

**5.15 USTEKINUMAB,  
Injection 90 mg in 1 mL pre-filled syringe,  
Solution concentrate for I.V. infusion 130 mg in  
26 mL  
Stelara<sup>®</sup>,  
Janssen-Cilag Pty Ltd.**

**1 Purpose of submission**

- 1.1 The Category 2 submission requested Authority Required listings for ustekinumab (UST) vial for intravenous (IV) infusion (Section 100) and pre-filled syringe for subcutaneous (SC) injection (General Schedule), for the treatment of moderate to severe ulcerative colitis (MSUC).
- 1.2 Listing was requested on the basis of a cost-minimisation approach versus VDZ. The PBAC recommended ozanimod (OZA) for the treatment of MSUC at the March 2022 PBAC meeting, but OZA is not yet listed on the PBS. The PBAC will also consider upadacitinib (UPA) for MSUC at the July 2022 PBAC.

**Table 1: Key components of the clinical issue addressed by the submission (as stated in the submission)**

<b>Component</b>	<b>Description</b>
Population	Adult patients with MSUC who have had an inadequate response (or who are intolerant <sup>^</sup> ) to conventional therapy.
Intervention	UST IV infusion (~6 mg/kg*) at Week 0, then UST 90 mg SC injection at Week 8 and every 8 or 12 weeks thereafter.
Comparator	Primary comparator: VDZ 300 mg IV infusion at Weeks 0, 2, 6 and every 8 weeks thereafter. Secondary comparator: ADA SC injection, 160 mg at Week 0, 80 mg at Week 2 then 40 mg every 2 weeks thereafter.
Outcomes	Indirect comparison of UST and VDZ was conducted for the following outcomes, for induction and maintenance therapy (taking into account differences in trial design): Clinical remission, clinical response, mucosal healing
Clinical claim	Primary comparator: UST is as effective as VDZ in induction and maintenance treatment, and non-inferior in terms of safety compared to VDZ. Secondary comparator: <ul style="list-style-type: none"> <li>○ Effectiveness: UST is more effective than ADA in induction and maintenance treatment.</li> <li>○ Safety: UST is non-inferior in terms of safety compared to ADA in induction and maintenance treatment.</li> </ul>

Source: Table 1-1, 21 of submission.

ADA = adalimumab; GOL = golimumab; IFX = infliximab; MSUC = moderate to severe ulcerative colitis; OZA = ozanimod; TOF = tofacitinib; UST = ustekinumab; VDZ = vedolizumab; IV = intravenous; SC = subcutaneous.

<sup>^</sup> Table 1-1 (p21 of the submission) reported the proposed population as patients with an inadequate response to conventional therapy, but the proposed PBS restriction includes patients who are intolerant to conventional therapy.

\* UST IV 260 mg for weight ≤ 55 kg; UST IV 390 mg for weight > 55 kg and ≤ 85 kg; UST IV 520 mg for weight > 85 kg.

## 2 Background

### Registration status

- 2.1 UST was TGA registered on 19 May 2020 for: ‘adult patients with moderately to severely active ulcerative colitis’.

### Previous PBAC consideration

- 2.2 The PBAC has not previously considered UST for MSUC. UST is PBS listed for chronic plaque psoriasis (March 2010), paediatric chronic plaque psoriasis (October 2021), psoriatic arthritis (May 2016) and Crohn’s disease (September 2017).
- 2.3 There are currently two formulations of UST listed on the PBS: UST 45 mg pre-filled syringe for SC injection and UST 130 mg solution concentrate for IV infusion (only listed for Crohn’s disease). For MSUC, the sponsor requested PBS listing for the UST 130 mg solution concentrate for IV infusion and a new UST 90 mg pre-filled syringe for SC injection. The submission stated that the PBAC will also consider at the July 2022 meeting a (Category 4) submission to list the UST 90 mg SC injection for other PBS indications (replacing the need to use 2x45 mg SC injections).

## 3 Requested listing

- 3.1 The sponsor requested PBS listing of the UST 130 mg solution concentrate for IV infusion for initial treatment, and the UST 90 mg pre-filled syringe for SC injection for initial and continuing treatment. An abbreviated version of the requested restrictions for initial and continuing treatment is presented below.

Name, restriction, manner of administration, form	Maximum quantity (packs)	Maximum quantity (units)	No. of repeats	Dispensed price for maximum quantity	Proprietary name and manufacturer
USTEKINUMAB					
<b>Initial treatment</b>					
130mg/26mL injection, 26mL vial	4	4	0	\$15,236.32* (public); \$15,284.10* (private)	Stelara®, Janssen-Cilag
<b>Initial treatment</b>					
90mg/1mL injection, 1mL vial	1	1	0 <sup>a</sup>	\$3,943.23*	Stelara®, Janssen-Cilag
<b>Continuing treatment</b>					
90mg/1mL injection, 1mL vial	1	1	2 <sup>b</sup> / 1 <sup>c</sup>	\$3,943.23*	Stelara®, Janssen-Cilag
Category/Program:	GENERAL – General Schedule (Code GE) for SC injection Section 100 – Highly Specialised Drugs Program {Community Access} for IV loading dose (tiered weight-based)				
PBS indication:	Moderate to severe ulcerative colitis				
Treatment phase:	Initial treatment 1 (new patient)				
Restriction:	<input checked="" type="checkbox"/> Authority Required - In Writing				
Treatment criteria:	Must be treated by a gastroenterologist or consultant physician [internal medicine specialising in gastroenterology] or consultant physician [general medicine specialising in gastroenterology]				

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Clinical criteria:	Patient must have failed to achieve an adequate response to a 5-aminosalicylate oral preparation in a standard dose for induction of remission for 3 or more months or have intolerance necessitating permanent treatment withdrawal, AND Patient must have failed to achieve an adequate response to azathioprine at a dose of at least 2 mg per kg daily for 3 or more months or have intolerance necessitating permanent treatment withdrawal; OR Patient must have failed to achieve an adequate response to 6-mercaptopurine at a dose of at least 1 mg per kg daily for 3 or more months or have intolerance necessitating permanent treatment withdrawal; OR Patient must have failed to achieve an adequate response to a tapered course of oral steroids, starting at a dose of at least 40 mg prednisolone (or equivalent), over a 6 week period or have intolerance necessitating permanent treatment withdrawal, and followed by a failure to achieve an adequate response to 3 or more months of treatment of an appropriately dosed thiopurine agent, AND Patient must have a Mayo clinic score greater than or equal to 6; OR Patient must have a partial Mayo clinic score greater than or equal to 6, provided the rectal bleeding and stool frequency subscores are both greater than or equal to 2 (endoscopy subscore is not required for a partial Mayo clinic score).
Population criteria:	Patient must be aged 18 years or older.
Prescriber criteria:	An assessment of a patient's response to this initial course of treatment must be conducted between 8 and 16 weeks of therapy. A maximum of 16 weeks of treatment with this drug will be approved under this criterion.
Category/Program:	GENERAL – General Schedule (Code GE) for SC injection
PBS indication:	Moderate to severe ulcerative colitis
Treatment phase:	Continuing treatment
Restriction:	<input checked="" type="checkbox"/> Authority Required - In Writing
Treatment criteria:	Must be treated by a gastroenterologist or consultant physician [internal medicine specialising in gastroenterology] or consultant physician [general medicine specialising in gastroenterology]
Clinical criteria:	Patient must have previously received PBS-subsidised treatment with this drug for this condition AND Patient must have demonstrated or sustained an adequate response to treatment by having a partial Mayo clinic score less than or equal to 2, with no subscore greater than 1 while receiving treatment with this drug.
Population criteria:	Patient must be aged 18 years or older.
Prescriber criteria:	Patients are eligible to receive continuing treatment with this drug in courses of up to 24 weeks providing they continue to sustain a response.

Source: Table 1-7, p54 of the submission.

\* Published price; the submission requested a special pricing arrangement, where the effective price is based on a cost-minimisation with VDZ using the effective AEMP (currently unknown to the sponsor).

<sup>a</sup> Week 8 dose for induction treatment.

<sup>b</sup> Continuing treatment; 8-weekly dosing.

<sup>c</sup> Continuing treatment; 12-weekly dosing.

3.2 The restriction criteria were equivalent to other PBS-listed treatments for MSUC. For initial treatment, the requested maximum quantity of 4 x 130 mg vials (no repeats) and 1 x 90 mg pre-filled syringe (no repeats) allows for a 16 week induction period, where clinicians can prescribe the appropriate weight-based dose for IV infusion at Week 0 (up to a maximum of 520 mg) and the 90 mg SC injection at Week 8. For continuing treatment, the requested maximum quantity of 1 x 90 mg pre-filled syringe

provides for 24 weeks of treatment at the recommended 12-weekly dosing regimen with 1 repeat, and the recommended 8-weekly dosing regimen with 2 repeats.

- 3.3 The submission requested a Special Pricing Arrangement (SPA). The proposed published AEMP of \$3,809.08 per 130 mg vial and a 90 mg pre-filled syringe is consistent with the published price of UST formulations listed for other PBS indications (currently the 130 mg vial and 45 mg pre-filled syringe; the PBAC will also consider an application to list the 90 mg pre-filled syringe for other indications at the July 2022 meeting). The sponsor requested an effective price based on a cost-minimisation analysis with VDZ using the effective AEMP (currently unknown to the sponsor). The submission presented an ‘illustrative’ cost-minimisation analysis using the published price of VDZ, and requested that an updated analysis using the effective AEMP of VDZ follow the same methodology.

*For more detail on PBAC’s view, see section 7 PBAC outcome.*

## **4 Population and disease**

- 4.1 Ulcerative colitis is a life-long, chronic relapsing and remitting inflammatory disease that involves ulceration of the mucosa of the colon. Patients with ulcerative colitis most commonly present with bloody diarrhoea, rectal bleeding, tenesmus (sensation of incomplete defecation), abdominal pain, and passage of mucus. Patients with MSUC may also have systemic symptoms, including fatigue, fever, anorexia, nausea, weight loss, and dehydration. The most serious complications of ulcerative colitis are bowel perforation and colorectal cancer.
- 4.2 The Mayo score is an indicator of disease activity based on assessment/grading of disease across up to four categories (endoscopy, stool frequency, rectal bleeding and physician’s global assessment). Over time, different permutations of the Mayo score have been developed to define severity of disease and assess response to treatment. The original full Mayo score incorporates the subscores of all four categories; the partial Mayo score excludes the endoscopic subscore; and the more recent modified/adapted Mayo score (recommended by the FDA in 2016<sup>1</sup>) excludes the physician rating sub-score (as well as excluding friability from endoscopic score of 1). The trials included in the submission all used the full Mayo score to define disease severity and response to treatment (i.e. clinical outcomes).
- 4.3 If listed, UST would become the first IL-12/23 inhibitor available on the PBS for MSUC and the sixth treatment option for patients including tofacitinib (TOF), infliximab (IFX), vedolizumab (VDZ), adalimumab (ADA), and golimumab (GOL).

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<sup>1</sup> FDA Guidance Document, 2016. *Ulcerative Colitis: Clinical Trial Endpoints Guidance for Industry*. Available from: <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/ulcerative-colitis-clinical-trial-endpoints-guidance-industry>

- 4.4 Under current PBS criteria, patients with MSUC (full Mayo score  $\geq 6$  or partial Mayo score  $>6$  provided both rectal bleeding and stool frequency subscores  $\geq 2$ ), who have failed (or are unable to tolerate) a 5-aminosalicylate (5-ASA) oral agent and at least one of azathioprine, mercaptopurine or oral steroids, are eligible for treatment with TOF (JAK inhibitor), IFX, GOL or ADA (TNF inhibitors), VDZ (integrin inhibitor). The addition of UST (IL-12/23 inhibitor) to the clinical management algorithm will not alter current practice, but will allow for an additional option with a different mechanism of action.

*For more detail on PBAC's view, see section 7 PBAC outcome.*

## 5 Comparator

- 5.1 The submission nominated VDZ as the main comparator (on the basis that it is the most commonly used treatment for MSUC) and ADA as a secondary comparator. The submission also acknowledged that the PBAC had previously considered any of the other currently listed treatments (including TOF, IFX and GOL) to be relevant comparators. The submission noted that ADA was a second-tier biologic with inferior effectiveness compared to alternative treatments (listed on the PBS on the basis of it being less effective but less costly than IFX and VDZ), and presented evidence to demonstrate that UST was superior to ADA.
- 5.2 The nomination of all PBS-listed treatments for MSUC as relevant comparators was appropriate given UST may reasonably replace any of these alternative treatments in practice. Given the PBAC recommended OZA for MSUC at the March 2022 and will consider UPA for MSUC at the July 2022, both of these treatments may be considered as near-market comparators.
- 5.3 A further consideration for PBAC is that, under Section 101(3B) of the *National Health Act 1953*, when the proposed medicine is substantially more costly than an alternative therapy, the committee cannot make a positive recommendation unless it is satisfied that, for some patients, the proposed medicine provides a significant improvement in efficacy and/or reduction of toxicity over the alternative therapy. If the committee is so satisfied, it must make a statement to this effect.

*For more detail on PBAC's view, see section 7 PBAC outcome.*

## 6 Consideration of the evidence

### ***Sponsor hearing***

- 6.1 The sponsor requested a hearing for this item. The clinician discussed the effectiveness of UST in MSUC and presented information on persistence to biologic therapy in the Australian context, based on PBS prescribing data. The hearing noted the persistence to therapy of UST was high in its current listings for Crohn's disease

and also highlighted that persistence to first-line therapy with VDZ was higher than IFX or ADA in MSUC. The clinician stated that the lower persistence to anti-tumour necrosis factor alfa (TNF-a) agents may be due to the development of anti-drug antibodies or other factors which may be contributing to a loss of effectiveness over time compared to agents with other mechanisms of action, such as VDZ.

### **Consumer comments**

- 6.2 The PBAC noted and welcomed the input from individuals (2), health care professionals (15) and organisations (2), including IBD Sydney and Crohn's and Colitis Australia, via the Consumer Comments facility on the PBS website. The comments from health professionals highlighted the effectiveness of UST in MSUC and noted it was associated with fewer infections than some of the alternative therapies for the condition, and described the burden of disease and quality of life impacts of ulcerative colitis and the ability for many patients to return to a normal life with effective treatments such as UST. The comments from individuals highlighted the disease burden of MSUC and outlined the benefits of UST treatment included substantial symptom improvement, which allowed them to live a normal life and undertake daily activities without the constant burden of disease symptoms.
- 6.3 The comments from IBD Sydney described ustekinumab as being effective for inflammatory bowel disease (IBD) conditions, without causing systemic immunosuppression and side effects compared to alternative drugs, and also appeared to be less prone to the development of anti-drug antibodies. The comments from Crohn's and Colitis Australia outlined the benefits and convenience of a self-administered injectable therapy for some patients for the management of their ulcerative colitis. The input from Crohn's and Colitis Australia also shared patient experiences with ustekinumab treatment for ulcerative colitis and Crohn's disease, where the patients described the effectiveness of ustekinumab for their condition and described a range of benefits of treatment including reduced sleep interruption, improved concentration at work and improved freedom have a social life and participate in sports and other activities.

### **Clinical trials**

- 6.4 There were no head-to-head trials of UST vs. VDZ (main comparator) or ADA (supplementary comparator) for the treatment of MSUC. The submission presented indirect comparisons using placebo (PBO) as common reference, based on:

Six randomised controlled trials (RCTs) for induction therapy:

- UST vs. PBO (one RCT): UNIFI (induction phase);
- VDZ vs. PBO (two RCTs): GEMINI 1 (induction phase), Motoya 2019 (induction phase);
- ADA vs. PBO (three RCTs): ULTRA I, ULTRA II (induction phase); Suzuki 2014 (induction phase).

Six RCTs for maintenance therapy:

- UST vs. PBO (one RCT): UNIFI (maintenance phase);
- VDZ vs. PBO (three RCTs): GEMINI 1 (maintenance phase), Motoya 2019 (maintenance phase); VISIBLE 1;
- ADA vs. PBO (two RCTs): ULTRA II (maintenance phase); Suzuki 2014 (maintenance phase).

6.5 For maintenance therapy, the submission argued that differences in trial designs and a long carry-over effect with UST (impacting patients re-randomised to PBO for maintenance therapy) meant that the standard indirect treatment comparisons biased against UST for maintenance treatment. To account for this bias, the submission proposed a modelling approach to convert results from the randomised withdrawal trials to mimic results of treat-through trials prior to conducting the indirect treatment comparisons (see Comparative effectiveness). For these ‘trial-design-adjusted’ indirect treatment comparisons, the submission excluded VISIBLE 1 because the open label induction phase meant that treat-through results could not be estimated; the submission also excluded Suzuki 2014 from the adjusted comparisons but did not provide any justification.

6.6 The submission also presented results from retrospective, population-level persistence studies using data from the 10% PBS sample as supportive evidence (Ko et al 2021<sup>2</sup> and an internal report by the sponsor). The studies compared persistence across four drugs currently listed on the PBS for MSUC (VDZ, IFX, ADA and GOL). The submission argued that persistence is a proxy measure of effectiveness on the PBS because continuing treatment requires patients to meet the PBS response criteria, but acknowledged it also accounts for safety and treatment acceptability by patients and physicians.

6.7 These population-level persistence studies did not provide any data to inform the comparative effectiveness between UST and other PBS-listed treatments for MSUC, but the submission argued that UST was likely to have similar treatment persistence to VDZ. In addition, the evaluation stated that treatment persistence may not be the most reliable outcome to compare relative effectiveness of treatments in this setting because factors unrelated to effectiveness (or safety) may explain the decision to discontinue treatment. These factors may include differences in population/setting (i.e. short-term IFX is recommended for acute disease) as well as potential for bias related to the data and classification rules used to define treatment persistence (i.e.

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<sup>2</sup> Ko Y, Paramsothy S, Yau U et al. Superior treatment persistence with ustekinumab in Crohn’s disease and vedolizumab in ulcerative colitis compared with anti-TNF biological agents: real-world registry data from the Persistence Australian National IBD Cohort (PANIC) study. *Aliment Pharmacol Ther* 2021; 54(3): 292-301.

treatment switching may not necessarily mean treatment failure, the dataset does not capture doses administered to public hospital inpatients or when overseas).

6.8 Details of the trials presented in the submission are provided in **Error! Not a valid bookmark self-reference..**

**Table 2: Trials and associated reports presented in the submission**

Trial ID	Protocol title/ Publication title	Publication citation
<b>Ustekinumab trial</b>		
UNIFI	Janssen. A phase 3, randomized, double-blind, placebo-controlled, parallel-group, multicenter study to evaluate the safety and efficacy of ustekinumab induction and maintenance therapy in subjects with moderately to severely active ulcerative colitis. UNIFI.	Clinical study report – report date: 3 December 2018.
	Sands BE, Sandborn R, Panaccione CD, et al. Ustekinumab as induction and maintenance therapy for ulcerative colitis.	<i>N Engl J Med.</i> 2019; 381 (13): 1201-1214.
<b>Vedolizumab trials</b>		
GEMINI 1	Feagan B, Rutgeerts P, Sands B, et al. Vedolizumab as induction and maintenance therapy for ulcerative colitis.	<i>N Engl J Med.</i> 2013; 369(8):699-710.
Motoya 2019	Motoya S, Watanabe K, Ogata H, et al. Vedolizumab in Japanese patients with ulcerative colitis: A phase 3, randomized, double-blind, placebo-controlled study.	<i>PLOS ONE</i> February 2019; 14(2): e0212989.
VISIBLE 1	Sandborn W, Baert F, Danese S, et al. Efficacy and safety of vedolizumab subcutaneous formulation in a randomized trial of patients with ulcerative colitis.	<i>Gastroenterology</i> 2020; 158: 562-572.
<b>Adalimumab trials</b>		
ULTRA 1	Reinisch W, Sandborn WJ, Hommes DW, et al. Adalimumab for induction of clinical remission in moderately to severely active UC: results of a randomised controlled trial.	<i>Gut.</i> 2011;60(6):780-787
ULTRA 2	Sandborn WJ, van Assche G, Reinisch W, et al. Adalimumab induces and maintains clinical remission in patients with moderate to severe UC.	<i>Gastroenterology.</i> 2012;142(2):257-65[e1-3]
Suzuki 2014	Suzuki Y, Motoya S, Hanai H, et al. Efficacy and safety of adalimumab in Japanese patients with moderately to severely active ulcerative colitis.	<i>J Gastroenterol.</i> 2014; 49:283-294.

