



Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Ustekinumab

Proprietary Product Name: Stelara

Sponsor: Janssen-Cilag Pty. Ltd.

October 2017

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- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
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Common abbreviations

Abbreviation	Meaning
5-ASA	5-aminosalicylic acid
6-MP	6-mercaptopurine
ADA	antidrug antibodies
ADR	adverse drug reaction
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the serum concentration versus time curve
AUC _{inf}	area under the serum concentration versus time curve from time zero to infinity with extrapolation of the terminal phase.
AUC _{last}	area under the serum concentration versus time curve from time zero to the time corresponding to the last quantifiable concentration.
AxSpA	axial spondyloarthritis
AZA	azathioprine
AZMP	azathioprine or 6-mercaptopurine
BALB	baseline albumin
BLQ	below the limit of quantification
BMI	body mass index
BSV	between-subject variability
BWGT	baseline body weight
CD	Crohn's disease
CDAI	Crohn's Disease Activity Index
CI	confidence interval
CKMB	creatinine kinase isoenzyme-MB
CL	total systemic clearance

Abbreviation	Meaning
Cmax	maximum observed serum concentration
CNTO 1275	Stelara, ustekinumab
CORT	corticosteroid usage
CRF	case report form
CRP	C-reactive protein
CSR	clinical study report
CV%	coefficient of variation
DP	drug product
ECG	electrocardiogram
ECL	electrochemiluminescent
ECLIA	electrochemiluminescent immunoassay
eCRF	electronic case report form
EIA	enzyme immunoassay
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Evaluation Agency
E-R	Exposure-response
EU	European Union
F	bioavailability
fCAL	faecal calprotectin
FDA	Food and Drug Administration (US)
FDR	false discovery rate
fLAC	faecal lactoferrin
FTNF	TNF failure
FVP (IV)	final vialled product for intravenous administration
GI	gastrointestinal
GMCSF	granulocyte macrophage-colony stimulating factor

Abbreviation	Meaning
h	hour/s
HSTCL	hepatosplenic T-cell lymphoma
IBCRP	baseline CRP
IBD	inflammatory bowel disease
IBDQ	Inflammatory Bowel Disease Questionnaire
ICAM-1	intercellular adhesion molecule 1
ICAM-3	intercellular adhesion molecule 3
IFN γ	Interferon- γ
IIV	inter-individual variability
IL	interleukin
IL-12	interleukin 12
IL-17A	interleukin-17A
IL-17F	interleukin-17F
IL-23	interleukin 23
IOV	inter-occasion variability
IP-10	interferon-gamma inducible protein 10
IRPT	positive for antidrug antibodies
IV	intravenous
Kg	Kilogram
LIV	liquid in vial
LLOQ	lower limit of quantitation
LOR	loss of response
LTE	long-term extension
mAb	monoclonal antibody
MACE	major adverse cardiovascular events
MCP-1	monocyte chemotactic protein 1

Abbreviation	Meaning
MCS	Mental Component Summary
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
MI	myocardial infarction
min	minute/s
MMP	matrix metalloproteinase
MPO	myeloperoxidase
MS	multiple sclerosis
MSD	Meso Scale Discovery
MTX	methotrexate
NMSC	nonmelanoma skin cancer
NR	non-responders
OR	odds ratio
PCS	Physical Component Summary
PD	pharmacodynamic(s)
P-Eq	Prednisolone Equivalent
PFS	prefilled syringe
PK	pharmacokinetic(s)
PPK	population pharmacokinetic
PsA	psoriatic arthritis
PT	Preferred term
q12w	every 12 weeks
q8w	every 8 weeks
R	responders
r ²	coefficient of determination
RA	rheumatoid arthritis

Abbreviation	Meaning
RANTES	Regulated on Activation, Normal T cell Expressed and Secreted
RMP	Risk Management Plan
RPLS	reversible posterior leukoencephalopathy
SAA	serum amyloid A
SAE	serious adverse event
SAEM	stochastic approximation of expectation-maximisation
SC	subcutaneous
SCE	Summary of Clinical Efficacy
SCP	Summary of Clinical Pharmacology
SCS	Summary of Clinical Safety
SD	standard deviation
SES-CD	Simplified Endoscopic Activity Score for Crohn's Disease
SF-36	36-item Short Form Health Survey
SIR	standardised incidence ratio
SMOH	history of smoking
SMOK	smoking currently
SmPC	Summary of Product Characteristics
SOC	system-organ class
Stelara	ustekinumab
TB	tuberculosis
Th1	T-helper cell 1
Th17	T-helper cell 17
TIMP-1	tissue inhibitor of matrix metalloproteinase 1
TNF	tumor necrosis factor
UC	ulcerative colitis
US	United States

Abbreviation	Meaning
UTI	urinary tract infection
V_2	volume of central compartment
V_3	volume of peripheral compartment
VAS	Visual Analog Scale
V_z	volume of distribution based on terminal phase
W	week
WLQ	Work Limitations Questionnaire

I. Introduction to product submission

Submission details

<i>Type of submission:</i>	Extension of indications, New dose strength and Route of administration
<i>Decision:</i>	Approved
<i>Date of decision:</i>	27 February 2017
<i>Date of entry onto ARTG</i>	1 March 2017
<i>Active ingredient(s):</i>	Ustekinumab
<i>Product name(s):</i>	Stelara
<i>Sponsor's name and address:</i>	Janssen-Cilag Pty. Ltd. 1-5 Khartoum Road, Macquarie Park NSW 2113
<i>Dose form(s):</i>	Solution for Injection
<i>Strength(s):</i>	5 mg of ustekinumab (rmc) in 1 mL; 45 mg of ustekinumab (rmc) in 0.5 mL; or 90 mg of ustekinumab (rmc) in 1.0 mL (the 90 mg vial, 45 mg pre-filled syringe and 90 mg prefilled syringe are not currently marketed).
<i>Container(s):</i>	Single-use (Type 1) glass vial. Single-use, sterile solution in a Type 1 glass syringe with a fixed 27G, half-inch needle and needle cover.
<i>Pack size(s):</i>	1 single use vial (45 mg)
<i>Approved therapeutic use:</i>	<i>Crohn's Disease</i> <i>Stelara is indicated for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a TNFα antagonist or have medical contraindications to such therapies.</i>
<i>Route(s) of administration:</i>	Intravenous (IV) and subcutaneous (SC)
<i>Dosage:</i>	Abbreviated: For the treatment of Crohn's disease, the recommended treatment regimen is to initiate Stelara with a single intravenous (IV) tiered dose based on body weight (Table 21 in PI). After the initial IV dose, Stelara should then be administered subcutaneously. The first subcutaneous dose of 90 mg Stelara should be administered 8 weeks after the initial intravenous dose, then every 8 weeks thereafter. For more details see PI (Attachment 1)
<i>ARTG number (s):</i>	282906 , 149550, 149549, 165953 and 165954

Product background

This AusPAR describes the application by the sponsor Janssen-Cilag Pty. Ltd to extend the Indications for Stelara (ustekinumab) to include Crohn's Disease and register a new strength (5 mg/mL) and route of administration (IV) for:

As the proposed treatment regimen requires IV administration during the induction phase, this submission includes data to support the new modified 5 mg/mL formulation with 130 mg ustekinumab in 26 mL (5 mg/mL) in each vial. It is also important to note that of the four SC preparations, only the 45 mg/0.5 mL vial is marketed here; the 90 mg/1.0 mL vial, 45 mg/ 0.5mL pre-filled syringe and 90 mg/ 1 mL pre-filled syringe are not currently marketed in Australia.

Ustekinumab is a human IgG1kappa monoclonal antibody that specifically binds to the shared p40 protein subunit of the human cytokines interleukin (IL)-12 and IL-23. Ustekinumab inhibits the bioactivity of human IL-12 and IL-23 by preventing p40 from binding to the IL-12Rbeta1 receptor protein expressed on the surface of immune cells. Ustekinumab cannot bind to IL-12 or IL-23 that is already bound to IL-12Rbeta1 cell surface receptors. IL-12 and IL-23 are heterodimeric cytokines secreted by activated antigen presenting cells, such as macrophages and dendritic cells. IL-12 stimulates natural killer (NK) cells and drives the differentiation of CD4+ T cells toward the T helper 1 (Th1) phenotype and stimulates interferon gamma (IFN γ) production. IL-23 induces the T helper 17 (Th17) pathway and promotes secretion of interleukin-17A (IL-17A), IL-21, and IL-22. Collectively, the roles of IL-12 and IL-23 in Th1 and Th17 signalling combined with data from murine models of inflammatory bowel disease (IBD), elevations in IL-12 and IL-23 in human Crohn's disease and genetic linkage data provide a strong rationale for inhibiting these cytokines in Crohn's disease.

Crohn's disease (CD) is a chronic, relapsing, immune-mediated IBD. Current available therapies include: 5-aminosalicylic acid, immunosuppressive agents such as azathioprine and mercaptopurine, corticosteroids, antibiotics and TNF- α antagonists. Many patients with moderate to severe Crohn's disease do not respond adequately to available treatment options. Infliximab and adalimumab are TNF α antagonist monoclonal antibody therapies with indications that include Crohn's disease. A recent approval of a biological agent to treat Crohn's disease was vedolizumab (Kynteles/ Entyvio) in June 2014. Vedolizumab is a humanised monoclonal antibody that binds to the α 4 β 7 integrin expressed on the surface of various leukocytes, including T lymphocytes. Vedolizumab is not marketed.

The sponsor has proposed the following dosage regimen for Crohn's Disease (CD):

A single intravenous (IV) tiered dose of Stelara based on body weight (Table 1) followed by 90 mg subcutaneous dosing 8 weeks later, then every 8 weeks thereafter. The intravenous dose is diluted to 250 mL and infused over at least one hour.

Table 1: Initial IV dosing of Stelara

Body weight of Patient	Dose	Number of 130 mg Stelara vials at the time of dosing
≤ 55 kg	260 mg	2
>55 kg to ≤ 85 kg	390 mg	3
>85 kg	520 mg	4

* Recommended dose (approximately 6 mg/kg)

For some patients, a single IV dose based on body weight (see above table) followed by 90 mg SC dosing 8 weeks later, then every 12 weeks thereafter may be acceptable. Patients who inadequately respond to 90 mg SC dosing every 12 weeks may benefit from an increase in dosing frequency to every 8 weeks.

Regulatory status

Ustekinumab was first approved for registration in Australia for the treatment of plaque psoriasis in 2010. The Australian Register of Therapeutic Goods (ARTG) start date was 19 August 2010. It has subsequently also been approved for treatment of psoriatic arthritis.

At the time the TGA considered this application, a similar application had been approved in the USA, European Union and Canada (see Table 2).

