). Comparing re-randomized maintenance studies to the treat-through maintenance phase in VIVID-1 is challenging, as these patients are systematically different in terms of drug exposure. In re-randomization studies participants who have received active treatment during the induction phase followed by re-randomization to placebo in the maintenance phase may have “carry over” effect and thus a heightened level of response at maintenance.

In treat-through trial design, like VIVID-1, it can be argued that the study provides conservative and unbiased results, as randomization is performed at the beginning of the study and remains throughout the study. Furthermore, it is increasingly being used to evaluate newer treatments and this change is also reflected in EMA and FDA guidelines (17, 18). However, comparing treat-through and re-randomized studies is challenging, because the underlying trial designs aim at answering different research questions.

Most studies in the DMC guideline investigate study endpoints during the induction phase in two different patient population; "conventional care failed" (CCF), which includes CCF or TNF-naïve patients (6, 11), and “biologic failed” which includes biologic failure, TNF-experienced (7, 11) or TNF-failure (6, 8). The VIVID-1 study categorizes patients as “biologic failed” or “not biologic failed”. Patients in VIVID-1 categorized as biologic failed are comparable to BTSD-experienced patients in the DMC’s treatment guideline. The definition of “not biologic failed” in VIVID-1 does not fully align with the definition of BTSD-naïve patients in the DMC treatment guideline. The group "not biologic failed" consists of 88% biologically naive patients (see Table 4). This group is used in this application to estimate outcomes for BTSD-naïve patients. Although a larger proportion of naïve patients would align more closely with the DMC treatment guideline, since they have not been exposed to therapies that may alter their disease course or treatment response, this definition provides conservative estimates for the effect of mirikizumab on BTSD-naïve patients, suggesting that the true effect of mirikizumab for this patient population may be greater.

Crohn’s Disease Activity Index (CDAI) is commonly used in trial settings for the assessment of clinical disease activity. CDAI has eight domains, each of which evaluates a specific aspect of CD. The score of each domain is weighted, with the final CDAI score being the sum of the eight individual domain values. VIVID-1 utilizes a total CDAI score of <150 to assess clinical remission. CDAI is used to assess superiority to placebo after the induction phase at week 12 and week 52, and to evaluate non-inferiority to ustekinumab at week 52.

Since the VIVID-1 study utilized a treat-through design, this application compares studies in the DMC guidelines using the same approach.

The VIVID-1 study aligns with the studies in the DMC’s treatment guideline for CD, demonstrating similar efficacy across advanced therapies for moderately to severely active CD, all showing superiority over placebo.

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

Baseline characteristics of patients in VIVID-1 are presented in table 4. The number of patients receiving treatment in a selection of studies included in the DMC treatment guideline are n=28 (10) in Targan et al. 1997, n=159 (7) in GAIN, n=193 in ACCENT-I (12), and n=747 in GEMINI 2(6) compared to n=579 in VIVID-1.

Gender distribution vary greatly across the studies with the proportion of males ranging from 31% (n=50) in GAIN (7) and 37 % (n=17) in IM-UNITI (19), to 62.5% (n=40) in EXTEND (20) compared to 57.3% (n=332) in VIVID-1. Mean age is reported to be between 38-39 years in CLASSIC-I (5), 34-40 years in CLASSIC-II (15), 35.6-36.3 years in GEMINI 2 (6), 35.7-37.5 years in GEMINI 3 (8) compared to 36 years in VIVID-1.

The distribution of white race was not reported in most of the studies included in the DMC treatment guideline. For a selection of studies, the proportion of white race ranged from 28% in Targan et al. 1997(10), to 82.75-92.2% in GEMINI 2(6) and 95-96% in ACCENT I (12), which is comparable to 71.5% in VIVID-1.

Mean weight in kg varied across the included studies with values ranging from 68.4 kg to 74.2 kg (8, 10), compared to 68 kg in VIVID-1. Only GEMINI 3(8) reported mean body mass index (BMI) of 23.2 m^2/kg for the combined group of naïve patients and experienced vedolizumab patients. Similar BMI's were reported for the naïve and experienced patients, separately. These findings are comparable to the average BMI for patients treated with mirikizumab in VIVID-1 of 23.2.