Source: Table 2-5, p83 of the submission. Shaded areas indicate data previously seen by the PBAC.

6.9 The key features of the randomised trials are summarised in

6.10 Table 3.

Table 3: Key features of the included evidence – indirect comparison

Trial	N	Design/ duration	Risk of bias	Patient population	Key outcome(s)
<b>UST v PBO</b>					
UNIFI [induction & maintenance]	IP: 961. MP: 783 <sup>b</sup>	P3, MC, R, PC, DB (8/16 <sup>a</sup> wk induction; maintenance to Wk 52); 3-arm.	IP: Low MP: Medium	TNFi-n & TNFi-e. Maintenance: Wk 8/16 active responders <sup>c</sup>	1 <sup>ary</sup> : clinical remission 2 <sup>ary</sup> : clinical response, mucosal healing <sup>1</sup> , sustained clinical response, sustained clinical remission, corticosteroid-free remission
<b>VDZ v PBO</b>					
GEMINI 1 [induction & maintenance]	IP Ct1:374 IP Ct2:521 MP:373	P3, MC, R, DB (58wk), RWD for maintenance (6wk induction, maintenance to Wk 52wk), 3-arm. Cohort 1 - randomised induction. Cohort 2- OL induction.	IP: Low MP: High	TNFi-n & TNFi-e. Maintenance: Wk6 active responders in cohort 1 and 2.	1 <sup>ary</sup> : clinical response 2 <sup>ary</sup> : clinical remission, mucosal healing, sustained clinical response, sustained clinical remission, corticosteroid-free remission
Motoya 2019 [induction & maintenance]	IP Ct 1: 246 IP Ct2: 46 <sup>d</sup> MP: 83	P3, MC, R, DB, RWD for maintenance (10wk induction, maintenance to Wk60). Randomised induction.	IP: Low MP: High	TNFi-n & TNFi-e	1 <sup>ary</sup> : clinical response 2 <sup>ary</sup> : clinical remission, mucosal healing
VISIBLE-1 [maintenance]	IP <sup>e</sup> : 383 MP: 216	P3, MC, R, DB, RWD for maintenance (6wk OL induction, maintenance to Wk52, R, DB maintenance).	MP: High	TNFi-n & TNFi-e	1 <sup>ary</sup> : clinical remission 2 <sup>ary</sup> : mucosal healing, sustained clinical response, sustained clinical remission, corticosteroid-free remission
<b>ADA v PBO</b>					
ULTRA 1 [induction]	390	P3, MC, R, PC, DB (8wk), 3-arm	Low	TNFi-n	1 <sup>ary</sup> : clinical remission 2 <sup>ary</sup> : clinical response, mucosal healing
ULTRA 2 [induction & maintenance]	494	P3, MC, R, PC, DB (52wk)	IP: Low MP: High	TNFi-n & TNFi-e	1 <sup>ary</sup> : clinical remission 2 <sup>ary</sup> : clinical response, mucosal healing, IBDQ response, sustained clinical remission, sustained clinical response, sustained mucosal healing
Suzuki 2014 [induction & maintenance]	274	P2/3, MC, R, PC, DB (52wk), 3-arm	IP: Low MP: High	TNFi-n (Japanese)	1 <sup>ary</sup> : clinical remission 2 <sup>ary</sup> : clinical response, mucosal healing

Source: Table 2-7, pp88-90 of the submission. Shaded areas indicate data previously seen by the PBAC.

1<sup>ary</sup>=primary, 2<sup>ary</sup>=secondary, ADA=adalimumab, DB=double blind; IBDQ= Inflammatory Bowel Disease Questionnaire; IP=induction phase; MC=multi-centre; MP=maintenance phase; OL=open label; P3=Phase 3; PBO=placebo, PC=placebo-controlled; R=randomised, RWD=randomised withdrawal design, TNFi-e=tumour necrosis factor inhibitor experience, TNFi-n= tumour necrosis factor inhibitor naïve, UST=ustekinumab, VDZ=vedolizumab, Wk=week.

<sup>a</sup> UNIFI: At Week 8, subjects who were not in clinical response were assigned treatment as follows: those randomised to PBO at Week 0 received UST IV ~ 6 mg/kg plus PBO SC (to maintain the blind); those randomised to UST at Week 0 received UST 90 mg SC plus PBO IV (to maintain the blind). A total of 417 subjects who were not in clinical response at Week 8 received an additional dose of study agent at Week 8.

<sup>b</sup> UNIFI: Total subjects enrolled in maintenance. Of these, 523 were in the primary population for the maintenance study (clinical response to UST IV induction) and were randomised. 260 subjects were not part of the primary population (PBO induction responders and UST induction delayed responders) and were not randomised.

<sup>c</sup> UNIFI: Additional subjects entering the maintenance study not part of the primary population include the following: subjects in clinical response to PBO IV induction received placebo SC; subjects who were delayed responders to UST induction (i.e., not in clinical response to UST at Week 8 but were in clinical response at Week 16) received UST 90 mg SC Q8W.

<sup>d</sup> Motoya: Cohort 2 patients received open-label VDZ (induction phase).

<sup>e</sup> VISIBLE 1: All patients received open-label VDZ IV induction treatment.

6.11 All of the included trials were large, phase 3 multi-centre trials, which provide comparative evidence of active treatment versus PBO for induction therapy, maintenance therapy or induction and maintenance treatment combined. The PBAC had considered evidence from all of the VDZ (GEMINI 1, Motoya 2019 and VISIBLE I) and ADA (ULTRA 1, ULTRA 2 and Suzuki 2014) trials in past decisions for MSUC. The

UNIFI trial consisted of a randomised induction phase and a re-randomised withdrawal maintenance phase for active induction responders (similar in design to GEMINI 1 and Motoya 2019). The submission relied on data from non-randomised patients included in GEMINI 1, Motoya 2019 and UNIFI (who received active or PBO maintenance therapy) for the trial-design-adjusted indirect treatment comparisons.

- 6.12 The induction trials / induction phases were fairly similar in terms of trial design as eligible patients were randomised to active treatment or PBO, with response to treatment assessed at Weeks 6-10. In contrast, the maintenance trials / maintenance phases differed in terms of the trial design, given the UST and VDZ trials used randomised withdrawal designs (active induction clinical responders – based on the full Mayo score - were re-randomised to active versus PBO) whereas the ADA trials used treat-through designs (patients were randomised once and continued the same treatment for induction and maintenance therapy).
- 6.13 Overall, the risks of bias in the induction trials were low, whereas the maintenance trials generally had a higher risk of attrition bias due to higher proportions of discontinuations due mostly to adverse events and loss of effect (for PBO, 24.6% discontinued during the maintenance phase in UNIFI, 24% to 62.5% discontinued in other maintenance trials / phases).
- 6.14 Based on available data, there were some differences in patient characteristics across the induction trials / phases that may potentially influence results, but any overall impact was uncertain. These differences included:
- UNIFI had a higher proportion of patients with disease located in the left side of the colon and a lower proportion with extensive disease compared to the VDZ and ADA trials.
  - Patients in UNIFI had a slightly longer average disease duration and slightly higher mean full Mayo score compared to most other trials (except ULTRA-2).
  - UNIFI had a higher proportion of patients with prior use of a biologic compared to the VDZ and ADA trials that enrolled patients with prior biologic exposure.
- 6.15 A comparison of baseline characteristics across the maintenance trials /phases was limited because most trials did not report separate characteristics for patients treated with maintenance treatment. Based on available data, patients (i.e. induction responders) enrolled in UNIFI appeared to be fairly similar to patients enrolled in VISIBLE 1.
- 6.16 Overall, a smaller proportion of patients in UNIFI used concomitant 5-ASAs compared to most other trials (except ULTRA 2 trial), and there was a wide variation across the trials in terms of concomitant corticosteroids and immunosuppressant drugs.

### ***Comparative effectiveness***

- 6.17 The clinically relevant outcomes for MSUC are clinical remission (absence of symptoms outcome) and clinical response (relative improvement in symptoms

outcome), as assessed using the Mayo score. The PBS continuation criteria requires that patients demonstrate clinical remission (defined as a partial Mayo score  $\leq 2$  with no sub-scores  $>1$ , see Requested listing), but the PBAC had previously accepted both clinical remission and clinical response (defined using the full Mayo score) as the clinically relevant trial outcomes to assess the relative effectiveness and non-inferiority of treatments (page 3, IFX Public Summary Document (PSD), March 2014; paragraph 7.2, ADA PSD July 2014; paragraph 6.12, VDZ PSD, July 2014; paragraph 6.12, TOF PSD, March 2019).

- 6.18 All of the trials used the same outcome definitions for clinical remission and clinical response based on the full Mayo score. The submission stated differences when outcomes were reported in the induction trials (i.e. at Week 6, 8 or 10) and maintenance trials (i.e. at Week 52 or 60) were unlikely to bias results. The definition of clinical response in the maintenance phase of UNIFI also appeared to be slightly stricter ('clinical response through to Week 52') compared to the other trials, as patients could be classified non-responders at unscheduled visits prior to Week 52.
- 6.19 The submission presented a series of indirect treatment comparisons using the Bucher method, comparing UST to VDZ and ADA in terms of clinical remission and clinical response for induction and maintenance treatment. The submission used meta-analysis to combine outcomes across the VDZ trials and ADA trials. The submission stated that failure of a prior biologic is an important treatment effect modifier in MSUC, therefore, the indirect treatment comparisons considered evidence by failure/exposure to prior biologic subgroups.
- 6.20 There was a subtle difference between subgroups defined by prior exposure and prior response to biologics (given not all patients without an inadequate response to biologics were biologic naïve), but the submission considered these subgroups as being equivalent. The PBAC had also previously considered that subgroup analysis by prior TNF exposure were problematic due to reduced statistical power and because the comparisons in patients with prior exposure may not be a fair representation of comparative efficacy when comparing a TNF inhibitor versus a drug of another class (paragraph 7.2, TOF PSD, Nov 2020).
- 6.21 The submission presented four risk statistics when performing the indirect comparisons: risk difference (RD), odds ratio (OR), relative risk (RR) expressed in terms of responders (measured in the trials) and RR expressed in terms of non-responders (the inverse population). The main reason to present RR in terms of non-response was that due to asymmetry in the variance of the RR statistic, results of indirect comparisons using RR (in both direction and size) can change depending on whether the outcome is framed in terms of a loss or gain. Based on a paper published by Furuya-Kanamori and Doi (2014), the submission then argued that the choice to frame in terms of loss or gain should depend on which has the highest baseline risk in the common comparator arms, given it has the smaller variance. The submission argued this was important for the indirect treatment comparison comparing UST and ADA since response/remission rate in the control group was low.

6.22 The evaluation noted recommendations of Furuya-Kanamori and Doi (2014) were aimed at improving outcome selection in clinical trial design rather than statistical considerations for the conduct of indirect treatment comparisons. An alternative paper by Eckerman Coory and Willan 2009 (also referenced by the submission) recommended using the OR rather than RR to estimate relative treatment effects given its symmetric properties. The submission also stated that non-response rates had previously been used in the sponsor’s submissions to the PBAC<sup>3</sup> and that the approach was considered broadly appropriate by the evaluations, but this claim could not be verified. For example, the PSD for UST in paediatric CPP in March 2021 noted the submission’s approach to use non-response rates was poorly justified. The small sample size of the included trials was considered the likely driver of the lack of statistical significance instead of framing. The ESC also commented that the conclusions should be consistent regardless of whether responders or non-responder are analysed (paras 6.28 and 6.29, ustekinumab PSD, March 2021).

#### Induction treatment

6.23 Tables 4 and 5 present the results of the indirect treatment comparisons for clinical remission and clinical response outcomes, respectively, for induction therapy (at Week 6, 8 or 10).

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<sup>3</sup> ustekinumab for adult CPP November 2009 PBAC meeting; guselkumab for adult CPP March 2018 PBAC meeting; ustekinumab for paediatric CPP in March 2021 PBAC meeting and Janssen’s response to Post Market Review for biologics in Feb 2017.

**Table 4: Indirect comparisons comparing UST versus VDZ and ADA for clinical remission at Week 6, 8 or 10 (induction therapy)**

Trial	Drug n/N (%)	Control n/N (%)	RR (95% CI)	RD (95% CI)	OR (95%CI)
<b>Clinical remission: UST IV 6mg/kg v PBO (Wk8)</b>					
UNIFI Wk8, ITT	50/322 (15.5)	17/319 (5.3)	<b>2.91 (1.72, 4.94)</b>	<b>0.10 (0.06, 0.15)</b>	<b>3.27 (1.84, 5.80)</b>
UNIFI Wk8, DMARD-IR	29/156 (18.6)	15/158 (9.5)	<b>1.96 (1.09, 3.51)</b>	<b>0.09 (0.01, 0.17)</b>	<b>2.18 (1.12, 4.24)</b>
UNIFI Wk8, bDMARD-IR	21/166 (12.7)	2/161 (1.2)	<b>10.18 (2.43, 42.73)</b>	<b>0.11 (0.06, 0.17)</b>	<b>11.51 (2.65, 49.96)</b>
<b>Clinical remission: VDZ IV 300mg v PBO (Wk6/10)</b>					
GEMINI 1 Wk6, ITT	38/225 (16.9)	8/149 (5.4)	<b>3.15 (1.51, 6.55)</b>	<b>0.12 (0.05, 0.18)</b>	<b>3.58 (1.62, 7.92)</b>
GEMINI 1 Wk6, TNF-naïve	30/130 (23.1)	5/76 (6.6)	<b>3.51 (1.42, 8.66)</b>	<b>0.16 (0.07, 0.26)</b>	<b>4.26 (1.58, 11.52)</b>
GEMINI 1 Wk6, TNF-IR	8/82 (9.8)	2/63 (3.2)	3.07 (0.68, 13.97)	0.07 (-0.01, 0.14)	3.30 (0.68, 16.11)
MOTOYA, ITT	30/164 (18.3)	10/82 (12.2)	1.50 (0.77, 2.92)	0.06 (-0.03, 0.15)	1.61 (0.75, 3.48)
MOTOYA, TNF-naïve	22/79 (27.8)	6/41 (14.6)	1.90 (0.84, 4.32)	0.13 (-0.01, 0.28)	2.25 (0.83, 6.10)
MOTOYA, TNF-exp.	8/85 (9.4)	4/41 (9.8)	0.96 (0.27, 3.40)	-0.00 (-0.11, 0.11)	0.96 (0.27, 3.40)
MA, ITT	68/389 (17.5)	18/231 (7.8)	<b>2.14 (1.03, 4.43)</b>	<b>0.10 (0.05, 0.15)</b>	<b>2.39 (1.09, 5.23)</b>
MA, TNF-naïve	52/209 (24.9)	11/117 (9.4)	<b>2.62 (1.43, 4.79)</b>	<b>0.15 (0.07, 0.23)</b>	<b>3.18 (1.58, 6.38)</b>
MA, TNF-exp/IR	16/167 (9.6)	6/104 (5.8)	1.62 (0.49, 5.37)	0.04 (-0.02, 0.11)	1.62 (0.49, 5.37)
<b>Clinical remission: ADA 160mg -&gt; 80mg v PBO (Wk8)</b>					
ULTRA 1, ITT/TNF-naïve Wk8	24/130 (18.5)	12/130 (9.2)	<b>2.00 (1.05, 3.83)</b>	<b>0.09 (0.01, 0.18)</b>	<b>2.23 (1.06, 4.67)</b>
SUZUKI, ITT/TNF-naïve Wk8	9/90 (10.0)	11/96 (11.5)	0.87 (0.38, 2.01)	-0.01 (-0.10, 0.07)	0.86 (0.34, 2.18)
ULTRA 2, ITT Wk8	41/248 (16.5)	23/246 (9.3)	<b>1.77 (1.10, 2.86)</b>	<b>0.07 (0.01, 0.13)</b>	<b>1.92 (1.11, 3.31)</b>
ULTRA 2, TNF-naïve Wk8	32/150 (21.3)	16/145 (11.0)	<b>1.93 (1.11, 3.37)</b>	<b>0.10 (0.02, 0.19)</b>	<b>2.19 (1.14, 4.19)</b>
ULTRA 2, TNF-exp. Wk8	9/98 (9.2)	7/101 (6.9)	1.33 (0.51, 3.42)	0.02 (-0.05, 0.10)	1.36 (0.49, 3.80)
MA, ITT	74/468 (15.8)	46/472 (9.7)	<b>1.58 (1.05, 2.40)</b>	0.05 (-0.00, 0.11)	<b>1.69 (1.04, 2.73)</b>
MA, TNF-naïve	65/370 (17.6)	39/371 (10.5)	<b>1.62 (1.02, 2.57)</b>	0.06 (-0.01, 0.13)	<b>1.74 (1.01, 3.00)</b>
<b>Indirect comparisons: clinical remission</b>					
UST (UNIFI) v VZD (MA), ITT			1.30 (0.63, 2.68)	0 (-0.07, 0.07)	1.37 (0.52, 3.62)
UST (UNIFI) v ADA (MA), ITT			1.84 (0.94, 3.60)	0.05 (-0.02, 0.12)	1.94 (0.91, 4.10)
UST (UNIFI) v VZD (MA), DMARD-IR/TNF-naïve			0.75 (0.40, 1.42)	-0.06 (-0.17, 0.05)	0.69 (0.26, 1.80)
UST (UNIFI) v ADA (MA), DMARD-IR/TNF-naïve			1.21 (0.57, 2.55)	0.03 (-0.0, 0.14)	1.25 (0.53, 2.96)
UST (UNIFI) v VZD (MA), bDMARD-IR/TNF-exp			6.28 (0.97, 40.68)	0.07 (-0.02, 0.16)	<b>7.11 (1.07, 47.24)</b>
UST (UNIFI) v ADA (ULTRA 2), bDMARD-IR/TNF-exp			<b>7.65 (1.37, 42.77)</b>	0.09 (-0.00, 0.18)	<b>8.46 (1.41, 50.70)</b>

Source: Tables 2-65, 2-66 and 2-67, pp184-185 of the submission.

Abbreviations: ADA = adalimumab; bDMARD = biologic disease-modifying antirheumatic drugs; DMARD = disease-modifying antirheumatic drugs; PBO = placebo; UST = ustekinumab; VDZ = vedolizumab; IR = inadequate response; IV = intravenous; MA = meta-analysis, TNF= tumour necrosis factor.