Table 2: International regulatory status

Country	Submission Date	Date of Approval	Indication
United States of America	N/A	23 September 2016	STELARA® is indicated for the treatment of adult patients with moderately to severely active Crohn's disease who have: - failed or were intolerant to treatment with immunomodulators or corticosteroids, but never failed treatment with a tumor necrosis factor (TNF) blocker or - failed or were intolerant to treatment with one or more TNF blockers.
European Union	N/A	11 November 2016	STELARA is indicated for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a TNF α antagonist or have medical contraindications to such therapies.
Canada	N/A	12 December 2016	STELARA® (ustekinumab) is indicated for the treatment of adult patients with moderately to severely active Crohn's disease, who have had an inadequate response, loss of response to, or were intolerant to either immunomodulators or one or more tumour necrosis factor-alpha (TNF α) antagonists, or have had an inadequate response, intolerance or demonstrated dependence on corticosteroids.

Product information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <<https://www.tga.gov.au/product-information-pi>>.

II. Quality findings

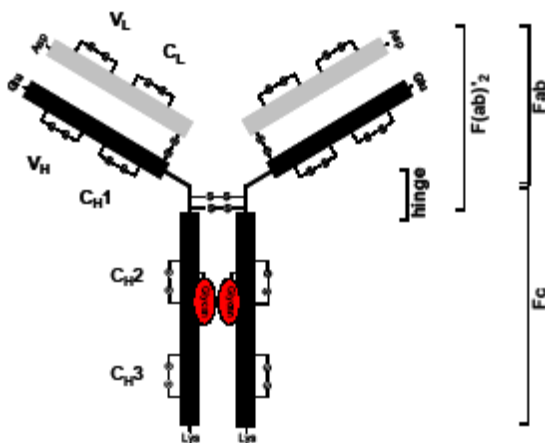
Drug substance (active ingredient)

Structure

Ustekinumab (CNTO 1275) is a fully human IgG₁ antibody. Like all human antibodies, Ustekinumab is heterodimeric with two protein chains (heavy chain and light chain) (Figure 1). The light chain is a κ type. The heavy and light chains are joined by a single disulphide bond, with two disulphide bonds joining the heavy chains. The folded structure is described by three regions, the Fab (Fragment, antigen binding), the hinge region (the flexible linker between the two main regions) and the Fc (Fragment, crystallisable). Human IgG₁ are usually N-glycosylated on the Fc Region, with the heavy chain having an N-glycan consensus region.

Ustekinumab is only glycosylated on this region, with a single biantennary oligosaccharide found on the heavy chain in the consensus region. Each of these N-glycans (one on each heavy chain) is a core-fucosylated structure containing four N-acetylglucosamine residues and three mannose residues. Heterogeneity is introduced by the presence of zero to two galactose residues and zero to two N-glycolylneuraminic acid residues.

Figure 1: Structure of Ustekinumab



The heavy (black) and light (grey) chains are shown with intra and inter chain disulphides, which form the Fab, hinge and Fc regions. F(ab)₂ is a fragment comprised of two Fab regions. Amino and carboxy terminal residues of each chain and the general location of heavy chain N-glycan sites in the Fc region are noted. Cysteine is the C terminal residue of the light chain.

Information on the ustekinumab drug substance (DS) has not changed from what was approved in the original application for Stelara ustekinumab.

Physical and Chemical Properties

Ustekinumab consists of two 449 amino acid heavy chains and two 214 amino acid light chains. The expected molecular mass of the protein ranges from 148079-149690 Daltons based on averaged weights for the different glycoforms present.

Characterisation of N and C-terminal sequences showed typical post-translational modification of the heavy chain C-terminal with clipping of the heavy chain terminal lysine residues.

Ustekinumab is glycosylated at Asn299, with a single biantennary oligosaccharide found on the heavy chain in the consensus region. Each of these N-glycans (one on each heavy chain) is a core-fucosylated structure containing four N-acetylglucosamine residues and three mannose residues. Heterogeneity is introduced by the presence of zero to two galactose residues and zero to two N-glycolylneuraminic acid (Neu5Gc) residues. Neu5Gc is the main sialic acid associated with Ustekinumab.

16 disulphide bonds are expected in IgG₁ and all of these were able to be accounted for in Ustekinumab. Five of these cysteine residues are found in the light chain and the remaining 11 are located on the heavy chain.

Potential process related impurities that may be introduced from the manufacturing process were divided into three categories, Cell-based Impurities, Media Components and Other Impurities. All of these classes of impurities were shown to be cleared below the limit of quantification (LOQ) through the manufacturing process.

Potential product related impurities, such as high or low molecular weight fragments and aggregates may be produced during the manufacture or storage of the drug substance. These are monitored by Dual Wavelength – Size Exclusion – HPLC.

The most common degradation pathway was found to involve cyclic imide mediated reactions such as isomerisation, deamidation and cyclisation. These can be monitored through peptide mapping and capillary isoelectric focusing (cIEF) analysis.

Drug product

The proposed new drug product is ustekinumab 5.0 mg/1mL solution for IV infusion injection vial.

Ustekinumab (Stelara) is classified as an interleukin inhibitor (ATC code: L04AC05). Ustekinumab is a fully human IgG1K monoclonal antibody.

Stelara has an approximate molecular weight of 148.6 kilo Dalton and is produced by a mouse recombinant cell line cultured by continuous perfusion.

The ustekinumab final vial drug product for IV administration [FVP (IV) DP] is supplied as a single-use, sterile solution designed to deliver 130 mg of ustekinumab in a 30 mL, Type-1 glass vial. The vials are stoppered with 20-mm Flurotec® coated Daikyo D777-1 stoppers and sealed with 20 mm aluminium flip-off seals.

The target composition of ustekinumab is, with nominal excipient concentrations of L-histidine, sucrose, polysorbate 80, methionine and EDTA disodium salt dihydrate at pH 6.0. The vials are filled at a target volume of 27.0 mL per vial to deliver no less than 26.0 mL, the nominal deliverable volume, for a 130 mg dose.

Relevant EU and the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidelines adopted in Australia regarding quality, biological medicines and stability have also been used in the evaluation of this submission.

Drug substance specifications are unchanged from approved product.

Stability

The sponsor proposed a shelf life of 24 months at 2-8°C, refrigerate only; do not freeze.

Stability data have been generated under real time and stressed conditions and were conducted in accordance with relevant ICH guidelines.

Stability data were generated under real time conditions to characterise the stability profile of the substance and to establish a shelf life. The real time data submitted support a shelf life of 24 months when stored at 2 to 8°C.

The product is not photostable. Photostability studies demonstrate that the secondary package proposed for commercial use will provide adequate protection from the effects of light conditions specified in ICH Q1B¹.

Temperature excursion studies have commenced but have not yet been completed up to the full product expiry period, therefore no temperature excursions are to be approved with this submission.

Biopharmaceutics

Biopharmaceutic data are not required for this product according to Section 3 of Australian Regulatory Guidelines for Prescription Medicines (ARGPM) Guidance 15: Pharmaceutical Studies.

Quality summary and conclusions

There are no outstanding issues.

Proposed Conditions of Registration

Compliance with Certified Product Details (CPD)

The Certified Product Details (CPD), as described in Guidance 7: Certified Product Details of the Australian Regulatory Guidelines for Prescription Medicines (ARGPM) [<http://www.tga.gov.au/industry/pm-argpm-guidance-7.htm>], in PDF format, for the above products should be provided upon registration of these therapeutic goods. In addition, an updated CPD should be provided when changes to finished product specifications and test methods are approved in a Category 3 application or notified through a self-assessable change

III. Nonclinical findings

Introduction

The treatment for Crohn's disease requires an initial IV infusion prior to ongoing SC treatment, using a new modified 5 mg/mL (as 130 mg/26 mL) formulation (solution for IV infusion).

The new IV formulation contains new excipients, L-methionine and EDTA disodium salt dehydrate (Australian Approved Name (AAN): disodium edetate), which are not present in the SC formulation. According to the draft PI, the solution for IV infusion (2, 3 or 4 vials) is intended to be diluted to 250 mL with an IV infusion solution, resulting in respective final ustekinumab concentrations of 1.04, 1.56 or 2.08 mg/mL in the 250 mL infusion solution, which is then administered over at least 1 h.

For the current approved indications of plaque psoriasis and psoriatic arthritis, the recommended dose is 45 mg SC in weeks 0 and 4, then every 12 weeks thereafter (a 90 mg dose may be used in patients > 100 kg). For the newly proposed indication of Crohn's

¹ ICH Q1B: Stability Testing: Photostability Testing Of. New Drug Substances and Products.

disease, the recommended dose is a single IV dose of approximately 6 mg/kg, then 90 mg SC every 8 weeks thereafter.

No nonclinical data were included in this application. However, a published nonclinical study was provided in the clinical dossier in support of a mechanism of action statement in the PI document² In addition, the sponsor provided a risk assessment in the Quality dossier examining the potential toxicity of the excipients disodium edetate and methionine in the new IV formulation. Further, given the addition of the new IV route of administration for the treatment of Crohn's disease, the local tolerance profile of ustekinumab required review.

Upon review of Ahern et al 2010², the proposed revised PI document for Stelara, the provided risk assessment of disodium edetate and methionine, and the previous TGA nonclinical evaluation of ustekinumab, the following conclusions are provided.

Pharmacology

Mechanism of action

The nonclinical statement regarding the mechanism of action is discussed in the PI section below. The following comments refer to the proposed PI document for Stelara.

The following text is proposed by the sponsor:

'In patients with Crohn's disease, IL-12 and IL-23 are elevated in the intestines and lymph nodes. This is accompanied by increases in serum IFN γ and IL-17A levels, suggesting that IL-12 and IL-23 promote Th1 and Th17 activation in Crohn's disease. Both IL-12 and IL-23 can also stimulate TNF α production by T cells, resulting in chronic intestinal inflammation and epithelial cell injury. Significant associations have been found between Crohn's disease and genetic polymorphisms in the IL23R and IL12B genes, suggesting a potential causal role for IL-12/23 signalling in the disease. This is supported by pre-clinical data demonstrating that IL-12/23 signalling is required for intestinal injury in mouse models of inflammatory bowel disease.'

It is the reference to 'pre-clinical data' that prompted nonclinical assessment of the Ahern et al 2010 study series.

The paper by Ahern et al 2010 presents a series of murine experiments investigating the role of IL-23 and cites other studies examining this mechanism of action as it relates to intestinal inflammatory conditions. The paper does not specifically discuss the role of IL-12 in murine models of inflammatory bowel disease; however, there are other published studies/reviews which have addressed this.³ It is concluded that there are adequate nonclinical data to support the proposed statement and no changes to the proposed PI wording are required with regard to the nonclinical aspects.