Mean duration of disease varied from 7.5-8.7 years in ACCENT I (12), 7.73-9.58 years in CLASSIC-II (15), 8.4 years in GEMINI 3 (8), 9.2 years in GEMINI 2 (6) & Watanabe et al., 2012 (21) compared to 7.4 years in VIVID-1. Further, mean CDAI score in VIVID-1 is 323.1 with 340 patients registered with a CDAI score of 300 or above. This is comparable to most induction studies in the DMC treatment guideline, which applies a CDAI score of 220-450 for disease severity at inclusion (5-8, 10, 11).

Most studies have not reported mean Inflammatory Bowel Disease Questionnaire (IBDQ) score in the DMC guideline. However, for the reported studies the mean IBDQ score ranged from 116-118 in Targan et al. 1997(10), 120 in GAIN (7) and 126-131 in ACCENT I (12). This is comparable to 127.4 in VIVID-1.

The proportion of patients treated with systematic steroid ranged from 16-27% (n=12-20) in CLASSIC-I (5), 53% (n=110) in GEMINI 3 (8) compared to 45.3%(n=262) in VIVID-1.

The percentage of patients previously treated with biologics ranged from 58.8% (n=20) in Watanabe et al., 2012 (21), 50.5-67.7% in GEMINI 2 (6) and 76% (n=158) in GEMINI 3 (8) compared to 54.7% (n=317) in VIVID-1.

Overall, the studies included in the DMC treatment guideline and VIVID-1 are comparable across baseline characteristics.

Table 4 Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety

	VIVID-1	
	Mirikizumab	**Placebo**
Patients, n	579	199
Male sex, n (%)	332 (57.3)	118 (59.3)
Mean (SD) age, years	36.0 (13.2)	36.3 (12.7)
Race, white, n(%)	408 (71.5)	144 (74.6)
Mean (SD) weight, kg	68.0 (18.3)	69.6 (19.0)
Mean (SD) BMI, kg/m²	23.2 (5.4)	23.8 (5.8)
Mean (SD) duration of CD, years	7.4 (8.2)	7.8 (7.4)
≥5 years CD duration, n (%)	274 (47.4)	107 (53.8)
Mean (SD) CDAI	323.1 (85.8)	318.9 (86.2)
CDAI ≥300, n (%)	340 (59.4)	110 (56.4)
Mean IBDQ score	127.4 (33.2)	131.2 (32.4)
Prior biologic failure	281 (48.5)	97 (48.7)
Prior anti-TNF failure, n(%)	265 (45.8)	89 (44.7)
Prior anti-integrin failure, n(%)	68 (11.7)	24 (12.1)
Prior ustekinumab failure, n(%)	4 (0.7)	2 (1.0)
No prior biologic failure, n(%)	298 (51.5)	102 (51.3)
Exposed but not failed	36 (6.2)	12 (6.0)
Not exposed	262 (45.3)	90 (45.2)

CD, Crohn's disease; TNF, tumour necrosis factor.

5.2 Comparative analyses of efficacy and safety

5.2.1 Efficacy and safety – results per study

The results from VIVID-1 for the outcomes defined in the DMC treatment guideline for CD, are described for the total population and the BTSD-naïve population below. In VIVID-1 in general, mirikizumab demonstrated key benefits by providing statistically significant improvements in patients with CD across a broad spectrum of outcomes. Detailed results of mirikizumab versus placebo are provided in Appendix B.

Overall population:

Mirikizumab achieved statistically significant difference on the primary endpoint of clinical remission at week 12 compared with those treated with placebo (37.7% vs. 25.1%; Δ=12.4; *p*=<0.000001).

The difference in proportion of patients achieving clinical response by PRO at week 12 and endoscopic remission SES-CD ≤4 at Week 52 (non-responder imputation, NRI) were statistically significant (15.9% vs. 2.0%, Δ=13.8; *p*=<0.000001).

There was a statistically significant difference (43.7% vs. 18.6%; Δ=25.0; p <0.00001) in the clinical response by PRO at week 12 AND corticosteroid-free from week 40 to 52 and clinical remission by CDAI at week 52 (NRI), between the patients receiving mirikizumab and placebo-treated patients.