Table 5: Indirect comparisons comparing UST versus VDZ and ADA for clinical response and non-clinical response at Week 6, 8 or 10 (induction therapy)

Trial	Drug n/N (%)	Control n/N (%)	RR (95% CI)	RD (95% CI)	OR (95%CI)
<b>Clinical response UST IV 6mg/kg v PBO (Wk8)</b>					
UNIFI, ITT	199/322 (61.8)	100/319 (31.3)	1.97 (1.64, 2.37)	0.30 (0.23, 0.38)	3.54 (2.56, 4.91)
UNIFI, DMARD-IR	104/156 (66.7)	56/158 (35.4)	1.88 (1.48, 2.39)	0.31 (0.21, 0.42)	3.64 (2.29, 5.80)
UNIFI, bDMARD-IR	95/166 (57.2)	44/161 (27.3)	2.09 (1.58, 2.78)	0.30 (0.20, 0.40)	3.56 (2.24, 5.65)
<b>Clinical response: VDZ IV 300mg v PBO (Wk6/10)</b>					
GEMINI 1, ITT	106/225 (47.1)	38/149 (25.5)	1.85 (1.36, 2.51)	0.22 (0.12, 0.31)	2.60 (1.66, 4.09)
GEMINI 1, TNF-naïve	69/130 (53.1)	20/76 (26.3)	2.02 (1.34, 3.04)	0.27 (0.14, 0.40)	3.17 (1.71, 5.86)
GEMINI 1, TNF-IR	32/82 (39.0)	13/63 (20.6)	1.89 (1.09, 3.29)	0.18 (0.04, 0.33)	2.46 (1.16, 5.23)
MOTOYA, ITT	65/164 (39.6)	27/82 (32.9)	1.20 (0.84, 1.73)	0.07 (-0.06, 0.19)	1.34 (0.77, 2.33)
MOTOYA, TNF-naïve	42/79 (53.2)	15/41 (36.6)	1.45 (0.92, 2.29)	0.17 (-0.02, 0.35)	1.97 (0.91, 4.27)
MOTOYA, TNF-exp.	23/85 (27.1)	12/41 (29.3)	0.92 (0.51, 1.67)	-0.02 (-0.19, 0.15)	0.90 (0.39, 2.05)
MA, ITT	171/389 (44.0)	65/231 (28.1)	1.51 (0.99, 2.29)	0.15 (0.00, 0.29)	1.90 (0.99, 3.65)
MA, TNF-naïve	111/209 (53.1)	35/117 (29.9)	1.74 (1.26, 2.40)	0.23 (0.13, 0.34)	2.63 (1.63, 4.26)
MA, TNF-exp/IR	55/167 (32.9)	25/104 (24.0)	1.33 (0.66, 2.69)	0.09 (-0.12, 0.29)	1.51 (0.56, 4.05)
<b>Clinical response: ADA 160mg -&gt; 80mg v PBO (Wk8)</b>					
ULTRA 1, ITT/TNF-naïve	71/130 (54.6)	58/130 (44.6)	1.22 (0.96, 1.57)	0.10 (-0.02, 0.22)	1.49 (0.92, 2.44)
SUZUKI, ITT/TNF-naïve	45/90 (50.0)	34/96 (35.4)	1.41 (1.00, 1.98)	0.15 (0.01, 0.29)	1.82 (1.01, 3.28)
ULTRA 2, ITT	125/248 (50.4)	85/246 (34.6)	1.46 (1.18, 1.80)	0.16 (0.07, 0.24)	1.92 (1.34, 2.76)
ULTRA 2, TNF-naïve	89/150 (59.3)	56/145 (38.6)	1.54 (1.20, 1.96)	0.21 (0.10, 0.32)	2.32 (1.45, 3.70)
ULTRA 2, TNF-exp.	36/98 (36.7)	29/101 (28.7)	1.28 (0.86, 1.91)	0.08 (-0.05, 0.21)	1.44 (0.79, 2.61)
MA, ITT	241/468 (51.4)	177/472 (37.5)	1.36 (1.18, 1.58)	0.14 (0.08, 0.20)	1.77 (1.37, 2.30)
MA, TNF-naïve	205/370 (55.4)	148/371 (39.8)	1.38 (1.18, 1.61)	0.15 (0.08, 0.23)	1.87 (1.39, 2.50)
<b>Not achieving clinical response: UST IV 6mg/kg v PBO (Wk8)</b>					
UNIFI, ITT	123/322 (38.2)	219/319 (68.7)	0.56 (0.48, 0.65)	-0.30 (-0.38, -0.23)	0.28 (0.20, 0.39)
UNIFI, DMARD-IR	52/156 (33.3)	102/158 (64.6)	0.52 (0.40, 0.66)	-0.31 (-0.42, -0.21)	0.27 (0.17, 0.44)
UNIFI, bDMARD-IR	71/166 (42.8)	117/161 (72.7)	0.59 (0.48, 0.72)	-0.30 (-0.40, -0.20)	0.28 (0.18, 0.45)
<b>Not achieving clinical response: VDZ IV 300mg v PBO (Wk6/10)</b>					
MA, ITT: GEMINI 1, Motoya	218/389 (56.0)	166/231 (71.9)	0.78 (0.69, 0.88)	-0.16 (-0.23, -0.08)	0.50 (0.35, 0.71)
MA, TNF-naïve: GEMINI 1, Motoya	98/209 (46.9)	82/117 (70.1)	0.67 (0.56, 0.81)	-0.23 (-0.34, -0.12)	0.38 (0.23, 0.61)
MA, TNF-exp/IR: GEMINI 1, Motoya	112/167 (67.1)	79/104 (76.0)	0.88 (0.76, 1.03)	-0.09 (-0.20, 0.02)	0.64 (0.37, 1.12)
<b>Not achieving clinical response: ADA 160mg -&gt; 80mg v PBO (Wk8)</b>					
MA, ITT: ULTRA 1/2, Suzuki	227/468 (48.5)	295/472 (62.5)	0.78 (0.69, 0.87)	-0.14 (-0.20, -0.08)	0.57 (0.44, 0.73)
MA, TNF-naïve: ULTRA 1/2, Suzuki	165/370 (44.6)	223/371 (60.1)	0.74 (0.64, 0.85)	-0.16 (-0.23, -0.08)	0.53 (0.40, 0.72)
ULTRA 2, TNF-exp.	62/98 (63.3)	72/101 (71.3)	0.89 (0.73, 1.08)	-0.08 (-0.21, 0.05)	0.69 (0.38, 1.26)
<b>Indirect comparisons: clinical response</b>					
UST (UNIFI) v VDZ (MA), ITT			1.31 (0.83, 2.06)	0.15 (-0.01, 0.31)	1.86 (0.90, 3.86)
UST (UNIFI) v ADA (MA), ITT			1.45 (1.15, 1.83)	0.16 (0.06, 0.26)	2.00 (1.32, 3.03)
UST (UNIFI) v VDZ (MA), DMARD-IR/TNF-naïve			1.08 (0.72, 1.61)	0.08 (-0.07, 0.23)	1.38 (0.71, 2.70)
UST (UNIFI) v ADA (MA), DMARD-IR/TNF-naïve			1.36 (1.02, 1.81)	0.16 (0.03, 0.29)	1.95 (1.12, 3.37)
UST (UNIFI) v VDZ (MA), bDMARD-IR/TNF-exp			1.57 (0.74, 3.35)	0.21 (-0.02, 0.44)	2.36 (0.79, 7.03)
UST (UNIFI) v ADA (ULTRA 2), bDMARD-IR/TNF-exp			1.63 (1.00, 2.66)	0.22 (0.06, 0.38)	2.47 (1.16, 5.26)
<b>Indirect comparisons: not achieving clinical response</b>					
UST (UNIFI) v VDZ (MA), ITT			0.72 (0.59, 0.87)	-0.14 (-0.25, -0.03)	0.56 (0.34, 0.91)
UST (UNIFI) v ADA (MA), ITT			0.72 (0.59, 0.87)	-0.16 (-0.26, -0.06)	0.49 (0.32, 0.75)
UST (UNIFI) v VDZ (MA), DMARD-IR/TNF-naïve			0.78 (0.57, 1.06)	-0.08 (-0.23, 0.07)	0.71 (0.36, 1.40)
UST (UNIFI) v ADA (MA), DMARD-IR/TNF-naïve			0.70 (0.53, 0.94)	-0.15 (-0.28, -0.02)	0.51 (0.29, 0.89)
UST (UNIFI) v VDZ (MA), bDMARD-IR/TNF-exp			0.67 (0.52, 0.86)	-0.21 (-0.36, -0.06)	0.44 (0.21, 0.90)
UST (UNIFI) v ADA (ULTRA 2), bDMARD-IR/TNF-exp			0.66 (0.50, 0.88)	-0.22 (-0.38, -0.06)	0.41 (0.19, 0.86)

Source: Tables 2-68, 2-69, 2-70 and 2-71, pp187-188 of the submission.

Abbreviations: ADA = adalimumab; bDMARD = biologic disease-modifying antirheumatic drugs; DMARD = disease-modifying antirheumatic drugs; PBO = placebo; UST = ustekinumab; VDZ = vedolizumab; IV = intravenous; IR = inadequate response; MA = meta-analysis, TNF= tumour necrosis factor.

- 6.24 For clinical remission, the indirect treatment comparisons indicated that a similar proportion of patients achieved the outcome with UST, VDZ and ADA in the ITT population and biologic / TNF inhibitor naïve subgroup; and significantly more patients met the criteria with UST compared to VDZ and ADA in the biologic / TNF inhibitor experienced subgroup. The findings were consistent across both relative and absolute measures of treatment effect. As discussed above, interpretation of results in the biologic / TNF inhibitor experienced subgroup are problematic for several reasons, including reduced statistical power, higher risk of bias due to confounding effects and differences in class of trial and prior biologics. The PBO response rates in biologic experienced subgroup of UNIFI (1.2%) was also much lower than other trials (range, 5.8 to 6.9%).
- 6.25 For clinical response, the indirect treatment comparisons generally indicated that UST was more effective than VDZ and ADA using the RD and OR statistics (with the exception of similar effectiveness versus VDZ in the biologic/TNF inhibitor naïve subgroup), but some of these differences were not statistically significant using RR. The submission argued that the inconsistent findings with the RR statistic were due to the non-symmetric nature of the variance of the log RR; and hence, it was reasonable to estimate the treatment effect using the rate of non-responders to improve statistical efficiency. Based on the proportion of patients who did not achieve clinical response, the indirect treatment comparisons generally indicated that UST was more effective than VDZ and ADA across both relative and absolute measures of treatment effect.

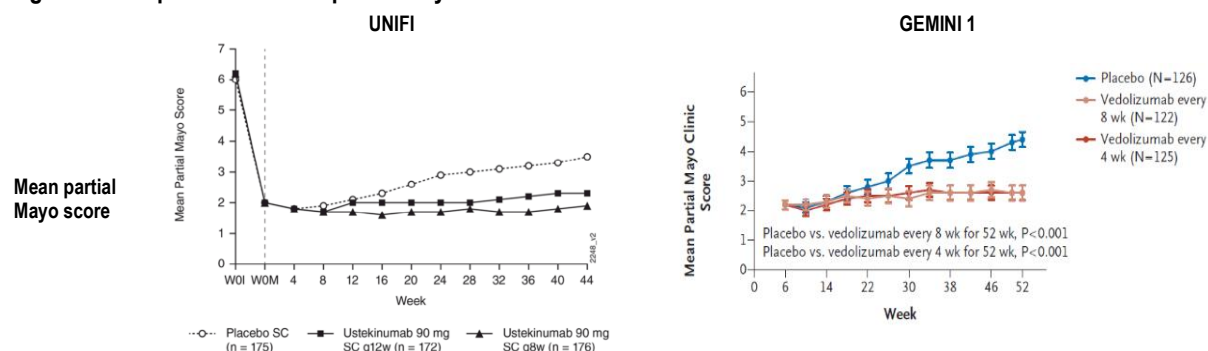
#### Maintenance treatment

- 6.26 For maintenance treatment, the submission argued that an indirect treatment comparison between:
- UST versus ADA was biased against UST because the UNIFI used a randomised withdrawal trial design whereas the ADA trials (ULTRA 2 and Suzuki 2014) used a treat-through design. In the treat-through design, patients in the PBO arm represented a ‘true placebo’ comparator because patients received PBO induction and PBO maintenance. In contrast, the PBO arm of randomised withdrawal trials do not represent a true placebo due to ‘carry-over’ benefits of active treatment given patients received active induction and PBO maintenance.
  - UST versus VDZ was biased against UST, despite both sets of trials using the same randomised withdrawal design, because the carry-over benefit for UST is larger than the carry over benefit for VDZ. The submission argued that the treatment effect of a single UST IV loading dose is more durable compared with VDZ (and other biologics) due to (i) greater bioavailability, (ii) a longer half-life and (iii) the anti-inflammatory effects of UST are likely to take longer to manifest or subside upon withdrawal because it acts earlier in the inflammatory cascade. The submission also argued that the larger carry over effect with UST compared to VDZ was demonstrated by comparing Mayo scores of PBO patients over time. The

submission noted that the median partial Mayo score for PBO patients in UNIFI remained similar to the UST arm through to 52 weeks, but the mean Mayo score for PBO patients in GEMINI 1 steadily increased and separated from the VDZ arm over time.

6.27 The evaluation considered the submission’s claim of a longer carry over benefit in PBO patients following UST induction treatment versus VDZ induction treatment was poorly justified given similar theoretical arguments of a long carry-over effect would also reasonably apply to VDZ (IV administration, similar half-life, and similar dosing frequency) and there was no evidence that patients experienced delayed benefit with UST versus VDZ (hence no reason to suggest that there would be a difference in the time for benefits to subside when treatment is withdrawn). In addition, a comparison between mean Mayo scores across trials showed PBO patients had a similar loss of response trajectory with separation occurring around 12 weeks after treatment withdrawal in line with the recommended dosing frequencies (Figure 1). Although a higher proportion of PBO patients in UNIFI compared to GEMINI 1 had maintained clinical response (44.6% v 23.8%, respectively) or achieved clinical remission (24% v 15.9%, respectively), the differences at Week 52 may not necessarily be due to longer carry over effect with UST, but rather other differences in the patients or trial settings. For example, at Week 52 in the trials, PBO patients had discontinued active treatment for 44 weeks in UNIFI (i.e. 8 week induction period) versus 46 weeks in GEMINI 1 (i.e. 6 week induction period). The numerical difference in response favouring UST Q8W versus UST Q12W also suggests that long carry over benefits with UST may not explain differences in PBO response rates at Week 52.

Figure 1: Comparison of mean partial Mayo scores over time in UNIFI and GEMINI 1

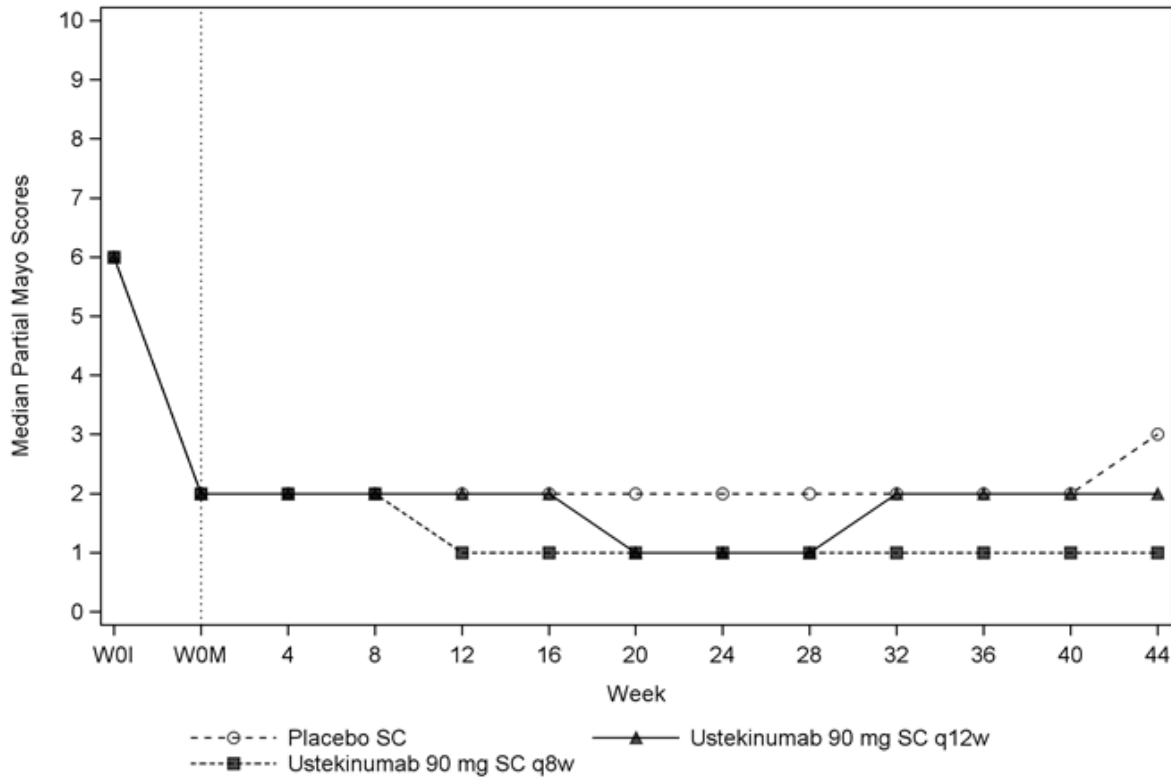


Source: Figures 2-9 and 2-10, p192 of the submission; Figure on p228 of the UNIFI maintenance CSR

6.28 The Pre-Sub-Committee Response (PSCR) noted the submission also presented data which showed the median partial Mayo score in the placebo arm of the UNIFI trial remained unchanged over 44 weeks and was similar to the UST arms, and therefore demonstrative of a carry-over effect (Figure 2 below). Further, the PSCR also argued that whilst both UST and VDZ have a similar dosing frequency, the mechanism of action of UST (as an IL-12/23 inhibitor), acts earlier and centrally on the inflammatory cascade, thus providing biological plausibility for a longer time to see a loss of treatment effect, an observation that was made for UST in its PBAC submission for

Crohn’s disease in 2017. To that end, the PSCR maintained that the different degree of carry-over effect between the UST and VDZ biases against UST for an indirect comparison approach which uses the placebo arms as-reported.

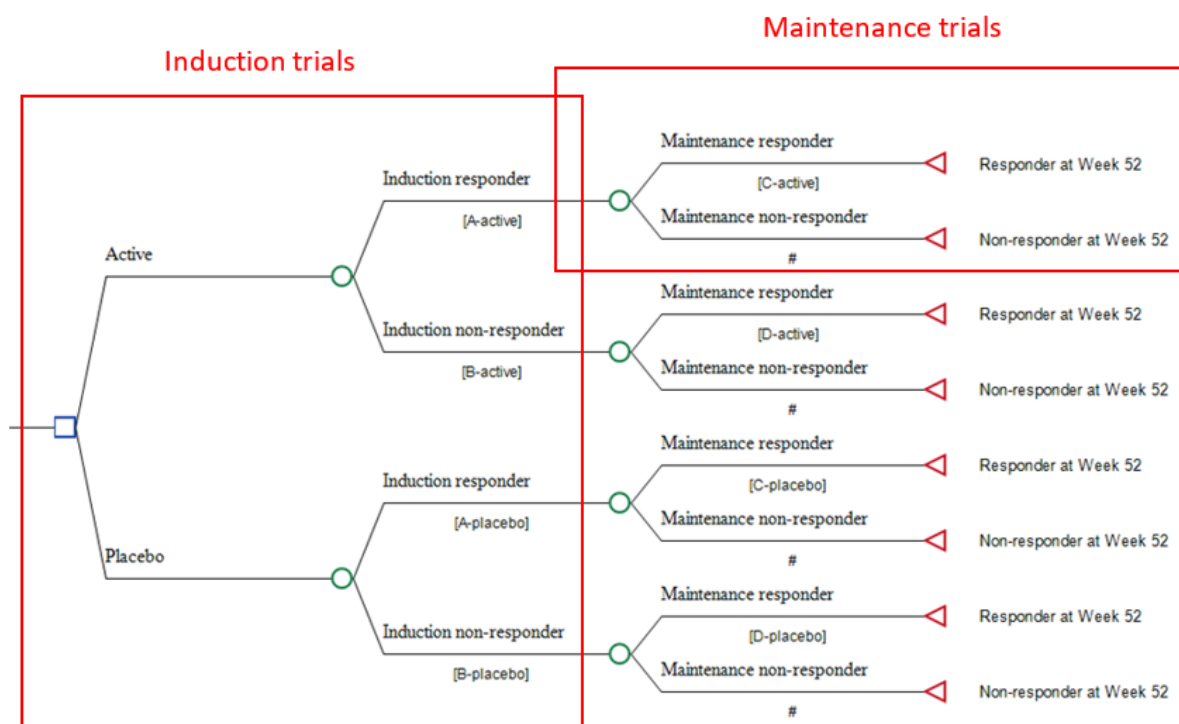
Figure 2: Median partial Mayo score in the maintenance phase of the UNIFI (UST) trial



Source: Figure 1 of the PSCR (pg. 5)

6.29 To adjust for this bias, the submission proposed a modelling approach in order to predict the proportion of responders in the UST and VDZ trials at Week 52 assuming patients remained on the same treatment from baseline (to mimic results of a treat-through trial design). Figure 2 summarises this approach, where the proportion of responders at Week 52 is equal to the proportion of responders to induction treatment (A) multiplied by the proportion of responders to maintenance treatment given response to induction treatment (C), plus the proportion of non-responders to induction treatment (B) multiplied by the proportion of responders to maintenance treatment given non-response to induction treatment (D).