² Ahern PP, Schiering C, Buonocore S, McGeachy MJ, Cua DJ, Maloy KJ, Powrie F (2010) Interleukin-23 drives intestinal inflammation through direct activity on T cells. *Immunity*, 33, 279-288.

³ Mizoguchi A, Mizoguchi E (2010) Animal models of IBD: linkage to human disease. *Current Opinion in Pharmacology*, 10(5), 578-587.

Neurath MF (2008) IL-12 family members in experimental colitis. *Mucosal Immunology*, 1 (Suppl 1), S28-S30.

Prattis S, Jurjus A (2015) Spontaneous and transgenic rodent models of inflammatory bowel disease.

Laboratory Animal Research, 31(2), 47-68. Sugimoto K, Ogawa A, Shimomura Y, Nagahama K, Mizoguchi A,

Bhan AK (2007) Inducible IL-12-producing B cells regulate Th2-mediated intestinal inflammation.

Gastroenterology, 133, 124-136.

Second round evaluation

In the sponsor's response to the first round evaluation, the sponsor did not provide any comment on the nonclinical question requesting any available nonclinical local tolerance information. In a follow-up email the sponsor indicated that no additional nonclinical data are available. Thus, assessment of the local tolerance of the new formulation, diluted in an IV infusion solution and administered by the IV route as proposed in this submission, will need to rely on clinical data.

There are no further nonclinical comments on the PI document at the second round evaluation.

Toxicology

Local tolerance

The present submission proposes a new IV formulation, dosage and route of administration for ustekinumab. The diluted IV infusion solution will contain ustekinumab at concentrations of 1.04, 1.56 or 2.08 mg/mL, plus the excipients disodium edetate (15-25 µg/mL Stelara, nominally 20 µg/mL) and L-methionine (0.30-0.50 mg/mL Stelara, nominally 0.40 mg/mL); with the dilution of up to 4 vials in 250 mL IV infusion solution, the final infused concentrations of these excipients would be up to 10.4 µg/mL and up to 208 µg/mL, respectively. Nonclinical assessment of IV local tolerance for a solution containing ustekinumab (and these excipients) at these concentrations (for example, in vitro haemolysis study) has not been conducted.

In the nonclinical dossier submitted for the original ustekinumab registration application, 3 studies employed IV administration in Cynomolgus monkeys at weekly doses up to 50 mg/kg for 4 weeks. In these studies, ustekinumab was formulated as a 2 or 10 mg/mL solution in normal saline and infused at approximately 3 mL/min. These IV studies were not focussed on local tolerance assessment, although no untoward local tolerance effects were described in the study reports.

The nonclinical local tolerance of ustekinumab administered by the SC route was assessed by the TGA in the original registration application. In Study T-2001-003 UHAW-148 dated 24 January 2002, Cynomolgus monkeys aged 2 years received ustekinumab 45 mg/kg SC twice weekly for 3 weeks (vehicle: 8.5% sucrose, 10 mM sodium phosphate, 0.001% polysorbate 80). The following is the summary of the study outcomes, from the Nonclinical Evaluation Report of that submission:

There were no deaths. Bruising of the inguinal region and/or arms was commonly observed in all groups. Thinning fur was also noted in CNTO 1275 treated monkeys. Minimal to mild signs of irritation, primarily oedema, was commonly observed at the injection sites in all groups. CNTO 1275 treated monkeys did not exhibit any body weight gain (compared to the other groups which gained about 0.2 kg or around 8%) compared to pre-study values, however mean body weights were similar. Physical examination data and clinical pathology values were difficult to interpret given the low animal numbers, hence wide range of variability and their presentation as individual data only making group differences difficult to discern. Nonetheless, apart from a few individual anomalies, which were not replicated at further time points and/or in the opposing sex, or were observed in all groups, findings were unremarkable. Histopathological examination of the injection site biopsies did not reveal any changes associated with CNTO 1275 or control solution administration. However, minimal chronic subcutaneous inflammation and eosinophil infiltrates were observed in the injection sites of two of the monkeys given IGIV.

In summary, CNTO 1275 was well tolerated in monkeys when administered at 45 mg/kg twice weekly SC for 3 weeks.

In summary, no nonclinical local tolerance studies of the new formulation diluted in an IV infusion solution and administered by the IV route, as proposed in this submission, have been submitted with this application. The local tolerance of the new IV product will therefore require clinical assessment. (It is noted that anaphylaxis or other serious infusion reactions have not been reported in Crohn's disease induction studies (draft PI: Adverse Effects, Hypersensitivity and Infusion Reactions)).

Excipients

With regard to the general toxicity of the excipients disodium edetate and methionine administered IV, the sponsor provided a risk assessment ('*Risk Assessment of Disodium EDTA and Methionine in CNTO 1275 DLiV for Crohn's Disease*'), which included the following key points and conclusions:

- **EDTA:** *A total of 1.04 mg (1 placebo bag) to 4.16 mg (4 placebo bags) of EDTA could potentially be administered to patients receiving Stelara DLiV for Crohn's disease (Table 1). These concentrations are calculated to be at least 143-times lower than the therapeutic EDTA dose of 810 mg given as chelation therapy (corrected for body weight). Additionally, there are a number of products on the market that contain EDTA or disodium EDTA for intravenous injection including those noted in Table 2. None of the products are formulated with calcium disodium EDTA. Notably, two of those products, Arzerra and Emend, contain disodium EDTA at levels up to 18-times higher than proposed for Stelara DLiV. Furthermore, when compared to the proposed concentration of EDTA in Stelara DLiV, 0.04 mg/mL, the lowest concentration of EDTA used for chelation therapy, 810 mg exceeds this concentration by at least 195-fold (810 mg/4.16 mg) which is a sufficient margin of safety. Thus, the specification of 0.04 mg/mL for EDTA in CNT01275 is justified and provides a considerable margin of safety.*
- **Methionine:** *Between 13 mg (1 placebo bag) to 52 mg (4 placebo bags) of methionine could potentially be administered to patients receiving Stelara DLiV for Crohn's disease (Table 1). The concentration of methionine in TPN is at least 40-times the level proposed for CNTO 1275 DLiV (corrected for body weight), and at least 20-times the recommended daily allowance for methionine. A 100 mg/kg body weight/day has been shown to be safe in humans, but this dose is about 7-times the daily requirement for sulfur-containing amino acids. If repeated on a daily basis for a week, increased serum homocysteine levels were observed. A daily dose of 250 mg (4 mg/kg/day) is approximately 25% of the daily requirement (16 mg/kg/day) and has been shown to be safe. A dose of 100 mg/kg/day in the methionine loading test does not cause any serious complications. Thus the specification of 0.5 mg/mL methionine in CNTO 1275 is also justified and provides a good margin of safety.*
- **Conclusions:** *It is concluded that the risk for toxicity from a CNTO 1275 DLiV formulation for single administration to Crohn's disease patients at volumes up to 104 mL containing both EDTA (0.04 mg/mL) and methionine (0.5 mg/mL) for the purpose of metal chelation and reduction of reactive oxygen species, respectively, is considered to be low to no-risk.*

To support these conclusions of the sponsor's risk assessment in the Australian context, a review of the Australian Register of Therapeutic Goods (ARTG) has identified both methionine and disodium edetate in several registered injectable IV formulations (see Table 3 below).

In context, the release criteria for Stelara indicate 15-25 µg/mL EDTA and 0.30-0.50 mg/mL methionine. From these upper ranges, and at the maximum single IV dose for Crohn's disease (4 vials for higher bodyweight, or 4x 130 mg/26 mL vials for 520 mg/104 mL):

- EDTA: (25 µg/mL⁴) (104 mL) = 2600 µg or 2.6 mg total⁵
- Methionine: (0.50 mg/mL⁶) (104 mL) = 52 mg total

Table 3 below indicates the concentrations of disodium edetate or methionine in selected products approved for IV administration on the ARTG.

Table 3: ARTG approved products containing disodium edetate or methionine

Formulation	Amount of disodium edetate or methionine	Dosing schedule	Total exposure to disodium edetate or methionine	Comparison to Stelara single IV exposure at MRHD*
Disodium Edetate Solution (Biological Therapies) (ARTG 22279)	3 g disodium edetate (in 100 mL vial)	<i>Pb poisoning</i> : initial test dose of 20 mg/kg; then usual dose of 50 mg/kg to a maximum of 3 g in 24 h. <i>Digitalis arrhythmia</i> : 15 mg/kg/h up to 60 mg/kg/day.	Up to 3 g total	1154 x
SMOFKabiven infusion (ARTG 173890)	approximately 2.2 g methionine/L	MRHD 35 mL/kg/day	5.39 g/day (70 kg)	104 x

*2.6 mg disodium edetate or 52 mg methionine

From the table above, it is clear that the potential systemic exposure to disodium edetate and methionine at the proposed IV maximum recommended human dose (MRHD) of Stelara is similar to or considerably less than the potential exposures at the approved MRHDs of other registered IV products.

⁴ Upper limit of the concentration range.

⁵ It is noted that the sponsor's Risk Assessment has been based on an EDTA concentration in the product of 0.04 mg/mL, with the maximal dose of 4 vials of STELARA leading to a total EDTA dose of 0.04 x 26 x 4 = 4.16 mg. However, the product specifications (Module 3.2.P.1 and 2.3.P.5) indicate the EDTA concentration as 15-25 µg/mL, leading to a total potential EDTA dose of 2.6 mg. The methionine concentration used in the sponsor's Risk Assessment (0.5 mg/mL in the product) complies with the specifications, with total potential exposure (4 vials) of 52 mg.

⁶ Upper limit of the concentration range.

Nonclinical summary and conclusions

As discussed above, the local tolerance of the IV formulation/IV route of Stelara has not been specifically assessed in nonclinical studies and adequate assessment will need to rely on clinical data.

There are no systemic toxicological concerns regarding the presence of the excipients methionine and disodium edetate at the specified concentrations and the proposed clinical MRHD.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

Information on the condition being treated

Crohn's disease is a chronic immune-mediated IBD with annual incidence rates ranging from 6 to 8 per 100,000 in the US and from 0.3 to 12.7 per 100,000 in the Europe; prevalence ranges from 100-200 per 100,000 in the US and approximately 0.6 to 322 per 100,000 in Europe.⁷ Incidence and prevalence in Australia is similar or higher than that observed in other industrialised nations.⁸ Peak age-specific incidence occurs between ages 15 and 30 years, thereby disproportionately affecting young adults during their prime working years; a second, smaller peak occurs in the sixth and seventh decades of life.⁹ Crohn's disease is associated with substantial morbidity and mortality. Clinically, Crohn's disease is characterised as a relapsing, remitting disease that occurs most commonly at the end of the small intestine (terminal ileum) and the beginning of the colon with clinical manifestations such as abdominal cramps / diarrhoea and systemic features such as cachexia, fever, anaemia, and weight loss; extra intestinal manifestations include pyoderma gangrenosum, uveitis, and arthritis.¹⁰ Complications include bowel fistulas, abscesses and luminal strictures, which often require multiple surgeries and can lead to short gut syndrome.¹¹ Studies suggest that 15 years after diagnosis, approximately 70% of patients with Crohn's disease will have undergone at least 1 major intra-abdominal surgery; by the same time-point, 35% of patients will have required two such operations and 20% will have required at least three. Patients also suffer from reduced quality of life and increased risk of clinical depression.