A lower proportion of SAEs was observed in mirikizumab-treated patients compared with placebo-treated patients during the induction phase, 5.9% vs. 9%, as well as for the treatment regimen analysis set (which evaluated the whole VIVID-1 study period from Week 0 to 52): 10.3% vs. 17.1%. For the treatment regimen analysis set, the system organ classes with SAEs reported in more than 1% of mirikizumab-treated participants were gastrointestinal disorders (5.4% in mirikizumab versus 10.4% in placebo) and infections and infestations (2.2% in mirikizumab versus 2.8% in placebo). Furthermore, most TEAEs were mild or moderate in severity. The most common TEAEs reported in mirikizumab-treated participants in the CD treatment regimen analysis were COVID-19 (16.5%), anaemia (6.7%), and headache (6.5%). For placebo the proportions for those same TEAEs were 13.7%, 6.6% and 4.3% respectively.

IBDQ response is defined as ≥16-point improvement from baseline and IBDQ remission is defined as an IBDQ total score ≥170. The difference of mirikizumab-treated patients achieving IBDQ response at week 52 were statistically significant compared to placebo (69.3% vs. 26.1%; Δ=43.2; p <0.00001). A larger proportion of mirikizumab-treated patients achieved an IBDQ remission at week 52 compared to placebo (58.5% vs. 19.6; Δ=39.0; p <0.00001).As mentioned in section 4, the endpoints for mirikizumab compared with placebo were also evaluated for mirikizumab compared with ustekinumab in the overall population but not all endpoints were adjusted for multiplicity. The results demonstrates that mirikizumab across most of the endpoints was associated with improvements that were at least similar and most often numerically higher compared with ustekinumab (data on file). More information can be provided upon request.

BTSD-naive population:

Not-biologic failed patients treated with mirikizumab achieved the primary endpoint of clinical remission at week 12 compared with those treated with placebo (39.6% vs. 25.5%; Δ=14.1; p=0. 011930).

The difference in proportion of patients achieving Clinical response by PRO at week 12 and endoscopic remission SES-CD ≤4 at Week 52 (NRI) were statistically significant (18.5.% vs. 2.9%, Δ=15.5; *p*=0.000031).

There was a statistically significant difference (46.6% vs. 24.5%; Δ=22.1; p <0.000072) in the Clinical response by PRO at week 12 AND corticosteroid-free from week 40 to 52 and clinical remission by CDAI at week 52 (NRI), between the patients receiving mirikizumab and placebo-treated patients.

IBDQ response is defined as ≥16-point improvement from baseline and IBDQ remission defined as IBDQ total score ≥170. The difference of mirikizumab-treated patients achieving IBDQ response at week 52 were statistically significant compared to placebo (70.5% vs. 33.3%; Δ=37.1; p <0.00001). A larger proportion of mirikizumab-treated patients achieved an IBDQ remission at week 52 compared to placebo (60.1% vs. 24.5; Δ=35.6; p <0.00001).

Analysis on SAEs were not stratified on biologic and not biologic failed in VIVID-1, hence data is not available to include in the application or in appendix B. Please see the results regarding the overall population.

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

Overall, the frequencies of TEAEs, SAEs, and discontinuations due to AEs were higher in the placebo group compared with the mirikizumab group in the CD induction analysis set, which evaluated the induction period of VIVID-1 from Week 0 to 12. Moreover, SAEs, and discontinuations were higher in placebo-treated participants compared with those receiving mirikizumab in the CD treatment regimen analysis set, which evaluated the whole VIVID-1 study period from Week 0 to 52.

In both CD analysis sets, most TEAEs were mild or moderate in severity. The highest proportion of severe TEAEs occurred in the placebo group of the CD induction analysis set (7.1%) and the CD treatment regimen analysis set (15.2%). These were mainly related to CD complications and most likely represented the lack of efficacy of placebo treatment. The most common TEAEs reported in mirikizumab-treated participants in CD treatment regimen analysis set were COVID-19 (16.5%, n=104), anaemia (6.7%, n=42), and headache (6.5%, n=41). Compared to placebo the proportions for those same TEAEs were 13.7% (n=29), 6.6% (n=14), and 4.3% (n=9) respectively.