Figure 3: Illustration of the modelling approach to convert re-randomised withdrawal trial results into treat-through trial results.



Source: constructed during the evaluation

- 6.30 To estimate the four key parameters (A, B, C, D) of the model, the submission relied on available data from the UST and VDZ induction and randomised withdrawal maintenance trials including non-randomised patients, as well as individual patient data (IPD) from other trials available to the sponsor (from UNIFI, PURSUIT-M and ACT 1). The estimates of key parameters not collected in the main comparison arms of the randomised trials (i.e. ‘C-placebo’, ‘D-active’ and ‘D-placebo’) were based on very small numbers of non-randomised patients and these estimates could not be verified during the evaluation. The submission also provided no clear rationale for selecting different data sources to impute the same parameter across different trials.
- 6.31 To conduct the indirect treatment comparison using the predicted results, the submission estimated the total number of patients in each of the adjusted treatment arms (i.e.  $n/N$ ). The submission stated that using the number of patients from the induction phase was an overestimate because patients were re-randomised to multiple maintenance treatments, and using the number of patients from the maintenance phase was an underestimate because this ignores induction non-responders. For the active treatment arms, the submission therefore re-distributed induction population based on the proportion assigned to each of the maintenance treatments to attain a closer estimate for each active-to-active treatment sequence. The submission stated that it was appropriate to use the number of patients randomised to PBO induction because those patients were not re-randomised. The submission’s approach of approximating the sample size (N) and back calculating the

numbers with response (n) to estimate the confidence intervals around the estimated treatment effects was poorly justified. Given the number of patients with response (n) is only an expectation (i.e. we do not observe all patients) there is additional uncertainty that is ignored by the submission's approach, which means that the estimated confidence intervals are narrower than otherwise expected. It would be more appropriate to obtain confidence intervals using bootstrapping or other non-parametric estimates of the uncertainty that reflect the process used to estimate the parameters.

- 6.32 The submission justified this modelling approach based on advice in the GOL PSD (paragraph 6.10, GOL PSD, Nov 2017), that presenting all data from a randomised withdrawal trial (including non-responding patients who were not randomised) to align with the data from the treat-through trials was an alternative approach to adjusting the treat-through trials to align with the randomised withdrawal trials. This advice, however, may have been specific to the PURSUIT-M trial, which also collected data in a non-randomised phase for (i) non-responders to GOL induction treatment who continued taking GOL; (ii) responders to PBO induction treatment who continued taking PBO; and (iii) non-responders to PBO induction treatment who crossed over to GOL. Given this, it was unclear whether this comment adequately endorses the general modelling approach adopted by the submission (i.e. for trials that collected less data).
- 6.33 The PSCR disagreed with the evaluation and argued that the fundamental issues for UST and GOL due to the randomised withdrawal trial designs were similar and therefore the modelled approach used was reasonable. The ESC considered that, while the modelling approach used in the submission should not be considered exclusively applicable to golimumab and the PURSUIT-M trial, the approach taken tended to introduce additional uncertainty into the clinical comparisons of UST and the nominated comparators. The ESC noted the PURSUIT-M trial also collected additional data (outlined above) which was not collected in the UST trials, which further increased the uncertainty of employing the modelling approach used in the submission.
- 6.34 Table 6 and Table 7 present the results of the trial-design-adjusted indirect treatment comparison for clinical remission and clinical response outcomes, respectively, for maintenance therapy (at Week 52 or 60). The results presented below were corrected for several errors/issues identified during the evaluation, but these do not change the overall conclusions of the analyses, including:
- The submission stated that the ADA trials only recruited non-biologic failure patients and therefore no data was available in the biologic failure population; but ULTRA 2 included patients with prior exposure to TNF inhibitor.
  - The submission incorrectly reported that 15/100 (14.1%) TNF inhibitor naïve patients randomised to PBO in ULTRA 2 had clinical remission at Week 52 (instead of 18/145, 12.4% reported in the publication).

- The submission did not include results from Suzuki 2014 and did not provide any rationale for excluding the trial from the analysis.
- The submission calculated the treatment effects for VDZ versus PBO by pooling the predicted (treat-through) results in GEMINI 1 and Motoya rather than via meta-analysis.

**Table 6: Trial-design-adjusted indirect comparisons comparing UST versus VDZ and ADA for clinical remission and non-clinical remission at Week 52/60 (maintenance therapy) –predicted results for the UST and VDZ trials**

Trial	Drug n/N (%)	Control n/N (%)	RR (95% CI)	RD (95% CI)	OR (95% CI)
<b>Clinical remission: UST SC 90 mg pooled v PBO (Wk 52, predicted)</b>					
UNIFI, DMARD-IR	47/111 (42.4)	20/158 (12.7)	<b>3.35 (2.10, 5.32)</b>	<b>0.30 (0.19, 0.40)</b>	<b>5.07 (2.78, 9.25)</b>
UNIFI, bDMARD-IR	29/104 (27.5)	10/161 (6.0)	<b>4.49 (2.29, 8.82)</b>	<b>0.22 (0.12, 0.31)</b>	<b>5.84 (2.70, 12.61)</b>
<b>Clinical remission: VDZ IV 300mg v PBO (Wk 52/60, predicted)</b>					
GEMINI 1, TNF-naïve	14/42 (32.8)	9/76 (12.3)	<b>2.81 (1.33, 5.95)</b>	<b>0.21 (0.05, 0.37)</b>	<b>3.72 (1.44, 9.59)</b>
GEMINI 1, TNF- IR	7/29 (23.5)	3/63 (5.3)	<b>5.07 (1.41, 18.21)</b>	<b>0.19 (0.03, 0.27)</b>	<b>6.36 (1.51, 26.81)</b>
Motoya, TNF-naïve	18/65 (28.1)	4/41 (10.9)	<b>2.84 (1.03, 7.80)</b>	<b>0.18 (0.04, 0.32)</b>	<b>3.54 (1.10, 11.37)</b>
Motoya, TNF-exp	11/57 (18.9)	2/41 (5.1)	3.96 (0.93, 16.90)	<b>0.14 (0.02, 0.27)</b>	4.66 (0.97, 22.32)
Pooled, TNF-naïve	32/106 (30.0)	14/117 (11.8)	<b>2.52 (1.43, 4.46)</b>	<b>0.18 (0.08, 0.29)</b>	<b>3.18 (1.59, 6.38)</b>
MA, TNF-naïve	32/107 (29.9)	13/117 (11.1)	<b>2.82 (1.55, 5.15)</b>	<b>0.19 (0.09, 0.30)</b>	<b>3.65 (1.75, 7.61)</b>
Pooled, TNF-exp/IR	18/86 (20.4)	5/104 (5.2)	<b>4.35 (1.69, 11.24)</b>	<b>0.16 (0.07, 0.26)</b>	<b>5.24 (1.86, 14.80)</b>
MA, TNF-exp/IR	18/86 (20.4)	5/104 (5.2)	<b>4.55 (1.74, 11.88)</b>	<b>0.16 (0.06, 0.26)</b>	<b>5.52 (1.91, 15.92)</b>
<b>Clinical remission: ADA v PBO (Wk 52)</b>					
SUZUKI, ITT/TNF-naïve	41/177 (23.0) <sup>^</sup>	7/96 (7.3)	<b>3.18 (1.48, 6.81)</b>	<b>0.16 (0.08, 0.24)</b>	<b>3.83 (1.65, 8.92)</b>
ULTRA 2, TNF-naïve	33/150 (22.0)	18/145 (12.4)	<b>1.77 (1.05, 3.00)</b>	<b>0.10 (0.01, 0.18)</b>	<b>1.99 (1.06, 3.72)</b>
ULTRA 2, TNF-exp	10/98 (10.2)	3/101 (3.0)	3.44 (0.97, 12.11)	0.07 (0.00, 0.14)	3.71 (0.99, 13.92)
MA, TNF-naïve	74/327 (22.6)	25/241 (10.4)	<b>2.22 (1.26, 3.91)</b>	<b>0.13 (0.07, 0.19)</b>	<b>2.59 (1.38, 4.89)</b>
<b>Not achieving clinical remission: UST pooled v PBO (Wk 52, predicted)</b>					
UNIFI, DMARD-IR	64/111 (57.7)	138/158 (87.3)	<b>0.66 (0.56, 0.78)</b>	<b>-0.30 (-0.40, -0.19)</b>	<b>0.20 (0.11, 0.36)</b>
UNIFI, bDMARD-IR	75/104 (72.1)	151/161 (93.8)	<b>0.77 (0.68, 0.87)</b>	<b>-0.22 (-0.31, -0.12)</b>	<b>0.17 (0.08, 0.37)</b>
<b>Not achieving clinical remission: ADA v PBO (Wk 52)</b>					
SUZUKI, ITT/TNF-naïve	136/177 (76.8)	89/96 (92.7)	<b>0.83 (0.75, 0.91)</b>	<b>-0.16 (-0.24, -0.08)</b>	<b>0.26 (0.11, 0.61)</b>
ULTRA 2, TNF-naïve	117/150 (78.0)	127/145 (87.6)	<b>0.89 (0.80, 0.99)</b>	<b>-0.10 (-0.18, -0.01)</b>	<b>0.50 (0.27, 0.94)</b>
ULTRA 2, TNF-exp	88/98 (89.8)	98/101 (97.0)	0.93 (0.86, 1.00)	<b>-0.07 (-0.14, -0.00)</b>	0.27 (0.07, 1.01)
MA, TNF-naïve	253/327 (77.4)	216/241 (89.6)	<b>0.86 (0.80, 0.92)</b>	<b>-0.13 (-0.19, -0.07)</b>	<b>0.39 (0.20, 0.73)</b>
<b>Indirect comparisons, clinical remission</b>					
UST (UNIFI) v VZD (MA), DMARD-IR/TNF-naïve			1.19 (0.56, 2.54)	0.11 (-0.04, 0.26)	1.39 (0.54, 3.59)
UST (UNIFI) v VZD (pooled), DMARD-IR/TNF-naïve			1.33 (0.64, 2.78)	0.12 (-0.03, 0.27)	1.59 (0.64, 4.00)
UST (UNIFI) v ADA (MA), DMARD-IR/TNF-naïve			1.51 (0.73, 3.14)	<b>0.17 (0.05, 0.29)</b>	1.96 (0.82, 4.69)
UST (UNIFI) v VZD (MA), bDMARD-IR/TNF-exp			0.99 (0.31, 3.19)	0.06 (-0.08, 0.20)	1.06 (0.29, 3.92)
UST (UNIFI) v VZD (pooled), bDMARD-IR/TNF-exp			1.03 (0.32, 3.30)	0.06 (-0.07, 0.19)	1.12 (0.31, 4.06)
UST (UNIFI) v ADA (ULTRA 2), bDMARD-IR/TNF-exp			1.31 (0.31, 5.46)	<b>0.15 (0.03, 0.27)</b>	1.57 (0.34, 7.27)
<b>Indirect comparisons, not achieving clinical remission</b>					
UST (UNIFI) v ADA (MA), DMARD-IR/TNF-naïve			<b>0.77 (0.64, 0.92)</b>	<b>-0.17 (-0.29, -0.05)</b>	0.51 (0.21, 1.23)
UST (UNIFI) v ADA (ULTRA 2), bDMARD-IR/TNF-exp			<b>0.83 (0.72, 0.96)</b>	<b>-0.15 (-0.27, -0.03)</b>	0.63 (0.14, 2.93)

Source: Tables 2-81, 2-82 and 2-83, pp205-206 of the submission; 'Attachment 20 – Maintenance ITC analyses.xlsx'

Abbreviations: ADA = adalimumab; bDMARD = biologic disease-modifying antirheumatic drugs; DMARD = disease-modifying antirheumatic drugs; PBO = placebo; UST = ustekinumab; VDZ = vedolizumab; IV = intravenous; IR = inadequate response; MA = meta-analysis, TNF= tumour necrosis factor

<sup>^</sup> Results at Week 52 pooled across both ADA arms in the trial (i.e. 40mg Q2W following induction with either 180mg then 80mg, or 80mg then 40mg at Week 0 and 2, respectively. Results for patients treated with the approved induction dose only (i.e. 180mg then 80mg) were similar, 18/90 (20.0%).

**Table 7: Trial-design-adjusted indirect comparisons comparing UST versus VDZ and ADA for clinical response at Week 52/60 (maintenance therapy) – predicted results for UST and VDZ trials**

Trial	Drug n/N (%)	Control n/N (%)	RR (95% CI)	RD (95% CI)	OR (95% CI)
<b>Clinical response: UST pooled v PBO (Wk 52, predicted)</b>					
UNIFI, DMARD-IR	78/111 (70.6)	36/158 (22.8)	<b>3.08 (2.26, 4.21)</b>	<b>0.47 (0.37, 0.58)</b>	<b>8.01 (4.62, 13.90)</b>
UNIFI, bDMARD-IR	52/104 (50.5)	29/161 (17.8)	<b>2.78 (1.90, 4.07)</b>	<b>0.32 (0.21, 0.43)</b>	<b>4.55 (2.61, 7.94)</b>
<b>Clinical response: VDZ v PBO (Wk 52/60, predicted)</b>					
GEMINI 1, TNF-naïve	21/42 (50.7)	13/76 (17.1)	<b>2.92 (1.64, 5.22)</b>	<b>0.33 (0.16, 0.50)</b>	<b>4.85 (2.07, 11.34)</b>
GEMINI 1, TNF- IR	10/29 (33.3)	10/63 (15.5)	<b>2.17 (1.02, 4.64)</b>	0.19 (-0.01, 0.38)	<b>2.79 (1.00, 7.75)</b>
Motoya, TNF-naïve	33/65 (51.5)	8/41 (18.7)	<b>2.60 (1.34, 5.07)</b>	<b>0.31 (0.14, 0.48)</b>	<b>4.25 (1.71, 10.60)</b>
Motoya, TNF-exp	20/57 (35.3)	7/41 (16.2)	2.06 (0.96, 4.40)	<b>0.18 (0.01, 0.35)</b>	2.63 (0.99, 6.99)
Pooled, TNF-naïve	54/106 (51.2)	21/117 (17.7)	<b>2.84 (1.85, 4.36)</b>	<b>0.33 (0.21, 0.45)</b>	<b>4.75 (2.59, 8.71)</b>
MA, TNF-naïve	54/106 (51.2)	21/117 (17.7)	<b>2.78 (1.80, 4.31)</b>	<b>0.32 (0.20, 0.44)</b>	<b>4.56 (2.45, 8.50)</b>
Pooled, TNF-exp/IR	30/86 (34.6)	16/104 (15.8)	<b>2.27 (1.33, 3.87)</b>	<b>0.19 (0.07, 0.32)</b>	<b>2.95 (1.47, 5.89)</b>
MA, TNF-exp/IR	30/86 (34.6)	17/104 (16.3)	<b>2.11 (1.23, 3.62)</b>	<b>0.18 (0.05, 0.31)</b>	<b>2.70 (1.33, 5.48)</b>
<b>Clinical response: ADA v PBO (Wk 52)</b>					
SUZUKI, ITT/TNF-naïve	55/177 (31%) <sup>^</sup>	17/96 (18%)	<b>1.75 (1.08, 2.85)</b>	<b>0.13 (0.03, 0.24)</b>	<b>2.09 (1.13, 3.87)</b>
ULTRA 2, TNF-naïve	55/150 (36.7)	35/145 (24.1)	<b>1.52 (1.06, 2.17)</b>	<b>0.13 (0.02, 0.23)</b>	<b>1.82 (1.10, 3.01)</b>
ULTRA 2, TNF-exp	20/98 (20.4)	10/101 (9.9)	<b>2.06 (1.02, 4.18)</b>	<b>0.11 (0.01, 0.20)</b>	<b>2.33 (1.03, 5.28)</b>
MA, TNF-naïve	110/327 (33.6)	52/241 (21.6)	<b>1.60 (1.20, 2.13)</b>	<b>0.13 (0.06, 0.20)</b>	<b>1.93 (1.30, 2.84)</b>
<b>Indirect comparisons, clinical response</b>					
UST (UNIFI) v VZD (Pooled), DMARD-IR/TNF-naïve			1.09 (0.64, 1.84)	0.14 (-0.02, 0.30)	1.69 (0.74, 3.83)
UST (UNIFI) v VZD (MA), DMARD-IR/TNF-naïve			1.11 (0.65, 1.89)	0.15 (-0.01, 0.31)	1.76 (0.77, 4.03)
UST (UNIFI) v ADA (ULTRA 2), DMARD-IR/TNF-naïve			<b>2.03 (1.26, 3.26)</b>	<b>0.34 (0.19, 0.49)</b>	<b>4.40 (2.09, 9.28)</b>
UST (UNIFI) v ADA (MA), DMARD-IR/TNF-naïve			<b>1.93 (1.26, 2.94)</b>	<b>0.34 (0.21, 0.47)</b>	<b>4.15 (2.11, 8.15)</b>
UST (UNIFI) v VZD (Pooled), bDMARD-IR/TNF-exp			1.23 (0.64, 2.36)	0.13 (-0.04, 0.30)	1.54 (0.63, 3.75)
UST (UNIFI) v VZD (MA), bDMARD-IR/TNF-exp			1.32 (0.68, 2.56)	0.14 (-0.03, 0.31)	1.69 (0.69, 4.15)
UST (UNIFI) v ADA (ULTRA 2), bDMARD-IR/TNF-exp			1.35 (0.61, 3.01)	<b>0.21 (0.06, 0.36)</b>	1.95 (0.73, 5.25)

Source: Tables 2-84, and 2-85, p207 of the submission; 'Attachment 20 – Maintenance ITC analyses.xlsx'

Abbreviations: ADA = adalimumab; bDMARD = biologic disease-modifying antirheumatic drugs; DMARD = disease-modifying antirheumatic drugs; PBO = placebo; UST = ustekinumab; VDZ = vedolizumab; IV = intravenous; IR = inadequate response; MA = meta-analysis, TNF= tumour necrosis factor.

<sup>^</sup> Results at Week 52 pooled across both ADA arms in the trial (i.e. 40mg Q2W following induction with either 180mg then 80mg, or 80mg then 40mg at Week 0 and 2, respectively. Results for patients treated with the approved induction dose only (i.e. 180mg then 80mg) were not reported separately.

6.35 Based on the modelled results for the UST and VDZ trials, the indirect treatment comparisons indicated that UST had similar effectiveness to VDZ and was more effective than ADA in terms of both clinical remission and clinical response at Week 52. The submission argued that non-statistically significant findings versus ADA using the RR statistic was due to the non-symmetric nature of the variance of the log RR, and this comparison became statistically significant using the non-responder results. The results of the submission’s trial-design-adjusted indirect treatment comparisons are considered highly uncertain given the unorthodox method used to estimate point estimates and confidence intervals. It is noted that the numerically higher response rates at Week 52 estimated for UST compared to the other active treatments was being driven by numerically higher initial response rates at Week 8.