Current treatment options

The current standard of medical care for Crohn's disease involves anti-inflammatory therapeutic approaches, which include 5-aminosalicylic acid (5-ASA) compounds, corticosteroids, immune-modulators including azathioprine (AZA) or its active metabolite

⁷ Talley NJ, Abreu MT, Achkar JP, et al. An evidence-based systematic review on medical therapies for inflammatory bowel disease. *Am J Gastroenterol.* 2011; 106 Suppl 1:S2-S25.

⁸ Wilson J, et al: High incidence of inflammatory bowel disease in Australia: a prospective population-based Australian incidence study. *Inflamm Bowel Dis.* 2010 Sep;16(9):1550-6. doi: 10.1002/ibd.21209

⁹ Ananthakrishnan AN. Epidemiology and risk factors for IBD. *Nat Rev Gastroenterol Hepatol.* 2015;12:205-217

¹⁰ Glickman RM. Inflammatory bowel disease: ulcerative colitis and Crohn's disease. In: Faluce AS, Braunwald E, eds. *Harrison's Principles of Internal Medicine*, 14th ed. New York, NY: McGraw-Hill; 1998:1633-1645

¹¹ Schalamon J, Mayr J, Höllwarth M. Mortality and economics in short bowel syndrome. *Best Pract Res Clin Gastroenterol.* 2003; 17(6):931-942

6-mercaptopurine (6-MP) and methotrexate (MTX), and biologic agents including tumour necrosis factor (TNF) antagonist therapies and anti-integrin therapies. Among these commonly prescribed agents, only the biologic agents and the corticosteroid budesonide are approved for the treatment of Crohn's disease, and even with combinations of the available therapeutic options, many patients do not attain clinical benefit or cannot tolerate the therapy.

Frequently used as acute therapy for Crohn's disease, corticosteroids are capable of inducing remission but are ultimately ineffective in maintaining it and their therapeutic benefit is often offset by the side effects of prolonged exposure. Immuno-modulators can take as long as 3 months to work, may only be partially effective and can result in neutropenia, pancytopenia, pancreatitis, nephrotoxicity, or hepatotoxicity in some patients, requiring additional serologic monitoring and frequent blood sample collections. The use of thiopurines (AZA/6-MP) is associated with a possibly increased risk of lymphoma in adults¹² and a very rare and rapidly fatal lymphoproliferative disorder, hepatosplenic T-cell lymphoma (HSTCL), has been reported in mostly young adult male patients with IBD (predominantly Crohn's disease) who were treated with thiopurines with or without TNF antagonists.¹³

TNF antagonist therapies (infliximab, adalimumab and certolizumab pegol [not approved in Australia]) have been the first-line biologic agents in Crohn's disease. Although many patients initially respond to TNF antagonist therapy, many others do not, and secondary failures due to intolerance or loss of initial response are common. Among patients who receive TNF antagonist therapies for Crohn's disease, 20% to 40% are primary non responders, and among those with an initial response, approximately 40% lose their response over time.¹⁴

For patients who have failed TNF antagonists, only one other class of biologic agent is available for the treatment of moderate to severe Crohn's disease, the integrin inhibitors, which interfere with lymphocyte trafficking. This class includes natalizumab and, more recently, vedolizumab. Natalizumab is available only via restricted distribution in some regions and is not approved in others, largely due to safety concerns associated with progressive multifocal leukoencephalopathy (PML). Vedolizumab is approved more broadly but is available only as an IV therapy and has shown mixed results in induction studies in Crohn's disease, especially in TNF-antagonist refractory populations.

With only two classes of biologic agents available for patients who have failed or are intolerant to conventional systemic therapies, there is an unmet need for additional treatment options for a disease that largely affects younger patients during their most formative and productive years. For those who have exhausted existing treatment options or are relatively new to treatment, the lifelong course of the disease and the lack of a single enduring treatment highlight the inevitable need for additional treatment options with durable efficacy, a favourable benefit-risk profile and minimally invasive dosing and frequency.

¹² Kandiel A, Fraser AG, Korelitz BI, et al. Increased risk of lymphoma among inflammatory bowel disease patients treated with azathioprine and 6-mercaptopurine. *Gut*. 2005; 54:1121-1125.

¹³ Kotlyar DS, Osterman MT, Diamond RH, et al. A systematic review of factors contribute to hepatosplenic T-cell lymphoma in patients with inflammatory bowel disease. *Clin Gastroenterol Hepatol*. 2011; 9(1):36-41. Mackey AC, Green L, Leptak C, Avigan M. Hepatosplenic T cell lymphoma associated with infliximab use in young patients treated for inflammatory bowel disease: update. *J Pediatr Gastroenterol Nutr*. 2009; 48:386-388. Mackey AC, Green L, Liang LC, et al. Hepatosplenic T cell lymphoma associated with infliximab use in young patients treated for inflammatory bowel disease. *J Pediatr Gastroenterol Nutr*. 2007; 44:265-267.

¹⁴ Ha C, Kornbluth A. Vedolizumab as a treatment for Crohn's disease and ulcerative colitis. *Gastroenterol Hepatol*. 2014; 10:793-800.

¹⁴ Ha C, Kornbluth A. Vedolizumab as a treatment for Crohn's disease and ulcerative colitis. *Gastroenterol Hepatol*. 2014; 10:793-800.

Clinical rationale

Clinical, genetic, and animal model data suggest that Crohn's disease is mediated by IL-12/23-mediated induction of Th1 and Th17 cells.¹⁵ In Crohn's disease, intestinal antigen-presenting cells secrete increased levels of IL-12 and IL-23.¹⁶ IL-12 induces immune cells toward a T helper 1 (Th1) phenotype (stimulates IFN γ production) while IL-23 induces a T helper 17 (Th17) pathway (promotes secretion of IL-17A, IL-21, and IL-22). Both cytokines stimulate TNF production, resulting in the intestinal inflammation and epithelial cell injury typical of Crohn's disease.

Anti-IL-12/23 p40 antibodies administered at early or late time points in rodent models of colitis improved clinical and histopathological changes¹⁷ and mice with a genetic deletion of the p19 chain of IL-23 are protected in several models of intestinal inflammation.¹⁸ Significant associations have been found between Crohn's disease and genetic polymorphisms in the genes encoding the IL-23 receptor (*IL23R*) and the IL-12/23 p40 protein (*IL12B*).¹⁹ Collectively, the roles of IL-12 and IL-23 in Th1 and Th17 signalling combined with data from murine models of IBD, elevations in IL-12 and IL-23 in human Crohn's disease and genetic linkage data provide a strong rationale for inhibiting these cytokines in Crohn's disease. Ustekinumab binds with high affinity and specificity to the p40 subunit common to both human IL-12 and human IL-23 and inhibits their binding to the IL-12 receptor β 1 chain and subsequent intracellular signalling by both cytokines.

Guidance

The final submission for Stelara ustekinumab is consistent with the pre-submission planning form lodged with TGA on 23 December 2015 apart from a minor difference which does not affect the scope of the submission.

The overall clinical design and dose selection was based on guidance and advice with regulatory authorities including those in the United States, the EU and Japan.

¹⁵ Berrebi D, Besnard M, Fromont-Hankard G, et al. Interleukin-12 expression is focally enhanced in the gastric mucosa of pediatric patients with Crohn's disease. *Am J Pathol.* 1998; 152(3):667-672.

Monteleone G, Biancone L, Marasco R, et al. Interleukin 12 is expressed and actively released by Crohn's disease intestinal lamina propria mononuclear cells. *Gastroenterology.* 1997; 112(4):1169-1178.

Parrello T, Monteleone G, Cucchiara S, et al. Up-regulation of the IL-12 receptor beta 2 chain in Crohn's disease. *J Immunol.* 2000; 165(12):7234-7239

¹⁶ Liu Z, Yadav PK, Xu X, et al. The increased expression of IL-23 in inflammatory bowel disease promotes intraepithelial and lamina propria lymphocyte inflammatory responses and cytotoxicity. *J Leukoc Biol.* 2011; 89:597-606

Monteleone G, Biancone L, Marasco R, et al. Interleukin 12 is expressed and actively released by Crohn's disease intestinal lamina propria mononuclear cells. *Gastroenterology.* 1997; 112(4):1169-1178.

¹⁷ Davidson NJ, Hudak SA, Lesley RE, Menon S, Leach MW, Rennick DM. IL-12, but not IFN-gamma, plays a major role in sustaining the chronic phase of colitis in IL-10-deficient mice. *J Immunol.* 1998; 161:3143-3149

Neurath MF. IL-23: a master regulator in Crohn disease. *Nat Med.* 2007; 13(1):26-28.

¹⁸ Hue S, Ahern P, Buonocore S, et al. Interleukin-23 drives innate and T cell-mediated intestinal inflammation. *J Exp Med.* 2006; 203:2473-2483.

Kullberg MC, Jankovic D, Feng CG, et al. IL-23 plays a key role in *Helicobacter hepaticus*-induced T cell dependent colitis. *J Exp Med.* 2006; 203:2485-2494.

Yen D, Cheung J, Scheerens H, et al. IL-23 is essential for T cell-mediated colitis and promotes inflammation via IL-17 and IL-6. *J Clin Invest.* 2006; 116:1310-1316.

¹⁹ Umeno J, Asano K, Matsushita T, et al. Meta-analysis of published studies identified eight additional common susceptibility loci for Crohn's disease and ulcerative colitis. *Inflamm Bowel Dis.* 2011; 17(12):2407-2415.

Duerr RH, Taylor KD, Brant SR, et al. A genome-wide association study identifies *IL23R* as an inflammatory bowel disease gene. *Science.* 2006; 314(5804):1403-1405

Moon CM, Shin DJ, Son NH, et al. Genetic variants in the *IL12B* gene are associated with inflammatory bowel diseases in the Korean population. *J Gastroenterol Hepatol.* 2013; 28:1588-1594.

Wang K, Zhang H, Kugathasan S, et al. Diverse genome-wide association studies associate the *IL12/IL23* pathway with Crohn Disease. *Am J Hum Genet.* 2009; 84(3):399-405.

Contents of the clinical dossier

Scope of the clinical dossier

The submitted dossier documented a clinical development program of pharmacology, dose-finding, pivotal and other clinical trials relating to the proposed extension of indications.