During the induction period the percentage of participants that reported at least 1 TEAEs was 56.4% (n=119) in placebo, and 51.7% (n=326) in the mirikizumab group. In the maintenance phase the proportion of patients reporting at least 1 was 73% (n=154) in the placebo group and 78.6% (n=495) in the mirikizumab group.

The frequency of serious infections was low overall. A comparable rate of serious infections was observed across treatment groups in the CD Induction Analysis Set; 0.5 (n=1) in placebo and 1.1% (n=7) in mirikizumab. Similar tendencies were observed during CD treatment regimen analysis set; 2.8% (n=6) in placebo and 2.2% (n=14) in mirikizumab.

Opportunistic infections were infrequently reported. During the induction period, 0 incidences were reported amongst patients receiving placebo. For mirikizumab 0.6% (n=4) of the group reported an opportunistic infection.

Infusion site reactions were infrequently reported. Only one participant (0.2%) in the mirikizumab group of the CD induction analysis set experienced an infusion reaction (pruritus at infusion site) compared to 0 patients in the placebo group. In the CD treatment regimen analysis set, the corresponding numbers were 6.5% (n=7) and 10.8% (n=65) reported in the placebo and mirikizumab group, respectively. Immediate hypersensitivity reactions were reported by 1.4% (n=3) patients in the placebo group and 1.9% (n=12) patients treated with mirikizumab during the induction phase. In the CD treatment regimen analysis set, 2.4% (n=5) and 3.8% (n=24) were reported in the placebo and mirikizumab group, respectively.

During the induction analysis hepatic events were reported by 2.8% (n=6) patients in placebo treatment and 1.9% (n=12) patients treated with mirikizumab. In the CD treatment regimen analysis set a frequency of 4.3% (n=9) and 6.2% (n=39) was observed amongst placebo and mirikizumab patients, respectively.

Based on safety data from VIVID-1, the overall safety profile of mirikizumab in patients with CD was consistent with the known safety profile. No new or unexpected safety findings were noted up to 52 weeks of treatment.

5.2.3 Method of synthesis

Not applicable as the current treatment guideline includes an NMA, and according to DMC guidance this section can be omitted.

5.2.4 Results from the comparative analysis

Not applicable as the current treatment guideline includes an NMA, and according to DMC guidance this section can be omitted.

6. Clinical question 2

6.1 Efficacy of mirikizumab compared to best available treatment for BTSD-experienced adult patients with moderately to severely active CD

6.1.1 Relevant studies

A total of 12 randomized controlled trials and 12 articles from the literature search have been included in the DMC treatment guideline. In addition, EMA's product summaries have been accessed when describing known and serious adverse reactions. The studies were published from 2002-2018 and include randomized controlled, double-blind and single-blind studies, which are primarily phase 2 and 3 studies. The patient populations are generally comparable in the included studies and in accordance with the Danish patient population.

This section presents data for the BTSD-experienced population. The DMC treatment guideline bases the comparison for PICO 2 on the outcomes outlined below in Table 5.

Table 5 Overview of outcomes included for PICO 2 in the DMC treatment guideline for CD

Outcome	Outcome measure
Clinical remission after induction therapy (weeks 6-8)	Proportion of patients with total CDAI-score ≤150.
Systemic steroid-free remission with maintenance therapy (week 52)	Proportion of systemic steroid-free patients having a total CDAI-score ≤150 at week 52
Adverse events*	Proportion of patients experiencing one or more SAE. Qualitative review of adverse reaction profile.
Endoscopic/imaging remission during maintenance treatment (week 52)	Proportion of patients achieving endoscopic/ diagnostic imaging remission
Quality of life*	Proportion of patients achieving a score ≥ 170 on the IBDQ. Difference in change from baseline on IBDQ.

* For these endpoints, data with the longest possible follow-up time is desired

Abbreviations: CDAI, Crohn's Disease Activity Index; IBDQ, Inflammatory Bowel Disease Questionnaire; SAE, Serious Adverse Event

Source: Medicinrådet 2021 (1, 22)

6.1.2 Comparability of studies

See description in section 5.1.2.