6.36 Assuming that different carry over effects were the only difference between patients enrolled and randomised in the maintenance phases of the UST and VDZ trials (i.e. no differences in observed or unobserved factors), then under that assumption, a naïve comparison comparing response rates with UST and VDZ directly would be more

straight-forward than the submission’s modelling approach and may provide a more reliable estimate. Based on the ITT population, naïve comparisons would also support a conclusion of similar effectiveness between UST (pooled Q8W and Q12W) versus VDZ for maintenance therapy in terms of clinical remission (RR = 0.91, 95%CI: 0.76, 1.08) and clinical response (RR = 1.12, 95%CI: 0.99, 1.27). For completeness, results of a standard indirect treatment comparison between UST versus VDZ in maintenance therapy based on observed trial results, conducted during the evaluation, indicated that UST was likely inferior to VDZ for maintenance treatment (see Table 8).

**Table 8: Indirect comparisons comparing UST versus VDZ for clinical remission and clinical response at Week 52/60 | clinical response following induction treatment<sup>^</sup> (maintenance therapy)**

	RR (95% CI)	RD (95% CI)	OR (95% CI)
<b>Indirect comparisons: clinical remission</b>			
UST pooled (UNIFI) v VDZ IV/SC pooled (MA), ITT	0.71 (0.47, 1.08)	<b>-0.11 (-0.22, -0.00)</b>	0.58 (0.32, 1.04)
UST pooled (UNIFI) v VDZ IV pooled (MA), DMARD-IR/TNF-naïve	0.72 (0.44, 1.19)	-0.11 (-0.27, 0.05)	0.59 (0.28, 1.24)
UST pooled (UNIFI) v VDZ IV pooled (MA), bDMARD-IR/TNF-exp	0.39 (0.14, 1.06)	<b>-0.23 (-0.38, -0.09)</b>	<b>0.24 (0.07, 0.75)</b>
<b>Indirect comparisons: clinical response</b>			
UST pooled (UNIFI) v VDZ pooled (MA), ITT	<b>0.64 (0.47, 0.87)</b>	-0.12 (-0.24, 0.00)	<b>0.56 (0.33, 0.98)</b>
UST pooled (UNIFI) v VDZ pooled (MA), DMARD-IR/TNF-naïve	0.68 (0.46, 1.01)	-0.11 (-0.29, 0.07)	0.69 (0.12, 4.19)
UST pooled (UNIFI) v VDZ pooled (MA), bDMARD-IR/TNF-exp	0.69 (0.37, 1.29)	-0.08 (-0.29, 0.13)	0.60 (0.22, 1.65)

Source: constructed during the evaluation from corresponding trial publications

Abbreviations: bDMARD = biologic disease-modifying antirheumatic drugs; DMARD = disease-modifying antirheumatic drugs; UST = ustekinumab; VDZ = vedolizumab; SC=subcutaneous; IV = intravenous; IR = inadequate response; MA = meta-analysis; TNF= tumour necrosis factor.

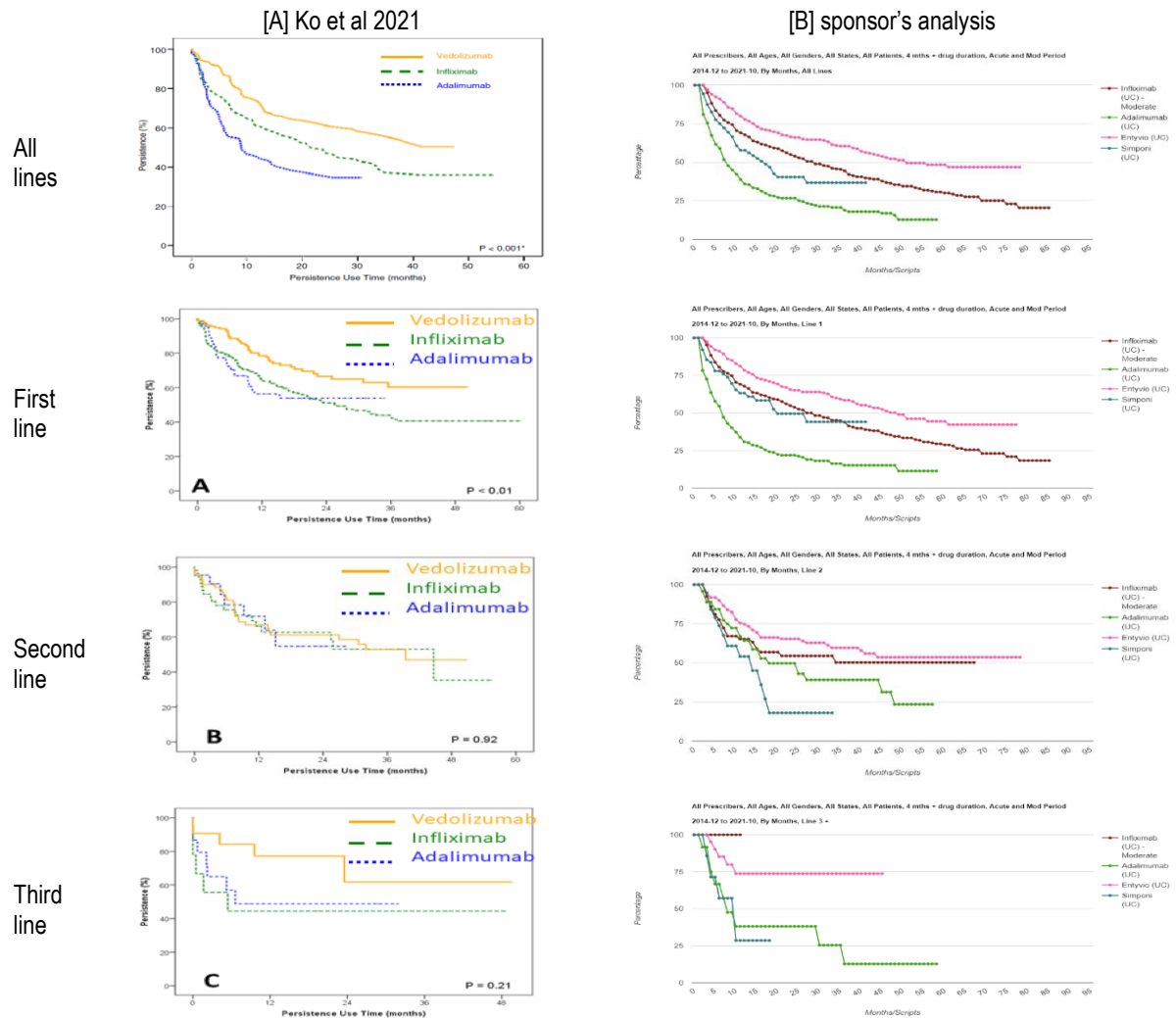
<sup>^</sup> Clinical response defined according to the full Mayo score

- 6.37 The Pre-Sub-Committee Response (PSCR) acknowledged there was some uncertainty in the modelled approach for indirect comparisons, however reiterated that the results were similar to the unadjusted comparisons, and argued the overall conclusions of the comparisons remained unchanged.
- 6.38 The ESC considered that, while the modelled indirect comparison approach used in the submission introduced additional uncertainties in the indirect comparisons, the argument of carry-over effects related to UST treatment into the placebo arms of the UST maintenance studies due to the randomised withdrawal design and biological effects of UST (as an IL-12/23 inhibitor) was plausible, however the magnitude of impact and reliability of the modelled approach to address this issue was uncertain. However, the ESC noted the results of the unadjusted comparison also did not indicate any substantial differences between UST and VDZ and considered, on balance, that the evidence tended to support non-inferiority of UST and VDZ in the maintenance phase.

Supplementary evidence – treatment persistence analysis

- 6.39 Figure 3 presents the (unadjusted) Kaplan-Meier curves of treatment persistence with PBS-listed treatments for MSUC (VDZ, IFX, ADA, GOL) reported in Ko et al 2021 and the sponsor's internal analysis. Both studies analysed data from the 10% PBS sample, over at least five years from market inception (seven years in the sponsor's analysis) and used similar definitions of persistence (slightly stricter definition in the sponsor's analysis). Ko et al 2021 included 864 courses of treatment for MSUC whereas the sponsor's internal analysis included 1,551 courses of treatment for MSUC. The Kaplan-Meier curves presented in the submission did not report the number of patients remaining at risk (or confidence intervals) over time. In addition, these analyses were specific to the IFX IV and VDZ IV dosing regimens, because the follow up periods do not capture patients who switched to IFX SC (available from July 2021) or VDZ SC (available from September 2021) for maintenance treatment.

Figure 4: Kaplan-Meier curve for persistence of biological agents in MSUC.



Source Figures 2-16, 2-17, 2-20, 2-21, pp.211-217 of the submission.

CI = confidence interval. Entyvio=vedolizumab, Simponi=golimumab

\* The median survival or its confidence interval cannot be calculated when event rate is higher than 50%. The log rank score P value for the persistence survival curve of the four biological agents is shown.

6.40 The results from both population-level persistence studies showed that treatment persistence was higher with VDZ (Entyvio®) compared to other treatments (GOL – Simponi®, IFX and ADA) overall and as first-line treatment, but there were small sample sizes for comparisons in subsequent lines. The submission stated that fewer patients use IFX for later lines of therapy, given IFX is often used in acute phase of MSUC. As treatment decisions in practice are not random, care should be taken when interpreting these (unadjusted) results because the analyses do not control for differences in observed or unobserved patient characteristics, or changes in other factors over time (e.g. prescribing behaviours) that may potentially explain differences in treatment persistence. The treatment persistence outcome may also not be the most reliable proxy for effectiveness in this setting because factors unrelated to effectiveness (or safety) may explain to decision to discontinue treatment. The

submission noted that patients treated with VDZ were generally older and more with prior treatment failure (i.e. VDZ more used as second- and third-line treatment), which the submission argued biased against VDZ.

- 6.41 Despite no persistence data comparing UST to other PBS-listed comparators for MSUC, the submission argued that UST would have at least similar treatment persistence as VDZ for the following reasons:
- UST, like VDZ, is less immunogenic than TNF inhibitors, resulting in fewer neutralising antibodies and a lower rate of loss of response;
  - UST has a more favourable safety profile compared with the TNF inhibitors;
  - UST is a highly effective biologic treatment for MSUC;
  - UST is dosed less frequently than other treatment, hence it is more convenient and acceptable to patients;
  - Population-level persistence data for Crohn’s disease, also reported in Ko et al 2021, shows high treatment persistence with UST compared to other biologics including VDZ.
- 6.42 The ESC did not consider the persistence data provided supported the claim that VDZ is the most effective biologic for the treatment of MSUC to be informative for decision-making, on the basis that there are many reasons why patients cease or change treatment and there was no evidence supported to validate persistence data as a valid surrogate measure of effectiveness.
- 6.43 The Pre-PBAC Response argued the persistence data provided was reliable for informing the claim that VDZ was the most effective PBS-listed therapy for MSUC, and noted a study published in 2021 (Blesl et al 2021)<sup>4</sup>, which retrospectively assessed the persistence of anti-TNF $\alpha$  therapy in patients with inflammatory bowel disease and found the limited long-term treatment persistence was mainly due to treatment failure (insufficient drug effect or loss of response) and/or side effect which contributed to near 80% of the discontinuation. Further, the sponsor also argued that persistence to therapy has meaningful clinical implications, and noted the results of Carter et al (2011)<sup>5</sup> which found persistence to IFX maintenance therapy in UC was associated with fewer hospitalisations. The sponsor also noted the clinician input in the sponsor hearing as further supportive evidence of the relationship between treatment persistence and clinical effectiveness (paragraph 6.1 refers). Overall, the PBAC considered there was plausible evidence to suggest a longer persistence to

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<sup>4</sup> Blesl, A., Binder, L., Högenauer, C., Wenzl, H., Borenich, A., Pregartner, G., Berghold, A., Mestel, S., Kump, P., Baumann-Durchschein, F., & Petritsch, W. (2021). Limited long-term treatment persistence of first anti-TNF therapy in 538 patients with inflammatory bowel diseases: a 20-year real-world study. *Alimentary pharmacology & therapeutics*, 54(5), 667–677. <https://doi.org/10.1111/apt.16478>

<sup>5</sup> Carter, C. T., Leher, H., Smith, P., Smith, D. B., & Waters, H. C. (2011). Impact of persistence with infliximab on hospitalizations in ulcerative colitis. *The American journal of managed care*, 17(6), 385–392.

treatment with VDZ over IFX or ADA in MSUC, however also noted no clear evidence to validate persistence as a surrogate for clinical effectiveness in MSUC was presented.

### Comparative harms

- 6.44 In UNIFI, the incidence of any adverse events (AEs) was similar between UST and PBO for induction and maintenance therapy, with few patients experiencing serious or severe AEs. During the maintenance phase, more patients treated with PBO experienced an AE leading to study discontinuation compared to UST SC (mostly attributed to worsening symptoms of ulcerative colitis in the CSR). Fewer patients experienced an AE with the UST Q12W dosing regimen compared to the UST Q8W dosing regimen.
- 6.45 To inform the relative safety profile of UST versus VDZ and ADA, the submission conducted a naïve comparison of adverse event outcomes reported at comparable time points across the trials, summarised in
- 6.46 Table 9 and
- 6.47 Table 10. Comparing safety outcomes across the treat through (ADA) and the randomised withdrawal (UST and VDZ) maintenance trials was problematic given patients in the PBO arm of the randomised withdrawal trials had received active induction treatment. It was also noted that the safety data was not reported consistently across the trials, and some trials only reported safety for induction only, maintenance only or both combined.

**Table 9: Summary of adverse events at Weeks 6/8/10 in induction trials for UST, VDZ and ADA**

Trial ID	Drug n/N (%)	PBO n/N (%)	RR (95% CI)	RD (95% CI)
<b>Any adverse event</b>				
UST IV ~ 6mg/kg v PBO (UNIFI)	160/320 (50.0)	153/319 (48.0)	1.04 (0.89, 1.22)	0.02 (-0.06, 0.10)
VDZ IV 300mg v PBO (MA: GEMINI-1, Motoya)	172/389 (44.2)	112/231 (48.5)	0.90 (0.76, 1.07)	-0.05 (-0.13, 0.03)
ADA 160->80mg v PBO (MA: ULTRA 1, Suzuki)	152/313 (48.6)	153/319 (48.0)	1.01 (0.86, 1.19)	0.01 (-0.07, 0.08)
<b>Serious adverse event</b>				
UST IV ~ 6mg/kg v PBO (UNIFI)	10/320 (3.1)	21/319 (6.6)	0.47 (0.23, 0.99)	-0.03 (-0.07, -0.00)
VDZ IV 300mg v PBO (MA: GEMINI-1, Motoya)	15/389 (3.9)	14/231 (6.1)	0.63 (0.17, 2.33)	-0.02 (-0.08, 0.04)
ADA 160->80mg v PBO (MA: ULTRA 1, Suzuki)	13/313 (4.2)	24/319 (7.5)	0.55 (0.29, 1.07)	-0.03 (-0.07, 0.00)
<b>Discontinuation due to adverse event</b>				
UST IV ~ 6mg/kg v PBO (UNIFI)	1/320 (0.3)	3/319 (0.9)	0.33 (0.03, 3.18)	-0.01 (-0.02, 0.01)
VDZ IV 300mg v PBO (Motoya)	8/164 (4.9)	2/82 (2.4)	2.00 (0.43, 9.21)	0.02 (-0.02, 0.07)
ADA 160->80mg v PBO (MA: ULTRA-1, Suzuki)	18/313 (5.8)	16/319 (5.0)	1.14 (0.59, 2.21)	0.01 (-0.03, 0.04)
<b>Serious Infections</b>				
UST IV ~ 6mg/kg v PBO (UNIFI)	1/320 (0.3)	4/319 (1.3)	0.25 (0.03, 2.22)	-0.01 (-0.02, 0.00)
VDZ IV 300mg v PBO (MA: GEMINI-1, Motoya <sup>a</sup> )	2/389 (0.5)	5/231 (2.2)	0.23 (0.05, 1.20)	-0.02 (-0.04, 0.00)
ADA 160->80mg v PBO (MA: ULTRA-1, Suzuki)	3/313 (1.0)	3/319 (0.9)	1.03 (0.02, 49.90)	0.01 (-0.42, 0.06)

Source: Table 2-53, p166 of the submission, with risk statistics conducted during the evaluation. Shaded areas indicate data previously seen by the PBAC.

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ADA=adalimumab; UST=ustekinumab; VDZ=vedolizumab; CI=confidence interval; MA=meta-analysis; n=number of participants with event; N=total participants in group, RD=risk difference, RR=risk ratio; IV = intravenous.

<sup>a</sup> Table 2-53 of the submission reported as NR (not reported) but the data was extracted from the Motoya source publication (text on p10).

**Table 10: Summary of adverse events in UST, VDZ and ADA maintenance trials**

Trial ID	Drug n/N (%)	PBO n/N (%)	RR (95% CI)	RD (95% CI)
<b>Any adverse event</b>				
UST SC 90 mg Q8W or Q12 QW pooled v PBO (UNIFI)	255/348 (73.3)	138/175 (78.9)	0.93 (0.84, 1.03)	-0.06 (-0.13, 0.02)
VDZ IV 300mg or SC 108mg pooled v PBO (MA: GEMINI-1, VISIBLE 1, Motoya)	643/821 (78.3)	296/373 (79.4)	1.00 (0.91, 1.09)	-0.00 (-0.07, 0.07)
ADA 80mg v PBO (ULTRA 2)	213/257 (82.9)	218/260 (83.8)	0.99 (0.92, 1.07)	-0.01 (-0.07, 0.05)
<b>Serious adverse event</b>				
UST SC 90 mg Q8W or Q12 QW pooled v PBO (UNIFI)	28/348 (8.0)	17/175 (9.7)	0.83 (0.47, 1.47)	-0.02 (-0.07, 0.04)
VDZ IV 300mg or SC 108mg pooled v PBO (MA: GEMINI-1, VISIBLE 1, Motoya)	98/821 (11.9)	46/373 (12.3)	0.95 (0.69, 1.32)	0.00 (-0.04, 0.04)
ADA 80mg v PBO (ULTRA 2)	31/257 (12.1)	32/260 (12.3)	0.98 (0.62, 1.56)	0.00 (-0.06, 0.05)
<b>Discontinuation due to adverse events</b>				
UST SC 90 mg Q8W or Q12 QW pooled v PBO (UNIFI)	14/348 (4.0)	20/175 (11.4)	0.35 (0.18, 0.68)	-0.07 (-0.13, -0.02)
VDZ 300mg v PBO (MA: Motoya, VISIBLE 1)	9/201 (4.5)	11/98 (11.2)	0.43 (0.18, 1.06)	-0.06 (-0.13, 0.01)
ADA 80mg v PBO (ULTRA 2)	23/257 (8.9)	34/260 (13.1)	0.68 (0.41, 1.13)	-0.04 (-0.10, 0.01)
<b>Serious Infections</b>				
UST SC 90 mg Q8W or Q12 QW pooled v PBO (UNIFI)	9/348 (2.6)	4/175 (2.3)	1.13 (0.35, 3.62)	0.00 (-0.02, 0.02)
VDZ 300mg v PBO (MA: GEMINI 1, Motoya <sup>a</sup> , VISIBLE 1 <sup>b</sup> )	15/821 (1.9)	9/373 (2.4)	0.74 (0.33, 1.67)	-0.00 (-0.02, 0.02)
ADA 80mg v PBO (ULTRA 2)	4/257 (1.6)	5/260 (1.9)	0.81 (0.22, 2.98)	0.00 (-0.03, 0.02)
<b>Malignancy</b>				
UST SC 90 mg Q8W or Q12 QW pooled v PBO (UNIFI)	2/348 (0.6)	0/175 (0)	2.52 (0.12, 52.24)	0.01 (-0.01, 0.02)
VDZ 300mg v PBO (GEMINI 1)	1/620 (0.2)	3/275 (1.1)	0.15 (0.02, 1.42)	-0.01 (-0.02, 0.00)
ADA 80mg v PBO (ULTRA 2)	2/257 (0.8)	0/260 (0)	5.06 (0.24, 104.84)	0.01 (-0.01, 0.02)

Source: Table 2-56, p170 of the submission, with risk statistics conducted during the evaluation. Shaded areas indicate data previously seen by the PBAC.