The clinical development program in Crohn's Disease consisted of two placebo-controlled Phase II studies, three placebo-controlled Phase III studies, and a Phase I study as follows.

- Clinical pharmacology: One Phase I PK comparability study in healthy subjects (CNT01275NAP1002).
- Two Dose-finding studies: Phase IIa Study C0379T07 and the Phase IIb Study C0743T26.
- Population PK studies: PopPK modelling was undertaken using PK data obtained from one Phase IIb study (C0743T26) and three Phase III studies; CRD3001, CRD3002 and CRD3003.
- Pivotal efficacy/ safety studies: Two Phase III studies CRD3001 (3001) and CRD3002 (3002)
- Other efficacy/ safety studies: Efficacy and safety data are also provided for the Phase II studies (C0379T07, 28 weeks; C0743T26, 36 weeks).

Paediatric data

No paediatric data were provided. No clinical studies of ustekinumab have been conducted in paediatric subjects (< 18 years) with Crohn's disease.

Good clinical practice

All studies included in this submission were conducted and reported in accordance with the ethical principles originating in the Declaration of Helsinki and in accordance with ICH Good Clinical Practice (GCP) guidelines, applicable regulatory requirements, and in compliance with the respective protocols.

Pharmacokinetics

Studies providing pharmacokinetic data

The following table summarises the studies providing pharmacokinetic data.

Table 4: Submitted pharmacokinetic studies

PK topic	Subtopic	Study ID	*
PK in healthy adults	General PK Single dose†	NAP1002	PKs of 2 IV formulations, 90 mg/mL and 5 mg/mL, following a single dose of 6 mg/kg.

PK topic	Subtopic	Study ID	*
PK in special pop ⁿ	Target pop ⁿ - subjects with Crohn's disease§	C0379T07	PK/PD following a single IV or multiple SC administrations in subjects with moderately to severely active disease despite treatment with 5-ASA compounds, antibiotics, corticosteroids, and/or immune-modulators
		C0743T26	PK/PD following an IV induction dose and multiple SC maintenance doses in subjects with moderately to severely active disease who had received treatment with 1 or more TNF antagonists and had not responded initially, responded and then lost response, or were TNF-intolerant.
		CRD3001	PK/PD following an IV induction dose in subjects with moderately to severely active disease had who previously failed or were intolerant to 1 or more TNF-antagonist therapies.
		CRD3002	PK/PD following an IV induction dose in subjects with moderately to severely active disease with evidence of active inflammation who failed conventional therapy.
		CRD3003	PK, immunogenicity and PDs following multiple SC doses in continuing subjects following IV induction in CRD3001 or CRD3002
PPK analyses	Target pop ⁿ	Population PK Study	To develop a PPK model to characterise the PK of ustekinumab following IV and SC administrations

* Indicates the primary PK aim of the study.

† Bioequivalence of different formulations.

§ Subjects who would be eligible to receive the drug if approved for the proposed indication.
popⁿ population

Evaluator's conclusions on pharmacokinetics

- Stelara (ustekinumab) is a human IgG1kappa monoclonal antibody. In patients with Crohn's disease, following the recommended IV induction dose, median peak serum ustekinumab concentration was 126.1 µg/mL. Starting at Week 8, subcutaneous maintenance dosing of 90 mg ustekinumab was administered every 8 or 12 weeks. Steady state ustekinumab concentration was achieved by the start of the second maintenance dose. Median steady-state trough concentrations ranged from 1.97 µg/mL to 2.24 µg/mL and from 0.61 µg/mL to 0.76 µg/mL for 90 mg ustekinumab

every 8 weeks or every 12 weeks respectively. The steady-state trough ustekinumab levels resulting from 90 mg ustekinumab every 8 weeks were associated with higher clinical remission rates as compared to the steady-state trough levels following 90 mg every 12 weeks.

- In healthy subjects, the mean peak plasma concentration (C_{max}), area under the concentration versus time curve from time zero to infinity (AUC_{inf}) and half-life ($t_{1/2}$) of ustekinumab following a 6 mg/kg IV dose of the proposed formulation strength of 90 mg/mL were 199.1 $\mu\text{g/mL}$, 3218.3 $\mu\text{g}\cdot\text{day/mL}$ and 25.1 days, respectively. Similarly, following the same IV dose of the formulation strength of 5 mg/mL ustekinumab, C_{max} , AUC_{inf} and $t_{1/2}$ were 196.7 $\mu\text{g/mL}$, 3132.4 $\mu\text{g}\cdot\text{day/mL}$ and 24.7 days, respectively.
- Following a 6 mg/kg IV dose in healthy subjects, the two proposed formulations strengths of ustekinumab (that is, 90 mg/mL and 5 mg/mL) were bioequivalent.
- Population pharmacokinetic (PopPK) analysis predicted that the bioavailability of Stelara following SC dosing relative to IV dosing was 78.3% in subjects with moderately to severely active Crohn's disease.
- In subjects with moderately to severely active Crohn's disease or fistulising Crohn's disease, patients who received a single 4.5 mg/kg IV dose of ustekinumab had higher serum ustekinumab concentrations in the first 3 weeks following initial administration than subjects who had received three weeks of weekly SC dosing with 90 mg. By contrast, following the fourth SC dose the median serum concentrations of ustekinumab were slightly higher in subjects receiving multiple SC administrations than in subjects receiving the single IV administration.
- Following a single IV administration of 1, 3 or 6 mg/kg ustekinumab, serum ustekinumab concentrations were proportional to dose and were detectable in almost all subjects through Week 8. Similarly, in subjects with Crohn's disease who received a single IV dose of 130 mg, 260 mg, 390 mg or 520 mg, median serum ustekinumab concentrations were approximately dose proportional and were detectable at all sampling time-points through Week 8. For example, 8 weeks after a single IV dose of 130 mg, 260 mg, 390 mg or 520 mg ustekinumab the median serum concentration values were 2.1, 3.9, 6.6 and 8.8 $\mu\text{g/mL}$, respectively, and the r^2 was 0.994.
- Following maintenance dosing with ustekinumab 90 mg SC every 8 weeks (q8w) or every 12 weeks (q12w), steady-state was reached at approximately 8 or 12 weeks after subjects began receiving ustekinumab 90 mg SC q8w, or ustekinumab 90 mg SC q12w, respectively. Median steady-state trough serum ustekinumab concentrations over time were 3 times greater in the ustekinumab q8w group (1.97 $\mu\text{g/mL}$ to 2.24 $\mu\text{g/mL}$) than in the q12w group (0.61 $\mu\text{g/mL}$ to 0.76 $\mu\text{g/mL}$).
- In healthy subjects, the volume of distribution corrected for body weight following a 6 mg/kg IV infusion of ustekinumab 90 mg/mL or 5 mg/mL were 4.7 L and 4.9 L, respectively. In subjects with Crohn's disease, the predicted volume of the central compartment was 2.74 L. Based on these findings, it appears that plasma protein binding is high in both healthy subjects and patient's with Crohn's disease and little to no ustekinumab is distributed to the tissues.
- The exact metabolic pathway for ustekinumab is unknown.
- Ustekinumab was eliminated following SC administration with a median $t_{1/2}$ of approximately 23 to 25 days and following IV administration with a median $t_{1/2}$ of approximately 17 to 23 days.
- PopPK modelling provided predictions of between-subject variability in terms of %co variance (CV) of 29.1% for clearance (CL) and 14.7% for volume of distribution (V2). Inter-occasion variability was deemed low and was not reported.

- Modelling indicated that there was no meaningful impact of alkaline phosphatase, a marker for hepatic function, on the PK of ustekinumab.
- PopPK analysis indicates that there is a possibility that ustekinumab CL could be higher in subjects with impaired renal function.
- Age, within the range of 18 to 76 years, had no meaningful impact on the PKs of ustekinumab.
- Ustekinumab CL and V2 were 17% higher in male subjects than in females.
- Model-predicted CL and V2 values increased slightly as body weight increased.
- Ustekinumab CL was 14% higher in Asian subjects than in the other race categories.
- The model-predicted CL was 13.0% higher in subjects positive for antibodies to ustekinumab. 1.8% of subjects in the pooled popPK analysis set developed antibodies to ustekinumab.
- PopPK analysis identified that a 2-compartment disposition model with first-order absorption following SC administration adequately fitted the pooled data set.
- Covariates for CL were gender; race; TNF-antagonist failure; baseline C-reactive protein (CRP); and for V2 were baseline albumin and gender. In addition, the following covariates were included in the base model: baseline body weight on all the disposition parameters (CL, V2, inter-compartmental clearance (Q) and peripheral volume of distribution (V3)) and baseline albumin on CL.
- The PK sections of the proposed PI are satisfactory.

Pharmacodynamics

Studies providing pharmacodynamic data

Analyses of antibodies to ustekinumab were performed in the Phase III studies and NAP1002 using a validated, drug-tolerant ECLIA, in which ustekinumab was used to capture and detect induced immune responses to ustekinumab. Anti-drug antibody positive samples were further characterised for titre and neutralising capability in the Phase III studies. In the Phase II studies (C0397T07 and C0743T26), the presence of antibodies to ustekinumab was determined by a bridging enzyme immunoassay.

Evaluator's conclusions on pharmacodynamics

- Stelara is a human IgG1kappa monoclonal antibody that specifically binds to the shared p40 protein subunit of the human cytokines IL-12 and IL-23, which prevents p40 from binding to the IL-12Rbeta1 receptor protein expressed on the surface of immune cells.
- In general, compared to placebo, inflammation-related markers in serum, including cytokines, chemokines, mitogens and matrix metalloproteinase, were lower at Weeks 1, 4 and 8 following a single administration of IV ustekinumab, whereas, subjects receiving SC ustekinumab also showed changes in biomarker expression, though generally at later time-points.
- In contrast, serum levels of the inflammatory cytokine IL-12p40, which is the target antigen for ustekinumab, increased up until week 4 of treatment and the elevated levels were maintained up until Week 8 following treatment with either SC or IV ustekinumab. This represented IL-12p40 complexed with ustekinumab and was therefore inactive. Serum levels of regulated on activation, normal T cell expressed and

secreted (Regulated on activation, normal T cell expressed and secreted (RANTES)), which plays a role in both promoting and controlling inflammation, was also increased following IV administration of ustekinumab.