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

See section 5.1.3 and Table 4 Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety.

6.2 Comparative analyses of efficacy and safety

6.2.1 Efficacy and safety – results per study

The results from VIVID-1, for the outcomes defined in the DMC treatment guideline for CD, are described for BTSD-experienced patients below. The results for the total population and the BTSD-naïve are described in section 5.2.1. The results are also provided in Appendix B. However, as stated in section 5.2.1, results for SAEs were not reported by BTSD status (prior biologic failed status) thus only presented for total population.

BTSD-experienced population:

More patients with prior biologic failure treated with mirikizumab achieved the primary endpoint of clinical remission at week 12 compared with those treated with placebo (35.6% vs. 24.7%; Δ=10.8; p=0. 059707).

The difference in proportion of patients achieving clinical response by PRO at week 12 and endoscopic remission SES-CD ≤4 at Week 52 (NRI) were statistically significant (13.2.% vs. 1%, Δ=12.1; *p*=0.000140).

There was a statistically significant difference (40.6% vs. 12.4%; Δ=28.2; p <0.000001) in the Clinical response by PRO at week 12 AND corticosteroid-free from week 40 to 52 and clinical remission by CDAI at week 52 (NRI), between the patients receiving mirikizumab and placebo-treated patients.

IBDQ response is defined as ≥16-point improvement from baseline and IBDQ remission defined as IBDQ total score ≥170. The difference of mirikizumab-treated patients achieving IBDQ response at week 52 were statistically significant compared to placebo (68.0% vs. 18.6%; Δ=49.4; p <0.00001). A larger proportion of mirikizumab-treated patients achieved an IBDQ remission at week 52 compared to placebo (56.9% vs. 14.4; Δ=42.5 p <0.00001).

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

Please see section 5.2.2.

6.2.3 Method of synthesis

Not applicable as the current treatment guideline includes an NMA, and according to DMC guidance this section can be omitted.

6.2.4 Results from the comparative analysis

Not applicable as the current treatment guideline includes an NMA, and according to DMC guidance this section can be omitted.

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Appendix A. Main characteristics of studies included

Table 6 Main characteristics of studies included

Trial name: Vivid-1 (I6T-MC-AMAM)	NCT number: NCT03926130
Objective	To test the safety and efficacy of mirikizumab in moderately to severely active Crohn's disease.
Publications – title, author, journal, year	Efficacy and safety of mirikizumab in patients with moderately-to-severely active Crohn's disease: a phase 3, multicentre, randomised, double-blind, placebo-controlled and active-controlled, treat-through study. Ferrante, MarcTron, Emiliano et al. 2024. The Lancet, Volume 404, Issue 10470, 2423 - 2436
Study type and design	A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-and Active-Controlled, treat-through study to evaluate the efficacy and safety of Mirikizumab in patients with moderately to severely active Crohn's disease. Treat-through study with participants being a 6:3:2 ratio to receive mirikizumab (900 mg IV Q4W at Weeks 0, 4, and 8), ustekinumab (~6 mg/kg IV at Week 0 and 90 mg SC Q8W starting at Week 8), or placebo during the 12-week induction phase. Participants in the mirikizumab and ustekinumab groups continued to receive the same medication in the blinded maintenance phase of the trial (Weeks 12 to 52) regardless of treatment response in the induction period. Placebo-treated participants who responded to treatment continued to receive placebo in the maintenance phase while non-responders received blinded mirikizumab.
Sample size (n)	The sample size consisted of 1065 modified intention-to-treat patients
Main inclusion criteria	• Diagnosis of CD for at least 3 months prior to baseline • Confirmed diagnosis of moderate to severe CD as assessed by SF, AP score, and SES-CD • Demonstrated intolerance, loss of response or inadequate response to conventional or to biologic therapy for CD • If female, subject must meet the contraception recommendations
Main exclusion criteria	• Have a current diagnosis of ulcerative colitis, inflammatory bowel disease-unclassified (IBD-U) (formerly known as indeterminate colitis) or short bowel syndrome • Currently have or are suspected to have an abscess. Recent cutaneous and perianal abscesses are not exclusionary if drained, adequately treated and resolved at least 3 weeks prior to baseline or 8 weeks prior to baseline for intra-abdominal abscesses, provided that there is no anticipated need for any further surgery