ADA=adalimumab; UST=ustekinumab; VDZ=vedolizumab; CI=confidence interval; MA=meta-analysis; n=number of participants with event; N=total participants in group, QxW=once every x weeks; RD=risk difference, RR=risk ratio; IV=intravenous; SC=subcutaneous.

<sup>a</sup> Table 2-56 of the submission reported as NR (not reported) but the data was extracted from the Motoya source publication (text on p11).

<sup>b</sup> Table 2-56 of the submission reported as NR (not reported) but data was extracted from the VISIBLE 1 source publication (text on p569).

6.48 The submission concluded that the safety profile of UST in the induction and maintenance phase was similar to VDZ and ADA. The submission stated that in clinical practice it is accepted by clinicians that UST offers safety advantages with regards to infections, serious infections and potentially malignancies over TNF inhibitors, and hence UST is preferred in patients where safety of biologics is more of a concern, such as elderly patients, or patients with co-morbid conditions. The submission also stated that significant differences in these AEs cannot be seen in comparisons of RCTs due to fewer patients recruited and shorter follow-up compared to large real world observation studies or registries. The submission claimed that UST has the potential to have superior safety over ADA given the known safety advantages of UST over TNF inhibitors. The submission did not present any evidence to support a claim of superior

safety with UST over TNF inhibitors, and the PBAC had previously considered UST as having a similar safety profile to TNF inhibitors for other indications.

### ***Benefits/harms***

6.49 Overall, for adults with MSUC, there were no expected clinically meaningful differences between UST and VDZ in terms of efficacy or between UST, VDZ and ADA in safety. Compared to ADA, indirect evidence suggested for every 100 adults treated, approximately 16 additional patients would achieve clinical response following induction treatment with UST (but no additional patients would achieve clinical remission).

### ***Clinical claim***

6.50 Based on the trial evidence (clinical remission and clinical response), the submission described UST as non-inferior in terms of effectiveness to VDZ and superior in terms of effectiveness to ADA, for both induction and maintenance therapy. In terms of safety, the submission described UST as non-inferior to VDZ and ADA. The submission also described VDZ as being more effective than other PBS-listed treatments based on population-level persistence data, and argued that UST would likely be non-inferior to VDZ in terms of treatment persistence (and by extension, also superior to other PBS-listed treatments).

6.51 The evaluation and ESC considered the therapeutic conclusion of non-inferior effectiveness and safety versus VDZ and superior effectiveness and non-inferior safety versus ADA was generally supported by the clinical evidence presented in the submission. Notwithstanding the concerns related to the submission's trial-design-adjusted indirect treatment comparisons for maintenance therapy, the trials showed a similar proportion of patients with clinical response following induction treatment maintained clinical response or achieved clinical remission at Week 52 with UST and VDZ. The PBAC had also previously accepted that ADA as having inferior effectiveness compared to other PBS-listed treatments. The descriptions provided in relation to real world effectiveness however should be interpreted with caution given its potential for bias. No persistence evidence was presented for UST in MSUC, thus the claims were speculative.

6.52 The PBAC considered claim of non-inferior comparative effectiveness and safety of UST to VDZ was reasonable. The PBAC also considered that, on balance, the claim of superior comparative effectiveness to ADA may also be reasonable, at least for induction therapy (paragraph 7.5 refers).

6.53 In addition, the PBAC considered the claim that VDZ (and by inference UST) is the most effective PBS-listed treatment option for MSUC, which was based on persistence data, was not adequately supported as no evidence was presented to validate persistence as a surrogate for clinical effectiveness was presented.

### **Economic analysis**

6.54 The submission presented an ‘illustrative’ cost-minimisation analysis between UST and VDZ IV based on published AEMP (because the effective AEMP of VDZ was unknown to the sponsor). The equi-effective doses were based on the recommended doses:

- UST IV weight-based dose (~6 mg/kg) at Week 0, UST SC 90 mg at Week 8, then UST SC 90 mg Q8W thereafter;
- UST IV weight-based dose (~6 mg/kg) at Week 0, UST SC 90 mg at Week 8, then UST SC 90 mg Q12W thereafter;
- VDZ IV 300 mg at Weeks 0, 2, 6, then Q8W thereafter.

The cost-minimisation analysis did not consider the VDZ SC dosing regimen for maintenance therapy. The PBAC recommended VDZ SC on a cost-minimisation to VDZ IV, assuming an equi-effective dose VDZ IV 300 mg every 8 weeks = VDZ SC 108 mg every 2 weeks. The cost-minimisation analysis between VDZ SC and VDZ IV was conducted over a two year period and accounted for IV administration costs (Table 12, VDZ PSD, Nov 2020). Given this, the submission stated that the UST SC 90 mg every 8 or 12 weeks should also be considered equi-effective to VDZ SC 108 mg every 2 weeks for maintenance therapy.

6.55 The submission stated that the cost-minimisation analysis should be updated with the effective AEMP as well as an appropriate unit cost for screening/monitoring for progressive multifocal leukoencephalopathy (PML) associated with VDZ, but otherwise follow the same proposed methodology:

- The analysis results in equivalent total costs for UST and VDZ over the first two years (i.e. 104 weeks) of treatment at the nominated equi-effective doses. This corresponded to 15 doses/vials of VDZ 300 mg and either 13 doses (Q8W regimen) or 9 doses (Q12W regimen) of UST. The UST IV loading dose was estimated to require an average of 3.04 x 130 mg vials based on the weight distribution of patients enrolled in UNIFI, and subsequent doses of UST each require one UST 90 mg pre-filled syringe.
- The analysis included a cost for IV administration assuming the same unit cost (MBS item 116) is applied to IV infusions with either UST or VDZ. The analysis also included a cost for screening and monitoring of PML for VDZ. A place-holder cost of zero dollars was assumed in the illustrative cost-minimisation analysis until the appropriate value is determined.
- The analysis was conducted separately for the initial treatment and the continuing treatment periods. The submission argued this was necessary because initial treatment with UST includes IV and SC formulations, whereas continuing treatment with UST only includes the SC formulation. First, the price was calculated for the UST SC pre-filled syringe to ensure cost equivalence with VDZ

over the maintenance period, then the price was calculated for UST IV to ensure cost equivalence with VDZ for the initial period. This step resulted in a different unit price for the UST IV and UST SC formulations.

- The analysis was also conducted separately for the UST Q8W and Q12W dosing regimens, given they require a different number of scripts for maintenance therapy. To estimate the weighted unit cost for the UST IV and UST SC formulations across the two dosing regimens, the submission assumed 88% of patients will use the Q8W dosing regimen and 12% of patients will use the Q12W dosing regimen based on a sponsor commissioned survey of Australian gastroenterologists (N=36).

6.56 The following issues were identified with the submission's proposed methodology for the cost-minimisation analysis that require consideration:

- The analysis assumed 15 doses of VDZ 300 mg would be required over the first 104 weeks of treatment. This was technically correct, but the 15th dose would be administered at Week 102 and provide treatment until Week 110. Hence, it might be more reasonable to cost 14.25 vials of VDZ 300 mg, corresponding exactly to 104 weeks of treatment.
- It may not be reasonable to assume the same unit cost for IV administration of VDZ and UST, given the VDZ is administered over 30 minutes whereas UST is administered over (at least) one hour. The submission also assumed no administration costs for SC injections, but some patients may require additional medical assistance or training prior to self-administration.
- It was unclear whether it was necessary to calculate different AEMPs for the UST IV and UST SC formulations. An alternative analysis could simply count the total number of vials and pre-filled syringes required over the first two years of treatment, and estimate an average price for the two formulations. This would mean, however, that costs for the initial and continuing treatment periods would no longer be equal across treatments.

6.57 The PSCR responded to the issues identified in the evaluation (paragraph 6.43 above) of the cost minimisation approach and provided updated cost minimised prices for UST, stating:

- The sponsor acknowledged the concerns regarding the number of VDZ vials and reduced the number to 14.25 from 15 (as suggested in the evaluation);
- To address the issues of differences in MBS costs, the revised cost minimisation approach applied differing IV infusion costs, attributing a higher cost to the UST infusions, which was more closely aligned to the administration times of UST and VDZ. Furthermore, the sponsor applied an MBS cost for the SC administration of UST, based on assumption that 10% of patients would require medical assistance to administer SC UST (assuming MBS item 3), an assumption the sponsor included in the cost minimisation approach for golimumab for MSUC;

- No adjustments were proposed to consider the impact of differential mark-ups for Section 100 (IV administration) and General Schedule items, on the basis that PBAC submission guidelines and previous precedent for cost minimisation analyses (including UST in Crohn’s disease and GOL in MSUC) state that these should be done at the ex-manufacturer price level.

6.58 The revised cost minimised prices for ustekinumab based on the PSCR-proposed changes are provided in the table below. The ESC noted the revised cost minimisation approach had not been independently evaluated.

**Table 11: Revised cost minimisation approach with updated inputs from the PSCR (based on published AEMP)**

Component	VDZ IV		UST (Q8W)			UST (Q12W)		
	Initial	Continuing	Initial		Continuing	Initial		Continuing
PBS item (max qty)	300 mg vial (1)	300 mg vial (1)	130 mg vial (1)	90 mg PFS (1)	90 mg PFS (1)	130 mg vial (1)	90 mg PFS (1)	90 mg PFS (1)
AEMP/vial	\$2,949.93	\$2,949.93	\$1,938.63	\$3,096.75	\$3,096.75	\$1,355.72	\$4,867.34	\$4,867.34
Units (infusions / injections)	3	11.25*	3.04	1	11	3.04	1	7
PBS costs	\$8,849.79	\$33,186.71	\$5,888.60	\$3,096.75	\$34,083.90	\$4,118.01	\$4,867.34	\$34,071.37
Admin. (IV infusion)/MBS	\$239.25	\$957.00	\$101.90	\$1.79	\$19.69	\$101.90	\$1.79	\$12.53
Total	\$9,089.04	\$34,083.90	\$9,089.04		\$34,083.90	\$9,089.04		\$34,083.90
Total / 104 weeks	\$43,172.94		\$43,172.94			\$43,172.94		
<b>Weighted average AEMP</b>								
<b>Dosing regimen</b>	<b>Proportional use</b>			<b>300 mg vial (1)</b>		<b>90 mg PFS (1)</b>		
UST Q8W	88%			\$1,938.63		\$3,096.75		
UST Q12W	12%			\$1,355.72		\$4,867.34		
	<b>Requested AEMP</b>			\$1,868.69		\$3,309.22		

Source: Consolidated from Tables 2 – 4 of the PSCR for consistency with format of the evaluation. Revised cost minimisation approach assumes use of MBS item 14245 for IV administration of ustekinumab and MBS item 116.

Abbreviations: IV=intravenous; MSUC=moderate to severe ulcerative colitis; PBO=placebo; PFS = pre-filled syringe; PML = progressive multifocal leukoencephalopathy; QxW = once every 8 weeks; SC= subcutaneous; UST=ustekinumab; VDZ=vedolizumab; TBC = to be confirmed with the Department of Health following PBAC recommendation.

### **Drug cost/patient/year**

6.59 Based on the proposed published DPMQs presented in the submission, the drug cost for UST per patient over the first year of treatment is \$33,267.37, assuming \$15,522.83 for initial treatment (Week 0 to 16; assuming public hospital price and an average of 3.04 vials for initial UST IV weight-based dose based on patients enrolled in UNIFI, followed by UST SC 90 mg at Week 8) and \$17,744.54 for continuing treatment (Week 16 to 52, 4.5 doses assuming UST SC 90 mg Q8W for maintenance, which is the main dosing frequency recommended in the PI). This is an overestimate of the annual cost per patient at the effective unit price.

### **Estimated PBS usage & financial implications**

6.60 This submission was not considered by DUSC. The submission used a market share approach to the financial estimates based on the published prices. Table 12 summarises the inputs used for the financial estimates.

Table 12: Key inputs for financial estimates

Component	Data source														
<b>Market share</b>															
Current market	<p><u>Usage of ADA, GOL, IFX, VDZ and TOF</u>: PBS/RPBS dispensed scripts reported by Services Australia from 2015 to 2021.</p> <p><u>Projected script usage for substituted treatments</u>: The submission indicated there was a need for a common unit for comparison across the biologics for the script volumes to be aggregated for analysis and forward estimations, and implemented the use of patient-weeks of treatment.</p> <ul style="list-style-type: none"> <li>• The script data extracted from the PBS/RPBS Services Australia database were converted to units of patient-weeks on treatment. The conversion was based on the average number of weeks of treatment per script expected to be dispensed to patients who follow the TGA approved and PBS listed dosing schedules for each agent, for the initial and continuing treatment periods. The submission calculated patient-weeks on treatment for historical script data from 2015 to 2021.</li> <li>• For extrapolation of the market in terms of the number of patient-weeks on treatment, the submission applied a linear trendline, on the basis it provided the best fit to the historical data. The submission acknowledged that the market is well-established, and also that market growth is declining. If the market is growing at a declining rate (as expected in a maturing market), it was possible that the estimated market growth may be overestimated.</li> <li>• Based on the projected patient-weeks on treatment, the submission estimated that the current market was █<sup>1</sup> scripts in Year 1, increasing to █<sup>2</sup> scripts in Year 6. The presentation of dispensed scripts in 2015 to 2021, derived patient weeks and current market size were presented by the submission as overall script and patient-week numbers, without distinguishing between initial and continuing treatment. The spreadsheet does however distinguish between different comparator script types/groupings based on DPMQ for costing purposes (see cost of medicines below).</li> </ul>														
Uptake and substitution	<p><u>Substitution rate</u>: The submission assumed that the uptake of UST was expected to be higher and quicker than that observed and forecast for ADA and GOL, due to UST having a better efficacy profile and a more convenient dosing schedule. The substitution rate assumed was 15% in Year 1, 20% in Year 2, 25% in Year 3, 29% in Year 4, 33% in Year 5 and 35% in Year 6. The substitution assumed proportion substitution from all comparator treatments, at the script level, based on their projected market shares, which seems reasonable. That is, the assumed 15% uptake of UST will lead to a 15% reduction in each of the comparator scripts.</p> <p><u>Number of scripts</u>: To estimate the number of UST scripts, the submission first estimated the reduction in comparator scripts using the assumed uptake of UST given the assumed proportional rate of substitution, then estimated the corresponding number of UST scripts based on script equivalence between UST and the comparators.</p> <p><u>Determination of script equivalence</u>: Calculated as the ratio of the number of scripts for UST and the number of scripts for the substituted agent over a 104-week period based on their respective script schedules. The script equivalence applied by the submission was as follows:</p> <p style="text-align: center;">Script equivalence</p> <table border="0" style="margin-left: 40px;"> <tr> <td>ADA : UST</td> <td>1:0.48</td> </tr> <tr> <td>GOL : UST</td> <td>1:0.48</td> </tr> <tr> <td>IFX IV : UST</td> <td>1:0.83</td> </tr> <tr> <td>IFX SC : UST</td> <td>1:0.46</td> </tr> <tr> <td>VDZ IV : UST</td> <td>1:0.83</td> </tr> <tr> <td>VDZ SC : UST</td> <td>1:0.46</td> </tr> <tr> <td>TOF : UST</td> <td>1:0.48</td> </tr> </table>	ADA : UST	1:0.48	GOL : UST	1:0.48	IFX IV : UST	1:0.83	IFX SC : UST	1:0.46	VDZ IV : UST	1:0.83	VDZ SC : UST	1:0.46	TOF : UST	1:0.48
ADA : UST	1:0.48														
GOL : UST	1:0.48														
IFX IV : UST	1:0.83														
IFX SC : UST	1:0.46														
VDZ IV : UST	1:0.83														
VDZ SC : UST	1:0.46														
TOF : UST	1:0.48														
<b>Utilisation</b>															
Number of scripts	<p><u>Expected UST usage</u>: The estimated total script numbers for UST was based on the proposed substitution rates and script equivalence (as described above); the submission then split total number of scripts into scripts for initial and continuing treatment based on the annual distribution of UST scripts for Crohn's disease.</p> <p><u>Grandfathered patients</u>: The submission stated that the sponsor requested a grandfather clause and at the time of the submission there were █<sup>3</sup> patients receiving UST; the sponsor may also</p>														

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Component	Data source
	initiate a Patient Familiarisation Program, and the sponsor can update on the number of patients requiring grandfathering closer to the listing date, if UST is recommended. The Section 4 estimates presented by the submission did not include these patients and their estimated script usage.
<b>Impact on other medicines</b>	
Other agents	Cost offsets for ADA, GOL, IFX, VDZ and TOF were applied, based on the nominated substitution rates and published prices for each agent.
<b>MBS usage and costs</b>	
MBS items	The submission indicated that two MBS items are used, MBS item 116 for administration of VDZ and the first dose of UST, and MBS item 14245 for IFX administration, at 80% benefit (\$63.80 and \$81.52, respectively). The submission provided cost offsets for these infusion costs. The submission assumed no administration costs for SC or oral therapies.

Source: Table 1-7, p54; Section 4.2.1, p251-p257; Section 4.3.2, p260; Section 4.5.2, p264-265 of the submission.

ADA = adalimumab; GOL = golimumab; IFX = infliximab; PI = product information; TOF = tofacitinib; UST = ustekinumab; VDZ = vedolizumab

The redacted values correspond to the following ranges:

<sup>1</sup> 60,000 to < 70,000

<sup>2</sup> 100,000 to < 200,000

<sup>3</sup> < 500

6.61 The submission estimated script numbers and costs for the PBS listing of UST for the treatment of MSUC in adult patients are provided below.

**Table 13: Estimated use and financial implications (based on published prices)**

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
<b>Estimated extent of use</b>						
Initiation scripts IV	<sup>1</sup>	<sup>1</sup>	<sup>1</sup>	<sup>1</sup>	<sup>1</sup>	<sup>1</sup>
Continuation scripts SC	<sup>2</sup>	<sup>2</sup>	<sup>7</sup>	<sup>7</sup>	<sup>8</sup>	<sup>8</sup>
Total number of scripts dispensed <sup>a</sup>	<sup>2</sup>	<sup>2</sup>	<sup>7</sup>	<sup>7</sup>	<sup>8</sup>	<sup>8</sup>
<b>Estimated financial implications<sup>b</sup> of UST for MSUC</b>						
Cost to PBS/RPBS less copayments	\$ <sup>3</sup>	\$ <sup>3</sup>	\$ <sup>9</sup>	\$ <sup>11</sup>	\$ <sup>13</sup>	\$ <sup>13</sup>
<b>Estimated financial implications of ADA, GOL, IFX, VDZ and TOF</b>						
Cost to PBS/RPBS less copayments	-\$ <sup>4</sup>	-\$ <sup>5</sup>	-\$ <sup>10</sup>	-\$ <sup>12</sup>	-\$ <sup>9</sup>	-\$ <sup>14</sup>
<b>Net financial implications<sup>b</sup></b>						
Net cost to PBS/RPBS	\$ <sup>5</sup>	\$ <sup>5</sup>	\$ <sup>5</sup>	\$ <sup>10</sup>	\$ <sup>10</sup>	\$ <sup>3</sup>
Net cost to MBS	-\$ <sup>6</sup>	-\$ <sup>6</sup>	-\$ <sup>6</sup>	-\$ <sup>6</sup>	-\$ <sup>6</sup>	-\$ <sup>6</sup>
<b>Net cost to Government</b>	<b>\$<sup>5</sup></b>	<b>\$<sup>5</sup></b>	<b>\$<sup>5</sup></b>	<b>\$<sup>10</sup></b>	<b>\$<sup>10</sup></b>	<b>\$<sup>3</sup></b>

Source: Table 4-10, p257; Table 4-12, p259; Table 4-15, p262; Table 4-20, p265; Table 4-21, p266 of the submission.