- IL-17A was significantly up-regulated in patients with Crohn's disease compared to healthy controls ($p < 0.0001$); however, 22 weeks following an IV induction dose of ustekinumab and SC doses starting at Week 8, IL-17A was significantly down-regulated among patients who demonstrated consistent responses during both induction and maintenance, whereas, there were marginal effects on IL-17F expression. By contrast, no significant modulation was observed among placebo-treated subjects or ustekinumab non-responders.
- IL-17A levels were significantly correlated with the inflammation markers CRP, faecal calprotectin (fCAL) and faecal lactoferrin (fLAC), whereas, there was no significant correlation between IL-17A or IL-17F with Crohn's Disease Activity Index (CDAI).
- Significantly different levels of IL-17A were identified in Crohn's disease subtypes, whereas IL-17F levels were significantly different for the Crohn's disease phenotypes.
- The populations with Crohn's disease in Studies CRD3001 and CRD3002 had similar serum marker profiles and the patterns of expression for serum amyloid A (SAA), IFN γ , IL-17A, myeloperoxidase (MPO), creatine kinase isoenzyme-MB (CKMB), IL-8, and TNF α were different to those seen in healthy subjects. By contrast, levels of IL23, IL12p40, IL-17F, IL6, MMP3, and GMCSF were similar in both diseased patients and healthy subjects.
- None of the markers measured consistently discriminated between R and NR at baseline across the CRD3001 and CRD3002 study populations with response defined as a decrease in CDAI of at least 100 points from baseline.
- IFN γ was identified as a pharmacodynamic (PD) marker and was significantly modulated by ustekinumab in both responders and non-responders following induction treatment.
- SAA, CRP and IL-6 were significantly modulated by ustekinumab in responders and less so or not at all in non-responders following both induction and maintenance therapy.
- IL-12p40 levels increased following treatment with ustekinumab due to the presence of the circulating antibody/ligand complex. A similar trend was observed for IL-23p19.
- Induction therapy had no effect on the baseline levels of IL-17A, TNF α , MPO, CKMB, IL-8 or haptoglobin, whereas maintenance therapy resulted in a significant reduction in IL-17A in R and increases in CKMB relative to decreased levels seen at baseline compared to healthy controls.
- Biopsies of colon and ileum from patients with Crohn's disease displayed transcript dysregulation in both the inflamed and non-involved areas compared to tissues taken from healthy subjects.
- In biopsies of colonic mucosa there was little change in expression of the apoptosis marker, FAS, following treatment with placebo (0.8%), whereas, in subjects who received either IV or SC ustekinumab at Week 0 the number of FAS expressing cells increased by 3.1% from baseline to Week 8. A similar pattern was identified for caspase 3; however, the magnitude of the difference between placebo and active drug treatment was much smaller (0.9%).
- Following ustekinumab treatment, the disease profile of colon and ileum including IL-12 receptor B1, IL-23, IL-6, and SAA showed significant resolution in responders (>25% of genes dysregulated in the disease profile are normalised by Week 6 and

maintained or further normalised by Week 22) while no significant changes were observed in non-responders or placebo treated patients.

- Following treatment with ustekinumab the number of subjects (either healthy or with Crohn's disease) who were positive for antibodies to ustekinumab was low and ranged from 0.2% to 2.3% of the study population. During maintenance ustekinumab therapy, no apparent impact on clinical efficacy was observed following the development of antibodies to ustekinumab, but interpretation was limited by low incidence of antibody development.
- A positive association was observed between serum ustekinumab concentration and clinical remission following both induction and maintenance dosing with ustekinumab.
- In the lowest serum ustekinumab concentration quartile where the lowest remission rates were observed, a substantial majority of subjects were receiving a q12w regimen and not a q8w regimen.

Dosage selection for the pivotal studies

The Phase IIb Study C0743T26 in 526 patients with Crohn's disease who had previously failed TNF antagonist therapy showed that ustekinumab administered at 1, 3 or 6 mg/kg IV at Week 0 and then at 90 mg SC at Week 8 and Week 16 was effective at inducing and maintaining clinical response. The 6 mg/kg dose appeared to be the most effective dose in inducing clinical response through Week 8. This dose also showed the greatest reduction in CDAI, and the highest proportions of subjects with normalisation of CRP, improvement in Inflammatory Bowel Disease Questionnaire (IBDQ), and fistula response compared with the other induction doses. The 6 mg/kg dose was also well-tolerated, with a safety profile generally comparable with those of the other treatment groups, including placebo. Hence, the decision was made to continue to evaluate doses approximating the 6 mg/kg induction dose in the Phase III studies, through a tiered dosing approach for the higher dose group that allowed administration of complete vials to subjects to simplify dosing: Ustekinumab 260 mg (weight ≤ 55 kg), Ustekinumab 390 mg (weight > 55 kg and ≤ 85 kg), Ustekinumab 520 mg (weight > 85 kg). This tiered dosing was targeted to achieve drug exposure comparable with that observed in the 6 mg/kg dose group in Study C0743T26.

Efficacy

Studies providing efficacy data

The proposed indication is for treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response, lost response, were intolerant to conventional therapy or a TNF α antagonist or have medical contraindications to such therapies. There were three pivotal Phase III studies:

CRD3001: A Phase III, randomised, double-blind, placebo-controlled, parallel-group, multicentre study to evaluate the safety and efficacy of Ustekinumab Induction Therapy in subjects with Moderately to Severely Active Crohn's Disease Who Have Failed or Are Intolerant to TNF Antagonist Therapy (UNITI-1)

CRD3002: A Phase III, randomised, double-blind, placebo-controlled, parallel-group, multicentre study to evaluate the safety and efficacy of Ustekinumab Induction Therapy in subjects with Moderately to Severely Active Crohn's Disease (UNITI-2)

CRD3003: A Phase III, randomised, double-blind, placebo-controlled, parallel-group, multicentre study to evaluate the safety and efficacy of Ustekinumab Maintenance Therapy in Subjects with Moderately to Severely Active Crohn's Disease (IM-UNITI).

Evaluator's conclusions on efficacy

Two Phase III pivotal, randomised, double-blind, placebo-controlled induction studies (CRD3001 and CRD3002) evaluated the efficacy and safety of ustekinumab in 1409 patients with moderately to severely active Crohn's disease. The Phase III pivotal randomised, double-blind, placebo-controlled Study CRD3003 evaluated efficacy of maintenance treatment with SC ustekinumab in 397 patients enrolled from the induction studies (CRD3001 and CRD3002). Overall, this submission includes a total of 52 weeks of efficacy and safety data from the Phase III studies (8 weeks from the induction studies and 44 weeks from the maintenance study). The endoscopic substudy with endoscopy data from 334 of 1409 subjects in the induction studies and 95 of 397 subjects from the maintenance study evaluated endoscopic healing of mucosa by ustekinumab induction and maintenance therapy in the Phase III pivotal studies (see Attachment 2 Efficacy 7.4).

The Phase III induction Studies CRD3001 and CRD3002 used an IV route of administration for ustekinumab and were essentially identical in design but targeted different, mutually exclusive patient populations, which together reflect the full spectrum of biologic-eligible patients with Crohn's disease. CRD3001 enrolled subjects with a history of inadequate response to, or intolerance to, TNF antagonists. CRD3002 enrolled subjects with a history of inadequate response to or intolerance of corticosteroids or immune-modulators; these subjects could have received TNF antagonists but could not have a history of an inadequate response or intolerance to them. In each induction study, subjects were randomised to receive a single IV dose of placebo or one of two doses of ustekinumab (a fixed 130 mg dose or a tiered [weight based] dose approximating approximately 6 mg/kg) at Week 0. The CRD3003 Phase III study was designed to evaluate 2 SC maintenance regimens of ustekinumab (90 mg q8w or 90 mg q12w) in subjects with moderately to severely active Crohn's disease who had received IV induction therapy in one of two induction studies (CRD3001 and CRD3002).

All pivotal Phase III studies were well-conducted; the study design (randomised, double-blind, placebo-controlled) and efficacy endpoints (clinical, laboratory and quality of life (QOL)), complied with the TGA adopted EU guidelines on the development of new medicinal products for the treatment of Crohn's disease. The patient population evaluated in these studies were representative of the target patient population.

Both CRD3001 and CRD3002 achieved the primary (clinical response at week 6) and all 4 major secondary endpoints for both IV induction doses. Both doses also showed consistent efficacy compared with placebo in additional efficacy measures, such as patient quality of life measures (such as IBDQ), significant reductions and normalisations in inflammatory markers and in a pooled analysis showed endoscopic improvement/healing. However, the magnitude of benefit seen with the lower 130 mg dose was generally less than that seen with the weight-tiered approximately 6 mg/kg dose. The following results provide evidence to support the proposed 6mg/kg IV induction dose for ustekinumab:-

Better efficacy, as illustrated by greater separation from IV placebo for approximately 6 mg/kg was most notable in the CRD3002 study population with higher rates of clinical remission at Week 8 (40.2%, 30.6% and 19.6% in the 130mg, approximately 6 mg/kg and placebo groups, respectively) These numbers represent a clinically meaningful near-doubling of the treatment effect, from 11% with 130 mg to 20.6% with approximately 6 mg/kg. While remission differences in Study CRD3001 were more modest (5% delta between doses), these differences are still clinically meaningful in this very refractory population of TNF-antagonists (from an 8.6% delta with 130 mg to 13.6% with approximately 6 mg/kg). Clinical response differences at Week 8 showed a similar pattern, though differences in response rates between the dose groups were less than 5% in Study CRD3001.

The 6 mg/kg IV induction dose was also associated with early onset of efficacy with differences in treatment effects apparent as early as Week 3, for clinical remission and

clinical response between the approximately 6 mg/kg and 130 mg groups. Only the approximately 6 mg/kg group demonstrated significant ($p < 0.05$) benefit in remission at Week 3 (in both the CRD3001 and CRD3002 studies). Proportions of subjects in clinical response at Week 3 were also numerically higher in both studies for approximately 6 mg/kg than those seen with the 130 mg dose.

The greater improvements in the key study endpoints with 6mg/kg (compared with the 130mg) IV induction dose were translated into meaningful improvements in QOL measures: Greater proportions of subjects achieved a ≥ 16 -point (clinically meaningful) improvement in the disease-specific IBDQ instrument at Week 8, with approximately 9% higher larger treatment effects seen for the approximately 6 mg/kg group in both CRD3001 and CRD3002. Reduction in inflammatory markers also showed slightly better efficacy for the 6mg/kg IV induction dose (the proportion of subjects attaining a normalisation of CRP at Week 8 (≤ 3 mg/L among those >3 mg/L at baseline) was greater for the approximately 6 mg/kg group in CRD3001 and CRD3002 compared with the 130 mg group (both approximately 5% higher proportions of subjects)

While proportions of subjects in clinical response at Week 6 (the primary endpoint) were nearly the same for the 2 doses in CRD3001 and only slightly higher for approximately 6 mg/kg group in CRD3002, the rates of clinical response increased for the approximately 6 mg/kg groups between Weeks 6 and 8 in both studies, while the proportion in response decreased slightly from 51.7% to 47.4% in the 130 mg group in CRD3002. This phenomenon was also seen in other endpoints, including change in CDAI, 70 point response and change in CRP. These trends are notable because differences with a suboptimal dose would be expected to become more apparent over time, as continually decreasing serum ustekinumab concentration would result in many subjects dropping to sub-therapeutic serum ustekinumab levels in the 130 mg dose group. The exposure-response (E-R) analyses are supportive that the approximately 6 mg/kg induction dose would be expected to provide more optimal efficacy for the entire 8 weeks post-induction dose.