Trial name: Vivid-1 (I6T-MC-AMAM)		NCT number: NCT03926130
	• Have a stoma, ileoanal pouch or ostomy • Have had a bowel resection within 6 months, or any kind of intra-abdominal or extra abdominal surgery within 3 months of baseline • Have ever received any monoclonal antibodies binding IL-23	
Intervention	In the induction period participants received mirikizumab 900 mg IV Q4W at Weeks 0, 4, and 8. In the maintenance period (week 12 to 52) participants received 300 mg SC Q4W. 579 participants received mirikizumab,	
Comparator(s)	Placebo given as an IV and SC dosing, as applicable, at weeks 12 to 20, then SC placebo weeks 24 to 52. Ustekinumab given as IV at week 0 and SC Q8W starting at week 8.	
Follow-up time	Participants who completed VIVID-1 at Week 52 were eligible to enroll in the LTE study, VIVID-2. Individuals who did not meet enrolment criteria for VIVID-2 or who declined to participate in VIVID-2 entered a post-treatment follow-up period consisting of two visits at 4 weeks and 12–16 weeks after the last study visit in VIVID-1.	
Primary, secondary and exploratory endpoints	Percentage of patients achieving clinical remission at week 12. Percentage of patients achieving clinical response at week 12 and corticosteroid-free clinical remission at week 52. Percentage of patients achieving clinical response at week 12 and endoscopic remission at week 52. Proportion of patients experiencing one or more SAE (up to 52 Weeks). Change from Baseline in IBDQ Total Score at week 52	
Method of analysis	All efficacy analyses were intention-to-treat analyses. Treatment comparisons of categorical efficacy measures between mirikizumab versus placebo or ustekinumab were made using the Cochran-Mantel-Haenszel (CMH) test adjusting for selected stratification factors with non-responder imputation (NRI). Treatment comparisons of continuous longitudinal efficacy measures were made using analysis of covariance (ANCOVA). Participants who completed study treatment up to the time point of interest but were sporadically missing binary endpoint data were imputed using NRI. NRI was also used for all visits after Week 12 when the estimate of interest used the hypothetical strategy for handling the additional intercurrent event of participants in the placebo group beginning study intervention with mirikizumab at Week 12. The ANCOVA with modified baseline observation carried forward (mBOCF) approach was used as the primary analysis for handling missing data for continuous variables. The study was powered for the overall population. A significance level of 0.05 was applied.	

Trial name: Vivid-1 (I6T-MC-AMAM)		NCT number: NCT03926130
Subgroup analyses	Subgroup analyses were conducted for all primary and major secondary endpoints using the mITT population. The categories of subgroups analysed included biologic-failed and not-biologic-failed. The study was powered for the overall population.	
Other relevant information	*N/A*	

Abbreviations: CD, Crohn's Disease; IBDQ, Inflammatory Bowel Disease Questionnaire; IV, intravenous; mg, milligram; mITT, modified intention-to-treat, N/A, not applicable; Q4W/Q8W, every 4 or 8 weeks; SAE, Serious adverse event; SC, subcutaneous

Appendix B. Efficacy results per study

Table 7 Results per study

Results of VIVID-1 (NCT03926130)											
				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 by CDAI at week 12	900 mg mirikizumab IV Q4W	579	37.7% (32.0, 43.3)*	12.4	2.2, 22.7*	0.001431	1.49	1.03, 2.17*	0.001431	The common risk difference is the difference in proportions adjusted for the stratification factor(s): baseline SES-CD total score (<12, >=12), either baseline SF >=7 and/or baseline AP >=2.5 (yes or unknown/no), where the confidence intervals are calculated using Mantel-Haenszel-Sato method. The relative risk and odds ratio are also adjusted for the same stratification factor(s). Confidence intervals are constructed using the	Data on file