ADA = adalimumab; GOL = golimumab; IFX = infliximab; MSUC = moderate to severe ulcerative colitis; TOF = tofacitinib; UST = ustekinumab; VDZ = vedolizumab

<sup>a</sup> Dispensed scripts were based on the assumed substitution rates and calculated script equivalence between each drug and UST.

<sup>b</sup> All Section 4 estimates presented by the submission, and the submission's Section 4 Excel workbook, used a requested DPMQ of \$3,970.30 for the SC formulation of UST. There appeared to be an error in the amount of wholesale mark-up added (\$54.14 instead of \$27.07) and this was corrected during the evaluation. Values in the table corrected during the evaluation.

The redacted values correspond to the following ranges:

<sup>1</sup> 500 to < 5,000

<sup>2</sup> 5,000 to < 10,000

<sup>3</sup> \$40 million to < \$50 million

<sup>4</sup> \$10 million to < \$20 million

<sup>5</sup> \$20 million to < \$30 million

<sup>6</sup> \$0 to < \$10 million

<sup>7</sup> 10,000 to < 20,000

<sup>8</sup> 20,000 to < 30,000

<sup>9</sup> \$60 million to < \$70 million

<sup>10</sup> \$30 million to < \$40 million

<sup>11</sup> \$80 million to < \$90 million

<sup>12</sup> \$50 million to < \$60 million

<sup>13</sup> \$100 million to < \$200 million

<sup>14</sup> \$70 million to < \$80 million

6.62 The total cost to Government of listing UST for the treatment of MSUC in adults was estimated to be \$40 million to < \$50 million in Year 6, and a total of \$100 million to < \$200 million in the first 6 years of listing. The estimates presented in the submission were not reliable for the following reasons:

- The analysis used the published rather than effective prices; much of the estimated net cost was due to the high published price for the UST IV loading dose (i.e. approximately \$15,000) compared to published prices of the comparators;
- The assumed linear growth trend (from close to market inception) potentially overestimated the size of the total MSUC market;
- The analysis made an implicit assumption that the proportion of substituted comparators scripts for initial and continuing treatment remains constant over time, which was unlikely and has implications for costs;
- The estimates do not account for grandfathered patients; the submission estimated approximately < 500 patients currently receiving UST as long-term following up in UNIFI or as compassionate use (in addition to any Patient Familiarisation Program); and
- The analysis did not consider differences in the costs to government related to different fees and mark ups for Section 100 (VDZ IV and UST IV) and Section 85 drugs (UST SC). The PBAC had previously stated that there should be no additional cost to the government noting different fees and mark up apply to S100 and S85 listings (paragraph 7.16, VDZ PSD, November 2020).

6.63 The PSCR acknowledged the estimates were conducted based on published prices and would require amendment following a positive PBAC recommendation and provided updated estimates to account for the anticipated < 500 grandfather patients. Whilst not reproduced in full, the revised estimates resulted in an approximate 0.8% increase) in prescriptions (90,000 to < 100,000 scripts over 6 years) and 1.7% increase in costs to the health budget (\$100 million to < \$200 million) of UST over 6 years. The ESC acknowledged the advice in the PSCR and considered these responses were reasonable. Overall, the ESC considered that, if UST were listed on a cost minimisation basis with the least costly alternative, the listing would likely be cost neutral or modestly cost saving to the PBS, assuming minimal substitution of ADA as a therapy the PBAC has previously considered to be inferior to other agents in MSUC.

*For more detail on PBAC's view, see section 7 PBAC outcome.*

## 7 PBAC Outcome

- 7.1 The PBAC recommended the Section 100 (Highly Specialised Drugs Program) and General Schedule listings of ustekinumab (UST) for the treatment of moderate to severe ulcerative colitis (MSUC). The PBAC noted the recommendation for Section 100 was for intravenous (IV) induction dosing at initiation, and General Schedule listing was for subcutaneous injection for subsequent dosing. The PBAC's recommendation for listing was based on, among other matters, its assessment that the cost-effectiveness of UST would be acceptable if it were cost minimised to the least costly alternative therapy of infliximab (IFX), tofacitinib (TOF), vedolizumab (VDZ) and golimumab (GOL). The PBAC accepted that UST is likely of non-inferior comparative effectiveness and safety to these agents in MSUC and considered there is sufficient evidence to conclude that UST, for some patients, provides a significant improvement in efficacy in the induction phase compared to adalimumab (ADA).
- 7.2 The PBAC considered the equi-effective doses of UST and the alternative therapies could be derived with reference to the therapeutic relativity sheets and relevant Product Information documents, noting the UST equi-effective dose component includes an IV dose at week 0 (at a dose of 6 mg/kg), followed by 90 mg SC dosing at Week 8 and every 8 or 12 weeks thereafter.
- 7.3 The PBAC considered it was reasonable for the listing of UST to be consistent with other disease modifying anti-rheumatic drugs (DMARDs) for MSUC, with prescribing restricted to eligible medical practitioners, an initial treatment period of 16 weeks followed by maintenance therapy with re-assessment at 24-week intervals, with maintenance dose regimens once every 8 or 12 weeks. The Committee noted the flow-on changes to other MSUC DMARD listings to include UST in the list of eligible therapies.
- 7.4 The PBAC noted the comments from health professionals, individuals and organisations supported the listing of UST for MSUC and highlighted the need for additional treatment options for MSUC with new mechanisms of action.
- 7.5 The PBAC noted that five treatments were currently listed for MSUC (with an additional two treatments either recommended or under consideration) and considered the clinical need for additional therapies was low; however, the Committee noted UST was the first IL-12/23 inhibitor seeking listing for this indication and agreed with the consumer comments the addition of treatments with new mechanisms of action may be beneficial for some patients.
- 7.6 The submission nominated VDZ as the main comparator and ADA as a supplementary comparator. The PBAC considered the nominated comparators were reasonable but noted UST may substitute for any of the DMARDs listed for MSUC, including GOL, IFX and TOF. The PBAC noted the clinical claim for UST was non-inferiority to VDZ and superiority to ADA in terms of effectiveness (induction and maintenance phase) and non-inferiority to VDZ and ADA in terms of safety. The PBAC noted the submission

further claimed that, as VDZ had better persistence to treatment than the other DMARDs, based on an analysis of treatment persistence from PBS 10% sample data it could be considered superior and by association, UST is also superior to other bDMARDs. These claims are discussed further below.

- 7.7 The PBAC noted no direct trials comparing UST to VDZ or ADA were available, and the submission relied on indirect treatment comparisons with placebo as the common comparator to support the clinical claims.
- 7.8 For induction treatment, the PBAC noted the results of the unadjusted indirect comparisons showed a statistically significant result favouring UST over ADA for the outcome of clinical response, but not for clinical remission. Further, the PBAC recalled it had previously considered ADA to be of inferior comparative effectiveness to TOF (as well as VDZ and IFX) in the induction phase (Table 9, tofacitinib November 2020 PSD) and considered, based on the available evidence, that ADA was also likely to be of inferior comparative effectiveness to UST in the same treatment phase. The Committee noted the results of the indirect comparisons did not show a statistically significant difference for either remission or response against VDZ and considered, based on the available evidence, that the evidence supported a conclusion that UST is likely of non-inferior comparative effectiveness to VDZ in induction therapy.
- 7.9 For maintenance treatment, The PBAC noted that, for maintenance treatment, the submission argued differences in trial designs and a long carry-over effect with UST meant that the standard indirect treatment comparisons biased against UST. To account for this, the submission presented a 'trial-design-adjusted' comparison for VDZ and ADA in maintenance. The PBAC noted the evaluation also conducted a standard indirect treatment comparison to VDZ. The PBAC agreed with the ESC and considered the modelling approach used to attempt to predict the effectiveness of UST in a treat-through clinical trial design, rather than the randomised withdrawal design used in the UNIFI trial, added additional uncertainty to the indirect treatment comparisons. The PBAC considered the argument that the randomised withdrawal design biased against UST due to longer carry-over effects of UST treatment in the placebo (PBO) arm of the UNIFI study was plausible, however it was uncertain how reliable the modelled adjustment approach was for considering the comparative effectiveness of UST to VDZ and ADA. The PBAC also noted additional standard indirect comparisons were available for VDZ in the maintenance phase (undertaken during the evaluation) and noted the results for the ITT comparisons did not show a statistically significant difference between UST and VDZ for the outcome of clinical remission, but favoured VDZ for the outcome of clinical response (based on the RR statistics). The PBAC noted there was some inconsistency in the results across statistical approaches, however considered based on the results of the unadjusted indirect comparisons, accounting for a plausible (but of uncertain magnitude) level of bias against UST for carry-over effects, that the claim of non-inferior comparative effectiveness to VDZ in the maintenance phase was reasonable. The PBAC noted no unadjusted indirect comparison versus ADA was available, however considered this was acceptable due

to differences in the trial designs.

- 7.10 The PBAC noted the submission argued VDZ should be considered the most effective agent for the treatment of MSUC, based on a claim that persistence to therapy with VDZ was higher than other alternative therapies. The PBAC noted the submission presented an analysis of persistence to therapy (based on PBS 10% sample data) to support this claim and further noted the sponsor hearing presentation focussed on this claim of superior persistence to therapy of VDZ in MSUC over at least ADA and IFX. However, the Committee agreed with the ESC and noted no clear evidence to validate persistence as a surrogate outcome for clinical effectiveness was presented and no clinical evidence to support this claim of superiority was provided. Therefore, the PBAC considered the claim that VDZ was the most effective therapy for the treatment of MSUC based on persistence data was not adequately supported.
- 7.11 The PBAC noted the submission described UST as being of non-inferior comparative safety to VDZ and ADA and considered these claims were reasonable and therefore considered, based on the available evidence and its previously expressed views of comparative safety between DMARDs for MSUC, that UST was likely to be of non-inferior comparative safety to the other listed DMARDs for the treatment of MSUC also.
- 7.12 The PBAC noted no clinical evidence was provided to support the superiority of UST versus IFX, TOF or GOL.
- 7.13 The PBAC considered that a listing based on a cost minimisation approach with costs over two years, consistent with the approach previously used for DMARDs, was appropriate to determine the cost-minimised price of UST. The PBAC considered that the cost of UST should be no greater than the alternative therapies (excluding ADA).
- 7.14 The PBAC considered that, under the parameters of its recommended listing on a cost minimisation with the least costly of VDZ, IFX, GOL and TOF, the listing of UST would likely be cost neutral to the PBS or result in a modest net save as it will predominantly replace therapies that are either of equivalent cost or more expensive.
- 7.15 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because UST is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over the alternative therapies, or not expected to address a high and urgent unmet clinical need given the presence of an alternative therapy, the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were not met.
- 7.16 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

**Outcome:**

Recommended

## 8 Recommended listing

### 8.1 Add new item(s):

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
USTEKINUMAB ustekinumab 130 mg/26 mL injection, 26 mL vial	NEW	4	4	0	STELARA
<b>Restriction Summary [new] 4567 / Treatment of Concept: [new] 1234</b>					
<b>Category / Program:</b> Section 100 – Highly Specialised Drugs Program (Public and Private Hospitals)					
<b>Prescriber type:</b> <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives					
<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required (in writing only via post/HPOS upload)					
<b>Administrative Advice:</b> Changes to common administrative advice concept 27221 at the end of this section.					
<b>Administrative Advice:</b> No increase in the maximum quantity or number of units may be authorised.					
<b>Administrative Advice:</b> No increase in the maximum number of repeats may be authorised.					
<b>Administrative Advice:</b> Special Pricing Arrangements apply.					
<b>Episodicity:</b>					
<b>Severity:</b> Moderate to severe					
<b>Condition:</b> Ulcerative colitis					
<b>Indication:</b> Moderate to severe ulcerative colitis					
<b>Treatment Phase:</b> Initial treatment - Initial 1 (new patient)					
<b>Treatment criteria:</b>					
Must be treated by a gastroenterologist (code 87); OR					
Must be treated by a consultant physician [internal medicine specialising in gastroenterology (code 81)]; OR					
Must be treated by a consultant physician [general medicine specialising in gastroenterology (code 82)].					
<b>AND</b>					
<b>Clinical criteria:</b>					
Patient must have failed to achieve an adequate response to a 5-aminosalicylate oral preparation in a standard dose for induction of remission for 3 or more months or have intolerance necessitating permanent treatment withdrawal					
<b>AND</b>					
<b>Clinical criteria:</b>					
Patient must have failed to achieve an adequate response to azathioprine at a dose of at least 2 mg per kg daily for 3 or more months or have intolerance necessitating permanent treatment withdrawal; OR					
Patient must have failed to achieve an adequate response to 6-mercaptopurine at a dose of at least 1 mg per kg daily for 3 or more months or have intolerance necessitating permanent treatment withdrawal; OR					
Patient must have failed to achieve an adequate response to a tapered course of oral steroids, starting at a dose of at least 40 mg prednisolone (or equivalent), over a 6 week period or have intolerance necessitating permanent treatment withdrawal, and followed by a failure to achieve an adequate response to 3 or more months of treatment of an appropriately dosed thiopurine agent,					
<b>AND</b>					
<b>Clinical criteria:</b>					
Patient must have a Mayo clinic score greater than or equal to 6; OR					

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	Patient must have a partial Mayo clinic score greater than or equal to 6, provided the rectal bleeding and stool frequency subscores are both greater than or equal to 2 (endoscopy subscore is not required for a partial Mayo clinic score).
	<b>AND</b>
	<b>Clinical criteria:</b>
	The treatment must not exceed a single dose to be administered at week 0 under this restriction.
	<b>AND</b>
	<b>Population criteria:</b>
	Patient must be aged 18 years or older
	<b>Prescribing Instructions:</b> Items 24856, 24883, 27220, 23934, 26614, 14943, 10418 and 11162 should apply.
	<b>Prescribing Instructions:</b> Two completed authority prescriptions should be submitted with every initial application for this drug. One prescription should be written under S100 (Highly Specialised Drugs) for a weight-based loading dose, containing a quantity of up to 4 vials of 130 mg and no repeats. The second prescription should be written under S85 (General) for the subsequent first dose, containing a quantity of 1 pre-filled syringe of 90 mg and no repeats.
	<b>Administrative advice:</b> Items 27176 and 28584 should apply.
	<b>Indication:</b> Moderate to severe ulcerative colitis
	<b>Treatment Phase:</b> Initial treatment - Initial 2 (change or re-commencement of treatment after a break in biological medicine of less than 5 years)
	<b>Treatment criteria:</b>
	Must be treated by a gastroenterologist (code 87); OR
	Must be treated by a consultant physician [internal medicine specialising in gastroenterology (code 81)]; OR
	Must be treated by a consultant physician [general medicine specialising in gastroenterology (code 82)].
	<b>AND</b>
	<b>Clinical criteria:</b>
	Patient must have received prior PBS-subsidised treatment with a biological medicine for this condition in this treatment cycle
	<b>AND</b>
	<b>Clinical criteria:</b>
	Patient must not have already failed, or ceased to respond to, PBS-subsidised treatment with this drug for this condition during the current treatment cycle
	<b>AND</b>
	<b>Clinical criteria:</b>
	The treatment must not exceed a single dose to be administered at week 0 under this restriction.
	<b>AND</b>
	<b>Population criteria:</b>
	Patient must be aged 18 years or older
	<b>Prescribing Instructions:</b> Items 27220, 23934, 26614, 24713 and 11162 should apply.
	<b>Prescribing Instructions:</b> Two completed authority prescriptions should be submitted with every initial application for this drug. One prescription should be written under S100 (Highly Specialised Drugs) for a weight-based loading dose, containing a quantity of up to 4 vials of 130 mg and no repeats. The second prescription should be written under S85 (General) for the subsequent first dose, containing a quantity of 1 pre-filled syringe of 90 mg and no repeats.
	<b>Administrative advice:</b> Item 25744 should apply.
	<b>Indication:</b> Moderate to severe ulcerative colitis
	<b>Treatment Phase:</b> Initial treatment – initial 3 (recommencement of treatment after a break in biological medicine of more than 5 years)
	<b>Treatment criteria:</b>
	Must be treated by a gastroenterologist (code 87); OR

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Must be treated by a consultant physician [internal medicine specialising in gastroenterology (code 81)]; OR Must be treated by a consultant physician [general medicine specialising in gastroenterology (code 82)].
<b>AND</b>
<b>Clinical criteria:</b>
Patient must have previously received PBS-subsidised treatment with a biological medicine for this condition
<b>AND</b>
<b>Clinical criteria:</b>
Patient must have had a break in treatment of 5 years or more from the most recently approved PBS-subsidised biological medicine for this condition
<b>AND</b>
<b>Clinical criteria:</b>
Patient must have a Mayo clinic score greater than or equal to 6; OR Patient must have a partial Mayo clinic score greater than or equal to 6, provided the rectal bleeding and stool frequency subscores are both greater than or equal to 2 (endoscopy subscore is not required for a partial Mayo clinic score).
<b>AND</b>
<b>Clinical criteria:</b>
The treatment must not exceed a single dose to be administered at week 0 under this restriction.
<b>AND</b>
<b>Population criteria:</b>
Patient must be aged 18 years or older
<b>Prescribing Instructions:</b> Items 27470, 24883, 27220, 23934, 26614 and 11162 should apply.
<b>Prescribing Instructions:</b> Two completed authority prescriptions should be submitted with every initial application for this drug. One prescription should be written under S100 (Highly Specialised Drugs) for a weight-based loading dose, containing a quantity of up to 4 vials of 130 mg and no repeats. The second prescription should be written under S85 (General) for the subsequent first dose, containing a quantity of 1 pre-filled syringe of 90 mg and no repeats.
<b>Administrative advice:</b> Item 28584 should apply.