Furthermore, the Phase III induction studies also did not show any consistent difference in safety profile between the 130 mg and approximately 6 mg/kg IV induction doses, supporting a dosing recommendation driven by the greater efficacy seen with the approximately 6 mg/kg dose for both the conventional therapy and TNF-antagonist failure populations.

Ustekinumab maintenance therapy was shown to be of significant benefit to ustekinumab induction responders over 44 weeks. Maintenance with 90 mg SC given q8w and q12w demonstrated statistically significant benefit for clinical remission (the primary endpoint) as well as clinical response at Week 44. The study demonstrated that among subjects who respond to ustekinumab induction therapy, continuous maintenance therapy is needed to maintain clinically meaningful improvements in signs and symptoms as well as patient reported outcomes and objective measures of inflammation. Among subjects withdrawn from ustekinumab after induction (that is, the SC placebo group), a gradual recurrence of disease was observed by every clinical measure as well as by laboratory measures of inflammation (that is, CRP and faecal calprotectin). By contrast, minimal recurrence of disease was observed among subjects who continued receiving maintenance doses of ustekinumab, such that by Week 44, a treatment effect of approximately 15% was seen for subjects who received ustekinumab maintenance for the endpoints of remission, response, corticosteroid-free remission, and sustained response and remission as compared with subjects withdrawn from ustekinumab after the induction dose (that is, the placebo group). Likewise, laboratory measures of inflammation (CRP and faecal calprotectin) demonstrated a significantly lower inflammatory burden among subjects who continued maintenance ustekinumab.

The following results provide evidence to support the 90 mg q8w as the primary maintenance ustekinumab dose:

- While efficacy was observed with both the q12w and q8w regimens compared with placebo, the magnitude of benefit was greater for the q8w dosing regimen for many endpoints including improvements in signs and symptoms and patient reported outcomes. The distinction between q8w and q12w dosing was more apparent in parameters evaluating the more clinically relevant stringent endpoints of remission (such as remission, especially in TNF antagonist naïve subjects, remission in remitters, steroid-free remission, and sustained remission) with differences ranging from approximately 4% to 10%. For example, higher proportions of subjects achieved clinical remission (53.1%) or were in sustained clinical remission (46.1%) with q8w than with q12w (48.8%, 40.3% respectively) administration. Additionally, all sensitivity analyses except the worst case remained significant for the q8w dosing regimen, indicating robustness for the primary endpoint of clinical remission for q8w versus placebo. These sensitivity analyses were not consistently robust for the q12w regimen, though the results trended in the same direction, with generally similar treatment effects.
- QOL effects greater with q8w dosing: proportions of subjects with at least a 16-point improvement in IBDQ score, a threshold widely considered clinically meaningful, was significantly better than placebo for q8w administration (67.9% versus 50.4%, $p=0.014$), but only numerically better than placebo at q12w maintenance intervals (61.3% versus 50.4%; $p=0.140$). Similarly, a significantly greater proportion of subjects in the ustekinumab q8w group compared with placebo achieved clinically meaningful (≥ 5 -point) improvement from baseline of this study in 36-item Short Form Health Survey (SF-36) Physical Component Summary (PCS) at Week 44 (52.1% versus 34.7%, $p=0.008$) while the q12w regimen was only numerically better than placebo (41.7% versus 34.7%, $p=0.269$).

Other dosing strategies were also evaluated in the Phase III Study CRD3003. Adjustment from 90 mg q12w to 90 mg q8w specifically in subjects who dose adjusted (after meeting study loss of response criteria) provided additional clinical benefit: clinical response was recaptured in 55.2% of these subjects, clinical remission in 41.4% and median change in CDAI improved by 141.0 points when assessed 16 weeks later. Improvement upon q12w to q8w dose adjustment was numerically better than that observed for subjects remaining on q8w after meeting loss of response criteria for dose adjustment (q8w to q8w). However, interpretation of these results was limited by small number of patients ($n=29$) who adjusted from q12w to q8w dosing. In an analyses of actual observed data over time (that is, not considering subjects who dose adjust as treatment failures) which allowed for an as-randomised comparison of a q8w only strategy versus q12w to q8w strategy, the key efficacy measures of clinical remission and clinical response were similar for the q12w to q8w dosing regimens.

Subgroup Analyses to Identify Subjects Appropriate for Initiation of Maintenance at q12w: Subjects above the median weight and with elevated inflammatory markers (at either induction or maintenance baseline) attained greater benefit compared with SC placebo for q8w dosing, compared to q12w, while the subgroups with low weight, and particularly those with low markers of inflammation did equally well on q12w. Further post-hoc analyses combining these factors suggested that higher inflammatory burden rather than weight was the more important factor and that subjects with low weight and particularly those with low markers of inflammation did equally well and showed no difference between q12w and q8w for all the key endpoints, whereas subjects with elevated inflammatory markers attained greater benefit for q8w dosing compared to q12w. These analyses suggest that subjects with low inflammatory burden could start on q12w regimen, with the caveat that they be able to dose adjust based on inadequate response to

q8w, as this is the best overall regimen. Meanwhile, subjects with a higher inflammatory burden (based upon pre- or post-treatment CRP or potentially faecal calprotectin), should be always started on q8w given the substantially better efficacy seen for these subjects on q8w. Given that not all patients with low inflammatory burden will achieve high levels of efficacy with q12w dosing, the ability to dose adjust as described above, would provide additional assurance that patients have every opportunity to achieve maximal response with ustekinumab therapy.

For the 467 subjects not in clinical response at Week 8 following ustekinumab IV induction dosing, more than half achieved clinical response 8 weeks later (16 weeks after IV induction) after receiving an additional ustekinumab 90 mg SC dose at Week 8. Of those subjects who subsequently continued on ustekinumab maintenance (receiving 90 mg q8w), 68.1% maintained clinical response and 50.2% were in clinical remission at Week 44. These results suggest that it may be appropriate to wait until 16 weeks after initiation of IV induction (with an additional SC 90 mg dose at Week 8) to make the ultimate assessment of efficacy and a decision on continuation of treatment. However, interpretation was again limited due to uncontrolled analysis in non-randomised subjects.

Among ustekinumab IV induction responder-primary population subjects randomised to SC placebo, initiation of maintenance with ustekinumab treatment at 90 mg SC q8w re-captured more than 70% of subjects who lost response, achieved clinical remission in 39.2% of subjects and achieved a median improvement in CDAI of 121.0 points when assessed 16 weeks after dose adjustment. This suggests that some benefit can be regained in many patients after interruption of ustekinumab treatment. However, interpretation was again limited due to uncontrolled analysis in non-randomised subjects.

Comparison with other biologics approved for Crohn's disease

No direct comparator studies have been performed. Review of published literature from Phase III programs for biologics approved within the last 15 years including, where comparable data are available, vedolizumab, adalimumab and certolizumab pegol, suggest that the efficacy and safety of ustekinumab therapy compares favourably with these approved agents. Infliximab was the first biologic approved in Crohn's disease and while it is widely used in Crohn's disease, comparative data is limited to only anti-TNF-naïve populations. Given the limitations of comparisons with infliximab, efficacy of ustekinumab induction and maintenance therapy is mainly compared with adalimumab, vedolizumab and certolizumab pegol. Data were extracted from published Phase III studies in the relevant patient populations comparing clinical response (100-point) and remission at time of primary endpoint.

In TNF-antagonist refractory population: results for ustekinumab were similar to adalimumab for the induction endpoints of clinical response and remission, it is noteworthy that adalimumab was studied only at the higher induction dose of 160/80 mg and in a narrower treatment-refractory population (that is, primary non responders were excluded and only infliximab failures were included, as infliximab was the only TNF antagonist approved at the time). In contrast, CRD3001 evaluated subjects who had failed one or more TNF antagonists (infliximab, adalimumab, or certolizumab pegol) and included both primary and secondary non-responders. Vedolizumab showed significance for remission at Week 10, but did not reach significance at the earlier time point of Week 6 (the primary endpoint of GEMINI III study). This suggests that vedolizumab may have more modest induction efficacy compared to ustekinumab at early time-points and appears to have a slower onset of efficacy. The data for certolizumab pegol are more difficult to interpret, as a placebo controlled induction trial in a defined population of TNF-antagonist failures was not conducted and the data shown are from a trial where the infliximab-exposed subjects were not required to demonstrate failure. Furthermore, certolizumab is not approved for Crohn's disease in Australia. Ustekinumab also compared

favourably to adalimumab, vedolizumab, and certolizumab pegol in the population of subjects who had not failed previous biologic therapy including subjects who were TNF-antagonist naïve, suggesting its potential role as a first-line biologic agent.

Evaluation of maintenance data shows similar patterns, although interpretation was limited due to differences in the populations studied for the maintenance trials regarding inclusion of previous biologic response. With regard to maintenance therapy in the broad Crohn's disease population, the absolute remission rates at 1 year of ustekinumab therapy were higher than those reported previously for any biologic though the treatment effects are comparable. However, this may be confounded by fact that in Study CRD3003, 100-point response was used as the criteria for selecting the population randomised to assess long-term maintenance, while the registration trials for adalimumab and vedolizumab used 70-point response. This difference was reflected in the rates of remission for patients entering the maintenance phase, with 60% of subjects entering the primary population in CRD3003 in remission compared with approximately 30% to 40% with vedolizumab and adalimumab, respectively.

Results from the Ustekinumab Endoscopy Substudy provided evidence to support efficacy of ustekinumab for induction of endoscopic healing of the mucosa, based on significant improvements in endoscopic disease activity in the ustekinumab group that were corroborated by improvements in histologic disease activity. However, this endoscopic substudy failed to provide definitive evidence to support efficacy of ustekinumab maintenance treatment on endoscopic activity. Among currently approved therapies for Crohn's disease, evidence of endoscopic improvement and healing of the mucosa has been reported for TNF antagonists²⁰ but not for biologics with other mechanisms of action.

Overall, indirect comparisons to biologic therapies approved for moderate to severe Crohn's disease suggest that ustekinumab has efficacy that is at least comparable and in some instances appears better or has a more rapid onset than currently approved biologics with a favourable safety profile. Although cross-study comparisons with other approved biologic agents can provide insight into the relative efficacy and safety of ustekinumab and its potential place in the treatment of patients with moderate to severe Crohn's disease although such indirect comparisons are limited by differences in populations, timing and study designs.