Results of VIVID-1 (NCT03926130)											
				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**		
										asymptotic method, without continuity correction (that is, normal approximation to the binomial distribution). Cochran-Mantel-Haenszel (CMH) test adjusted by baseline SES-CD total score (<12, >=12), either baseline SF >=7 and/or baseline AP >=2.5 (yes or unknown/no).	
	~6 mg/kg Ustekinumab IV + 90 mg SC Q8W	287	37.3% (29.3, 45.3)*	12.0	0.3, 23.7*	0.005126	1.47	0.99, 2.20*	0.005126		
	Placebo	199	25.1%								

Results of VIVID-1 (NCT03926130)											
				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**		
			(16.5, 33.8)*								
BTSD-naïve: Clinical remission by CDAI at week 12	900 mg Mirikizumab IV Q4W	298	39.6% (31.6, 47.5)	13.6	-0.7, 28.0*	0.012798	1.53	0.92, 2.55*	0.012798	See above	Data on file
	~6 mg/kg Ustekinumab IV + 90 mg SC Q8W	148	38.5% (27.3, 49.7)	12.3	-3.9, 28.4	0.039555	1.47	0.86, 2.52*	0.039555		
	Placebo	102	25.5% (13.4, 37.6)								

Results of VIVID-1 (NCT03926130)											
				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**		
BTSD-experienced: Clinical remission by CDAI at week 12	900 mg mirikizumab IV Q4W	281	35.6% (27.6, 43.6)	11.1	-3.4, 25.7*	0.044322	1.45	0.84, 2.50*	0.044322	See above	Data on file
	~6 mg/kg ustekinumab IV + 90 mg SC Q8W	139	36.0% (24.5, 47.4)*	11.7	-5.1, 28,5*	0.057601	1.48	0.82, 2.67*	0.057601		
	Placebo	97	24.7% (12.4, 37.0)*								
Clinical response by PRO week 12 AND	900 mg mirikizumab IV Q4W (induction)+	579	43.7% (37.9, 49.5)*	25.0	15.2, 34.7*	<0.000001	2.34	1.51, 3.63*	<0.000001		Data on file

Results of VIVID-1 (NCT03926130)											
				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**		
Corticosteroid-free from Week 40 to Week 52 and clinical remission by CDAI at week 52	300 mg SC Q4W (maintenance)										
	~6 mg/kg ustekinumab IV + 90 mg SC Q8W	287	39.0% (30.9, 47.1)*	20.3	9.2, 31.4*	0.000002	2.09	1.32, 3.30*	0.000002		
	Placebo	199	18.6% (10.9, 26.3)*								
BTSD-naïve: Clinical response by PRO week 12 AND Corticosteroi	900 mg mirikizumab IV Q4W (induction)+ 300 mg SC Q4W	298	46.6% (38.5, 54.8)*	22.1	12.0, 32.2*	p=0.000089	1.90	1.13,3.20*	0.000089		Data on file

Results of VIVID-1 (NCT03926130)											
				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**		
d-free from Week 40 to Week 52 and clinical remission by CDAI at week 52	(maintenance)										
	~6 mg/kg ustekinumab IV + 90 mg SC Q8W	148	43.2% (31.8, 54.7)*	18.3	1.9, 34.8*	0.002832	1.74	1.01, 3.02*	0.002832		
	Placebo	102	24.5% (12.6, 36.6)*								
BTSD-experienced: Clinical response by	900 mg mirikizumab IV Q4W (induction)+	281	40.6% (32.3, 48.8)*	28.2	15.3, 40.6*	<0.000001	3.27	1.48, 7.24*	<0.000001		Data on file

Results of VIVID-1 (NCT03926130)											
				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**		
PRO week 12 AND Corticosteroid-free from Week 40 to Week 52 and clinical remission by CDAI at week 52	300 mg SC Q4W (maintenance)										
	~6 mg/kg ustekinumab IV + 90 mg SC Q8W	139	34.5% (23.2, 45.9)*	22.3	7.6, 37.0*	0.000127	2.81	1.23, 6.45*	0.000127		
	Placebo	97	12.4% (3.0, 21.8)*								
Clinical response by PRO at Week 12 AND endoscopic remission	900 mg mirikizumab IV Q4W (induction)+ 300 mg SC Q4W	579	15.9% (11.6, 20.2)*	13.8	8.7-18.9*	<0.000001	7.8	1.91, 32.57*	<0.000001	The common risk difference is the difference in proportions adjusted for the stratification factor(s): baseline SES-CD total score (<12, >=12), either baseline SF >=7 and/or baseline AP >=2.5 (yes or unknown/no),	Data on file