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	Nº.of Rpts	Available brands
USTEKINUMAB ustekinumab 90 mg/1 mL injection, 1 mL pre-filled syringe	NEW	1	1	0	STELARA

**Restriction Summary [new] / Treatment of Concept: [new]**

<b>Category / Program:</b> General Schedule
<b>Prescriber type:</b> <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required (in writing only via post/HPOS upload)
<b>Administrative Advice:</b> Changes to common administrative advice concept 27221 at the end of this section.
<b>Administrative Advice:</b> No increase in the maximum quantity or number of units may be authorised.
<b>Administrative Advice:</b> No increase in the maximum number of repeats may be authorised.
<b>Administrative Advice:</b> Special Pricing Arrangements apply.
<b>Episodicity:</b>
<b>Severity:</b> Moderate to severe
<b>Condition:</b> Ulcerative colitis

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	<b>Indication:</b> Moderate to severe ulcerative colitis
	<b>Treatment Phase:</b> Initial treatment - Initial 1 (new patient)
	<b>Treatment criteria:</b>
	Must be treated by a gastroenterologist (code 87); OR  Must be treated by a consultant physician [internal medicine specialising in gastroenterology (code 81)]; OR  Must be treated by a consultant physician [general medicine specialising in gastroenterology (code 82)].
	<b>AND</b>
	<b>Clinical criteria:</b>
	Patient must have failed to achieve an adequate response to a 5-aminosalicylate oral preparation in a standard dose for induction of remission for 3 or more months or have intolerance necessitating permanent treatment withdrawal
	<b>AND</b>
	<b>Clinical criteria:</b>
	Patient must have failed to achieve an adequate response to azathioprine at a dose of at least 2 mg per kg daily for 3 or more months or have intolerance necessitating permanent treatment withdrawal; OR  Patient must have failed to achieve an adequate response to 6-mercaptopurine at a dose of at least 1 mg per kg daily for 3 or more months or have intolerance necessitating permanent treatment withdrawal; OR  Patient must have failed to achieve an adequate response to a tapered course of oral steroids, starting at a dose of at least 40 mg prednisolone (or equivalent), over a 6 week period or have intolerance necessitating permanent treatment withdrawal, and followed by a failure to achieve an adequate response to 3 or more months of treatment of an appropriately dosed thiopurine agent,
	<b>AND</b>
	<b>Clinical criteria:</b>
	Patient must have a Mayo clinic score greater than or equal to 6; OR  Patient must have a partial Mayo clinic score greater than or equal to 6, provided the rectal bleeding and stool frequency subscores are both greater than or equal to 2 (endoscopy subscore is not required for a partial Mayo clinic score).
	<b>AND</b>
	<b>Clinical criteria:</b>
	The treatment must not exceed a single dose to be administered at week 8 under this restriction.
	<b>AND</b>
	<b>Population criteria:</b>
	Patient must be aged 18 years or older
	<b>Prescribing Instructions:</b> Items 24856, 24883, 27220, 23934, 26614, 14943, 10418 and 11162 should apply.
	<b>Prescribing Instructions:</b> Two completed authority prescriptions should be submitted with every initial application for this drug. One prescription should be written under S100 (Highly Specialised Drugs) for a weight-based loading dose, containing a quantity of up to 4 vials of 130 mg and no repeats. The second prescription should be written under S85 (General) for the subsequent first dose, containing a quantity of 1 pre-filled syringe of 90 mg and no repeats.
	<b>Administrative advice:</b> Items 27176 and 28584 should apply.
	<b>Indication:</b> Moderate to severe ulcerative colitis
	<b>Treatment Phase:</b> Initial treatment - Initial 2 (change or re-commencement of treatment after a break in biological medicine of less than 5 years)
	<b>Treatment criteria:</b>
	Must be treated by a gastroenterologist (code 87); OR  Must be treated by a consultant physician [internal medicine specialising in gastroenterology (code 81)]; OR  Must be treated by a consultant physician [general medicine specialising in gastroenterology (code 82)].
	<b>AND</b>

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<b>Clinical criteria:</b>
Patient must have received prior PBS-subsidised treatment with a biological medicine for this condition in this treatment cycle
<b>AND</b>
<b>Clinical criteria:</b>
Patient must not have already failed, or ceased to respond to, PBS-subsidised treatment with this drug for this condition during the current treatment cycle
<b>AND</b>
<b>Clinical criteria:</b>
The treatment must not exceed a single dose to be administered at week 8 under this restriction.
<b>AND</b>
<b>Population criteria:</b>
Patient must be aged 18 years or older
<b>Prescribing Instructions:</b> Items 27220, 23934, 26614, 24713 and 11162 should apply.
<b>Prescribing Instructions:</b> Two completed authority prescriptions should be submitted with every initial application for this drug. One prescription should be written under S100 (Highly Specialised Drugs) for a weight-based loading dose, containing a quantity of up to 4 vials of 130 mg and no repeats. The second prescription should be written under S85 (General) for the subsequent first dose, containing a quantity of 1 pre-filled syringe of 90 mg and no repeats.
<b>Administrative advice:</b> Item 25744 should apply.
<b>Indication:</b> Moderate to severe ulcerative colitis
<b>Treatment Phase:</b> Initial treatment – initial 3 (recommencement of treatment after a break in biological medicine of more than 5 years)
<b>Treatment criteria:</b>
Must be treated by a gastroenterologist (code 87); OR
Must be treated by a consultant physician [internal medicine specialising in gastroenterology (code 81)]; OR
Must be treated by a consultant physician [general medicine specialising in gastroenterology (code 82)].
<b>AND</b>
<b>Clinical criteria:</b>
Patient must have previously received PBS-subsidised treatment with a biological medicine for this condition
<b>AND</b>
<b>Clinical criteria:</b>
Patient must have had a break in treatment of 5 years or more from the most recently approved PBS-subsidised biological medicine for this condition
<b>AND</b>
<b>Clinical criteria:</b>
Patient must have a Mayo clinic score greater than or equal to 6; OR
Patient must have a partial Mayo clinic score greater than or equal to 6, provided the rectal bleeding and stool frequency subscores are both greater than or equal to 2 (endoscopy subscore is not required for a partial Mayo clinic score).
<b>AND</b>
<b>Clinical criteria:</b>
The treatment must not exceed a single dose to be administered at week 8 under this restriction.
<b>AND</b>
<b>Population criteria:</b>
Patient must be aged 18 years or older
<b>Prescribing Instructions:</b> Items 27470, 24883, 27220, 23934, 26614 and 11162 should apply.
<b>Prescribing Instructions:</b>

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	Two completed authority prescriptions should be submitted with every initial application for this drug. One prescription should be written under S100 (Highly Specialised Drugs) for a weight-based loading dose, containing a quantity of up to 4 vials of 130 mg and no repeats. The second prescription should be written under S85 (General) for the subsequent first dose, containing a quantity of 1 pre-filled syringe of 90 mg and no repeats.
	<b>Administrative advice:</b> Item 28584 should apply.

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
USTEKINUMAB					
ustekinumab 90 mg/1 mL injection, 1 mL pre-filled syringe	NEW	1	1	1/2*	STELARA

\*A maximum of 2 repeats is required for patients using an 8-weekly course of ustekinumab.

**Restriction Summary [new] 4567 / Treatment of Concept: [new] 1234**

	<b>Category / Program:</b> General Schedule
	<b>Prescriber type:</b> <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
	<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required (in writing only via post/HPOS upload)
	<b>Administrative Advice:</b> Changes to common administrative advice concept 27221 at the end of this section.
	<b>Administrative Advice:</b> No increase in the maximum quantity or number of units may be authorised.
	<b>Administrative Advice:</b> Increase in the maximum number of repeats of up to 2 may be authorised in patients whose dosing frequency is every 8 weeks.
	<b>Administrative Advice:</b> Special Pricing Arrangements apply.
	<b>Episodicity:</b>
	<b>Severity:</b> Moderate to severe
	<b>Condition:</b> Ulcerative colitis
	<b>Indication:</b> Moderate to severe ulcerative colitis
	<b>Treatment Phase:</b> Continuing treatment
	<b>Treatment criteria:</b>
	Must be treated by a gastroenterologist (code 87); OR
	Must be treated by a consultant physician [internal medicine specialising in gastroenterology (code 81)]; OR
	Must be treated by a consultant physician [general medicine specialising in gastroenterology (code 82)].
	<b>AND</b>
	<b>Clinical criteria:</b>
	Patient must have previously received PBS-subsidised treatment with this drug for this condition
	<b>AND</b>
	<b>Clinical criteria:</b>
	Patient must have demonstrated or sustained an adequate response to treatment by having a partial Mayo clinic score less than or equal to 2, with no subscore greater than 1 while receiving treatment with this drug
	<b>AND</b>
	Patient must not receive more than 24 weeks of treatment under this restriction
	<b>AND</b>
	<b>Population criteria:</b>
	Patient must be aged 18 years or older
	<b>Prescribing Instructions:</b> Items 17150, 17047, 19535, 26394, 23934, 26614 and 23943 should apply.
	<b>Administrative advice:</b> Item 28500 should apply.

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<b>Restriction Summary [new] 4567 / Treatment of Concept: [new] 1234</b>	
	<b>Category / Program:</b> General Schedule
	<b>Prescriber type:</b> <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
	<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required (in writing only via post/HPOS upload)
	<b>Administrative Advice:</b> Changes to common administrative advice concept 27221 at the end of this section.
	<b>Administrative Advice:</b> No increase in the maximum quantity or number of units may be authorised.
	<b>Administrative Advice:</b> No increase in the maximum number of repeats may be authorised.
	<b>Administrative Advice:</b> Special Pricing Arrangements apply.
	<b>Episodicity:</b>
	<b>Severity:</b> Moderate to severe
	<b>Condition:</b> Ulcerative colitis
	<b>Indication:</b> Moderate to severe ulcerative colitis
	<b>Treatment Phase:</b> Initial treatment – Grandfather treatment
	<b>Treatment criteria:</b>
	Must be treated by a gastroenterologist (code 87); OR
	Must be treated by a consultant physician [internal medicine specialising in gastroenterology (code 81)]; OR
	Must be treated by a consultant physician [general medicine specialising in gastroenterology (code 82)].
	<b>AND</b>
	<b>Clinical criteria:</b>
	Patient must be receiving treatment with this drug for this condition at the time of application
	<b>AND</b>
	<b>Clinical criteria:</b>
	Patient must have previously received non-PBS-subsidised treatment with this drug for this condition prior to <<PBS listing date>>
	<b>AND</b>
	<b>Clinical criteria:</b>
	Patient must have had a Mayo clinic score greater than or equal to 6 prior to commencing non-PBS-subsidised treatment with this drug for this condition; OR
	Patient must have had a partial Mayo clinic score greater than or equal to 6, provided the rectal bleeding and stool frequency subscores were both greater than or equal to 2 (endoscopy subscore is not required for a partial Mayo score) prior to commencing non-PBS-subsidised treatment with this drug for this condition; OR
	Patient must have a documented history of moderate to severe refractory ulcerative colitis prior to having commenced non-PBS-subsidised treatment with this drug for this condition where a Mayo clinic or partial Mayo clinic baseline assessment is not available
	<b>AND</b>
	<b>Clinical criteria:</b>
	Patient must not receive more than 24 weeks of treatment under this restriction
	<b>AND</b>
	<b>Population criteria:</b>
	Patient must be aged 18 years or older
	<b>Prescribing Instructions:</b> Items 27842, 12980, 17110, 23637, 23643, 17150, 17047 and 19535 should apply.
	<b>Administrative advice:</b> Item 28500 should apply.

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	<b>Indication:</b> Moderate to severe ulcerative colitis
	<b>Treatment Phase:</b> Initial 1 (new patient) or Initial 2 (change or recommencement of treatment after a break in biological medicine of less than 5 years) or Initial 3 (recommencement of treatment after a break in biological medicine of more than 5 years) - balance of supply
	<b>Treatment criteria:</b>
	Must be treated by a gastroenterologist (code 87); OR  Must be treated by a consultant physician [internal medicine specialising in gastroenterology (code 81)]; OR  Must be treated by a consultant physician [general medicine specialising in gastroenterology (code 82)].
	<b>AND</b>
	<b>Clinical criteria:</b>
	Patient must have received insufficient treatment with this drug under the Initial 1 (new patient or recommencement of treatment after more than 5 years break in therapy) restriction to complete 16 weeks of treatment; OR  Patient must have received insufficient treatment with this drug under the Initial 2 (Change or Re-commencing of treatment after less than 5 years break in therapy) to complete 16 weeks of treatment; OR  Patient must have received insufficient treatment with this drug under the Initial 3 (Change or Re-commencing of treatment after a break in therapy of more than 5 years) to complete 16 weeks of treatment; OR  Patient must have received insufficient therapy with this drug under the Continuing treatment restriction to complete 24 weeks of treatment
	<b>AND</b>
	<b>Clinical criteria:</b>
	<del>The treatment must provide no more than the balance of up to 16 weeks treatment available under the above restrictions</del>
	<b>AND</b>
	<b>Population criteria:</b>
	<del>Patient must be aged 18 years or older</del>
	<b>Administrative advice:</b> Item 28500 should apply.

	<p><b>Administrative Advice:</b>  <b>TREATMENT OF ADULT PATIENTS WITH MODERATE TO SEVERE ULCERATIVE COLITIS</b>  The following information applies to the prescribing under the Pharmaceutical Benefits Scheme (PBS) of adalimumab, golimumab, infliximab, tofacitinib and vedolizumab for adult patients with ulcerative colitis. Patients are eligible for PBS-subsidised treatment with either adalimumab, golimumab, infliximab, tofacitinib, ustekinumab or vedolizumab at any one time.</p> <p>Where the term 'biological medicine' appears in the following notes and restrictions, it refers to the tumour necrosis factor (TNF) alfa antagonists (adalimumab, golimumab, infliximab), the alpha-4 beta-7 integrin inhibitor (vedolizumab) the human IgG1kappa monoclonal antibody ustekinumab and the Janus kinase (JAK) inhibitor (tofacitinib).</p> <p>From 1 July 2021, under the PBS, all adult patients will be able to commence a treatment cycle where they may trial PBS-subsidised biological medicine without having to experience a disease flare when swapping to one of the alternate agents. Under these arrangements, within a single treatment cycle, a patient may continue to receive long-term treatment with a PBS subsidised biological medicine while they continue to show a response to therapy.</p> <p>A patient who received PBS-subsidised biological medicine treatment prior to 1 July 2021 is considered to start their first cycle as of 1 July 2021. Within the same treatment cycle, a patient cannot trial and fail, or cease to respond to, the same PBS-subsidised biological medicine more than once. Once a patient has either failed or ceased to respond to treatment 3 times, they are deemed to have completed a treatment cycle and they</p>
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must have, at a minimum, a 5-year break in PBS-subsidised therapy before they are eligible to commence the next cycle. The 5-year break is measured from the date of the last approval for PBS-subsidised biological medicine treatment in the most recent cycle to the date of the first application for initial treatment with a PBS-subsidised biological medicine under the new treatment cycle.

Serious adverse reaction of a severity resulting in the necessity for permanent withdrawal of treatment, including serious infusion or injection related reactions, Steven's Johnson Syndrome, development of a demyelinating lesion, progressive multifocal leukoencephalopathy and malignancy related to treatment with the biological medicine, is not considered as a treatment failure.

A patient who has failed fewer than 3 trials of a biological medicine in a treatment cycle and who has a break in therapy of less than 5 years may commence a further course of treatment within the same treatment cycle under the Initial 2 treatment restriction.

A patient who has failed fewer than 3 trials of a biological medicine in a treatment cycle and who has a break in therapy of more than 5 years, may commence a new treatment cycle under the Initial 3 treatment restrictions.

There is no limit to the number of treatment cycles a patient may undertake in their lifetime.

How to prescribe PBS-subsidised biological medicine treatment after 1 July 2021.

(1) Initial treatment.

Applications for initial treatment should be made where:

- (i) an adult patient has not received prior PBS-subsidised biological medicine treatment and wishes to commence such therapy (Initial 1 - New patient); or
- (ii) an adult patient has received prior PBS-subsidised biological medicine therapy (initial or continuing) and wishes to trial an alternate medicine (Initial 2 - Change or Recommencement of treatment after a break in biological medicine therapy of less than 5 years) [further details are under 'Swapping therapy' below]; or
- (iii) an adult patient wishes to recommence treatment with a specific biological medicine following a break in PBS-subsidised therapy of less than 5 years with the same agent (Initial 2 - Change or Recommencement of treatment after a break in biological medicine therapy of less than 5 years); or
- (iv) an adult patient wishes to recommence treatment with a biological medicine following a break in PBS-subsidised therapy of more than 5 years (Initial 3 - recommencement of treatment after a break in biological medicine of more than 5 years).

Treatment authorisations under Initial 1, Initial 2 and Initial 3 will be limited to provide for a maximum of 16 weeks of therapy for adalimumab, ustekinumab and tofacitinib, 14 weeks of therapy for golimumab, infliximab and vedolizumab.

A patient must be assessed for response to a course of initial PBS-subsidised treatment following a minimum of 12 weeks of treatment for adalimumab, *ustekinumab* or infliximab subcutaneous form or vedolizumab subcutaneous form, a minimum of 8 weeks for tofacitinib, and up to 12 weeks after the first dose (6 weeks following the third dose) for golimumab, infliximab intravenous form or vedolizumab intravenous form.

Infliximab subcutaneous form only:

Initial treatment to subcutaneous form of infliximab should be permitted after administration of at least 2 initial intravenous infusions of infliximab. A maximum quantity and number of repeats to provide for weeks 6, 8, 10, 12, 14 and 16 will be authorised.

Vedolizumab subcutaneous form only:

initial treatment to subcutaneous form of vedolizumab should be permitted after administration of at least 2 of the 3 initial intravenous infusions of vedolizumab. Where two initial doses of vedolizumab (at weeks 0 and 2) is administered via intravenous infusion, initial treatment with subcutaneous form will commence at week 6. A maximum quantity and number of repeats to provide for weeks 6, 8, 10, 12, 14 and 16 will be authorised. Where three initial doses of vedolizumab (at weeks 0, 2 and 6) is administered via intravenous infusion, initial

treatment with subcutaneous form will commence at week 14 (8 weeks after the third dose). A maximum quantity to provide for weeks 14 and 16 will be authorised.

(2) Continuing treatment.

Following the completion of an initial treatment course with a specific biological medicine, a patient may qualify to receive up to 24 weeks of continuing treatment with that drug providing they have demonstrated an adequate response to treatment. The patient remains eligible to receive continuing biological medicine treatment with the same drug in courses of up to 24 weeks providing they continue to sustain the response.

It is recommended that a patient is reviewed for response following a minimum of 12 weeks of therapy and no later than 4 weeks from the completion of the most recent course of treatment.

Adalimumab and infliximab only:

For the first continuing treatment course of PBS-subsidised biological medicine treatment, it is recommended that a patient is reviewed for response following a minimum of 12 weeks of therapy and no later than 4 weeks from the completion of the most recent course of treatment under the Initial 1, Initial 2 or Initial 3 treatment restrictions.

For the second and subsequent continuing courses of PBS-subsidised biological medicine treatment, it is recommended that an assessment of a patient's response is conducted following a minimum of 12 weeks of therapy and no later than 4 weeks from the completion of the most recent course of treatment.

Infliximab patients:

A patient may swap between the intravenous and subcutaneous forms of infliximab at any time under the continuing treatment restrictions provided the patient has demonstrated adequate response to treatment with infliximab.

Vedolizumab patients:

A patient may swap between the intravenous and subcutaneous forms of vedolizumab at any time under the continuing treatment restrictions provided the patient has demonstrated adequate response to treatment with vedolizumab.

(3) Swapping therapy.

Once initial treatment with the first PBS-subsidised biological medicine treatment is approved, a patient may swap to an alternate biological medicine treatment within the same treatment cycle without having to requalify with respect to the indices of disease severity (i.e. Mayo clinic score or partial Mayo clinic score), or the prior corticosteroid therapy and immunosuppressive therapy.

A patient may trial an alternate biological medicine treatment at any time, regardless of whether they are receiving therapy (initial or continuing) at the time of the application. However, they cannot swap to a particular biological medicine if they have failed to respond to prior treatment with that drug once within the same treatment cycle.

To ensure a patient receives the maximum treatment opportunities allowed under these arrangements, it is important that they are assessed for response to every course of treatment.

A patient who is not able to complete a minimum of 12 weeks of an initial treatment course (except tofacitinib) will be deemed to have failed treatment with that agent, unless they have experienced a serious adverse reaction of a severity necessitating permanent treatment withdrawal.

(4) Recommencement of treatment after a 5-year break in PBS-subsidised therapy.

A patient who wishes to trial a second or subsequent treatment cycle following a break in PBS-subsidised biological medicine therapy of at least 5 years, must requalify under Initial 3 treatment restriction and meet the relevant criteria with respect to the scores of disease severity.

***This restriction may be subject to further review. Should there be any changes made to the restriction the sponsor will be informed.***

## **9 Context for Decision**

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

## **10 Sponsor's Comment**

The sponsor had no comment.