Results of VIVID-1 (NCT03926130)											
				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**		
SES-CD ≤4 at Week 52	(maintenance)									where the confidence intervals are calculated using Mantel-Haenszel-Sato method. The relative risk and odds ratio are also adjusted for the same stratification factor(s). Confidence intervals are constructed using the asymptotic method, without continuity correction (that is, normal approximation binomial distribution). Cochran-Mantel-Haenszel (CMH) test adjusted by baseline SES-CD total score (<12, >=12), either baseline SF >=7 and/or baseline AP >=2.5 (yes or unknown/no).	

Results of VIVID-1 (NCT03926130)											
				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**		
	~6 mg/kg ustekinumab IV + 90 mg SC Q8W	287	14.6% (8.8, 20.5)*	12.6	6.2, 19.1*	0.000003	7.24	1.73, 30.41*	0.000003		
	Placebo	199	4.0% (0.1, 7.9)*								
BTSD-naïve: Clinical response by PRO at Week 12 AND endoscopic remission SES-CD ≤4 at Week 52	900 mg mirikizumab IV Q4W (induction)+ 300 mg SC Q4W (maintenance)	298	18.5% (12.1, 24.8)*	15.3	7.3, 23.1*	0.000146	6.15	1.20, 31.59*	0.000146	See above	Data on file
	~6 mg/kg ustekinumab	148	18.2% (9.3, 27.2)*	15.2	5.1, 25.3*	0.000322	6.07	1.15, 32.00*	0.000322		

Results of VIVID-1 (NCT03926130)											
				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**		
	IV + 90 mg SC Q8W										
	Placebo	102	2.9% (0.0, 7.6)*								
BTSD-experienced: Clinical response by PRO at Week 12 AND endoscopic remission SES-CD ≤4 at Week 52	900 mg mirikizumab IV Q4W (induction)+ 300 mg SC Q4W (maintenance)	281	13.2% (7.5, 18.8)	12.3	5.9, 18.7*	0.000551	13.24	0.75, 100*	0.000551	See above	Data on file
	~6 mg/kg ustekinumab IV + 90 mg SC Q8W	139	10.8% (3.4, 18.2)	10.0	2.1, 17.8*	0.002254	10.94	0.62, 100*	0.002254		

Results of VIVID-1 (NCT03926130)											
				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**		
	Placebo	97	1.0% (0.0, 3.9)								
Change from Baseline in IBDQ Total Score at week 52	900 mg mirikizumab IV Q4W (induction) + 300 mg Q4W mirikizumab SC (maintananc e)	579	43.8%	27.9	22.7- 33.2*	<0.000001	N/A	N/A	N/A		Data on file
	~6 mg/kg ustekinumab IV + 90 mg SC Q8W	287	41.04%	25.1	19.2, 31.0*	<0.000001	NA	NA	NA		
	Placebo	199	15,9%								

Results of VIVID-1 (NCT03926130)											
				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**		
Proportion of patients experiencing one or more SAE (up to 52 Weeks)	300 mg mirikizumab SC Q4W	630	10.3%	N/A	N/A	N/A	N/A	N/A	N/A		Data on file
	~6 mg/kg ustekinumab IV + 90 mg SC Q8W	309	10.7%	N/A	N/A	N/A	N/A	N/A	N/A		
	Placebo	211	17.1%								

* 99. 5% CI

CDAI, Crohn's Disease Activity Index; IV, intravenous; N/A, not applicable; PRO, patient reported outcomes, Q4W, every four weeks; SAE, Serious adverse event; SC, subcutaneous

Appendix C. Comparative analysis of efficacy

Not applicable as DMC has conducted a NMA which forms the basis for relative efficacy and safety versus other comparators in the treatment guideline.

Appendix D. Literature searches for clinical assessment

Not applicable as DMC has conducted an NMA which forms the basis for relative efficacy and safety versus other comparators in the treatment guideline.

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