Limitations:

- 95% CI for the primary and main secondary endpoints were not provided (only p-values for comparison versus placebo were provided in the study report). Only the sensitivity analysis 3 (excluding those enrolled prior to study restart) showed the odds ratios and 95% CI values. The sponsors have been requested to provide the 95% CI for the primary and major secondary endpoints.

Efficacy data beyond 1 year of treatment are currently not available in Crohn's disease although the long-term extension of Study CRD3003 through Week 272 should provide efficacy data of an additional 4 years.

²⁰ Rutgeerts P, Van Assche G, Sandborn WJ, et al. Adalimumab induces and maintains mucosal healing in patients with Crohn's disease: data from the EXTEND trial. *Gastroenterology*. 2012;142(5):1102-1111.e2
Rutgeerts P, Diamond RH, Bala M, et al. Scheduled maintenance treatment with infliximab is superior to episodic treatment for the healing of mucosal ulceration associated with Crohn's disease. *Gastrointest Endosc*. 2006;63(3):433-44

Hébuterne X, Lémann M, Bouhnik Y, et al. Endoscopic improvement of mucosal lesions in patients with moderate to severe ileocolonic Crohn's disease following treatment with certolizumab pegol. *Gut*. 2013;62(2):201-208

Colombel JF, Sandborn WJ, Reinisch W, et al; SONIC Study Group. Infliximab, azathioprine, or combination therapy for Crohn's disease. *N Engl J Med*. 2010;362(15):1383-1395

Safety

Studies providing safety data

Safety data for the 5 Crohn's disease studies, focused on the pooled Phase III data, analysed separately for: the induction phase of treatment (Week 0 through Week 8), the maintenance phase of treatment (Week 0 of maintenance up to Week 44) and the combined induction and maintenance phases of treatment (up to 1 year of treatment; 8 weeks exposure in induction studies and 44 weeks exposure in the maintenance study).

Patient exposure

The safety database from the 5 Crohn's disease clinical studies comprises 1749 ustekinumab-treated subjects (a total of 1106 subject-years of follow-up) and includes 849 subjects exposed for at least 6 months, and 464 subjects exposed for at least 1 year. Of these 1749 subjects, 1664 subjects received a single IV induction dose of ustekinumab in the Phase II studies (C0379T07 and C0743T26), Phase III induction studies (CRD3001 and CRD3002) and Phase III maintenance study (CRD3003): 601 received approximately 6 mg/kg; 754 received 130 mg; and 309 received other doses. Of the 314 randomised subjects in the Phase III maintenance Study CRD3003, 132 subjects received ustekinumab 90 mg SC q12w and 131 received ustekinumab 90 mg SC q8w prior to meeting loss of response criteria. An additional 51 subjects received ustekinumab 90 mg SC q8w following loss of response to placebo SC. Therefore, 263 randomised subjects received ustekinumab maintenance treatment (90 mg q8w or q12w) in the CRD3003 study. An additional 72 subjects received ustekinumab 90 mg SC q8w as maintenance treatment in the Phase IIb Study C0743T26 following response to ustekinumab IV induction.

Overall for Studies CRD3003 and C0743T26 combined, of the subjects randomised as responders, 335 received ustekinumab SC (90 mg q8w or q12w) as maintenance treatment. Of these 335 subjects, 69.0% of subjects randomised as responders were exposed to ustekinumab SC for at least 6 months. For all treated subjects in maintenance Study CRD3003, in addition to the 263 subjects randomised to ustekinumab maintenance treatment following response to ustekinumab IV, 419 non-responders to induction treatment (either placebo or ustekinumab) received ustekinumab maintenance treatment (90 mg q8w or q12w) (that is, did not discontinue at Week 8). Overall, 1205 subjects received ustekinumab 90 mg SC maintenance dosing (every 8 or 12 weeks).

Furthermore, one PK comparability study in healthy normal subjects (CNT01275NAP1002) was conducted to support the registration of a 5mg/ml formulation intended for IV induction use in Crohn's disease. Results from this study were not included in any of the pooled analyses of safety data.

The safety database for clinical studies in the approved psoriatic disease indications (psoriasis and PsA) comprised of 4135 ustekinumab-treated subjects and includes 3255 subjects exposed for at least 6 months and 1669 subjects exposed for at least 1 year. Of these 4135 subjects, 2298 were treated with ustekinumab 90 mg SC either q8w or q12w.

Through 1 year of follow-up across all pooled indications, a total 5884 subjects were treated with ustekinumab (1749 subjects in the combined Crohn's disease studies, 3117 in the combined psoriasis studies, and 1018 in the combined PsA studies) with a total of 4521 subject-years of follow-up.

Safety issues with the potential for major regulatory impact

Tests of clinical chemistry consisted of laboratory measurements of alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total and direct bilirubin, sodium, potassium, chloride, blood urea nitrogen (BUN)/urea, serum creatinine,

albumin, total protein, calcium and inorganic phosphate at scheduled study visits in all 5 Crohn's disease studies.

Postmarketing data

Ustekinumab has not received marketing approval in any country for proposed indication in treatment of Crohn's disease.

However, ustekinumab has been approved for psoriasis and psoriatic arthritis. Post marketing information has been accruing since the first approval of ustekinumab on 12 December 2008. As of 31 December 2014, ustekinumab was approved in 84 countries. Global post marketing exposure through 31 December 2014 has been estimated as 379,596 person-years. Annual Periodic Safety Update reports (PSURs) have been generated for this product reflecting the assessment of active ongoing post marketing surveillance of targeted safety events as described in clinical study safety analyses, as well as broad overall safety surveillance. A large safety database is already available from previous studies of ustekinumab which includes 5 years of long-term safety data in psoriasis subjects; no dose differentiation based on safety data was identified between the 45 mg and 90 mg doses q12w in these studies, and no increase in the risk of death, serious infection, major adverse cardiac events (MACE) or malignancies over time was observed in either dose group.

Evaluator's conclusions on safety

Overall, IV ustekinumab at doses of 130 mg and approximately 6 mg/kg was well tolerated in the pooled Phase III induction studies (CRD3001 and CRD3002) with a safety profile generally comparable with placebo through Week 8. In addition, SC ustekinumab at doses of 90 mg q12w and 90 mg q8w was also well tolerated in randomised subjects in the Phase III maintenance Study CRD3003, with a safety profile generally comparable with placebo through Week 44. When safety data from the Phase II studies (C0379T07 and C0743T26) were pooled with data from the Phase III studies, results were generally consistent with observations from the pivotal Phase III studies alone.

The proportions of subjects with AEs, SAEs and discontinuations due to AEs during the induction phase of the pooled Phase III studies (CRD3001 and CRD3002) and in randomised subjects in the Phase III maintenance study (CRD3003) were comparable across treatment groups with no evidence of a dose effect. There were no new types or patterns of AEs identified with the exception of the new adverse drug reactions (ADRs) of acne, asthenia, vomiting and vulvovaginal mycotic infections.

The proportion of subjects with serious infections was low and generally comparable across treatment groups with no evidence of a dose effect during the induction phase of the pooled Phase III studies (CRD3001 and CRD3002) and in randomised subjects in the Phase III maintenance study (CRD3003). Overall, in the 5 Crohn's disease studies, no single opportunistic infection occurred in more than 1 subject with the exception of cases of nonserious oesophageal candidiasis which occurred in 2 placebo-treated subjects and 3 ustekinumab-treated subjects. Through Week 44 of the combined Crohn's disease studies, there was 1 event of presumed active primary tuberculosis (TB) reported in a subject (10 months after their last ustekinumab dose) who was randomised to ustekinumab 130 mg IV as induction treatment and then received placebo maintenance treatment in Study CRD3003.

The proportion of subjects with AEs temporally associated with infusions (defined as AEs reported during or within 1 hour following the IV infusion) was low and generally comparable across treatment groups (2.9% in the placebo-treated subjects and 3.4% in ustekinumab-treated subjects) across the 5 Crohn's disease studies. None of these events were considered to be serious or severe in subjects treated with ustekinumab.

During the placebo-controlled period no malignancies, serious MACE, deaths, anaphylactic reactions, reversible posterior leukoencephalopathy syndrome (RPLS) or definitive cases of progressive multifocal leukoencephalopathy (PML) were reported in the 5 Crohn's disease studies through 1 year.

The proportions of subjects experiencing markedly abnormal values in haematology and chemistry laboratory test results were low and were generally comparable among the treatment groups (placebo and all ustekinumab dose groups). The incidence of antibodies to ustekinumab in the Crohn's disease studies was low and no subject who was positive for antibodies had a reaction related to study agent administration.

Overall, no trends were apparent with regard to differences in the proportions of subjects with AEs, SAEs, infections, or who discontinued due to AEs, when evaluated by demographics, baseline disease characteristics, concomitant Crohn's disease medications (immune-modulators and/or corticosteroids) or tumor necrosis factor (TNF) antagonist failure history.

There were no meaningful differences between ustekinumab treatment groups and placebo treatment groups in the overall safety profile for both induction treatment (ustekinumab 130 mg IV and 6 mg/kg IV) and maintenance treatment (ustekinumab 90 mg SC q8w and q12w) through 1 year. In addition, no apparent dose effect between ustekinumab treatment groups was seen. Safety data from the Crohn's disease studies were consistent with those from the approved indications of psoriasis and PsA. With the exception of the new nonserious adverse drug reactions (ADRs) of acne, asthenia, vomiting and vulvovaginal mycotic infections there were no new types or patterns of AEs identified. There is no clear impact of ustekinumab on the safety events of serious infection, malignancy, infusion reactions, and serious MACE.

Through 1 year of follow-up across all pooled indications, a total 5884 subjects were treated with ustekinumab, with a total of 4521 subject-years of follow-up: 1749 subjects in the combined Crohn's disease studies, 3117 in the combined psoriasis studies, 1018 in the combined PsA studies. Overall, the safety data from the Crohn's disease studies does not appear to have altered the well-characterised ustekinumab safety profile established in the approved indications of psoriasis and PsA.

Ustekinumab was well tolerated in Crohn's disease, including subjects who received the proposed induction and maintenance dosages (that is, 6 mg/kg IV followed by 90 mg SC q8w). The comprehensive safety analyses presented in the Crohn's disease population, in 5 studies with 1,749 ustekinumab-treated subjects with up to 1 year of follow-up, combined with data from the psoriatic indications, support the safety of ustekinumab in the treatment of patients with moderately to severely active Crohn's disease.

First round benefit risk assessment

First round assessment of benefits

Indication	
Benefits	Strengths and Uncertainties
IV induction therapy with proposed dose of 6mg/kg showed statistically and clinically significant benefits over placebo in both pivotal induction studies (CRD3001 and CRD3002).	<u>Clinical response at Week 6:</u> Study CRD3001: 33.7%, 34.3% and 21.5% in ustekinumab IV 6mg/kg, 130mg and placebo groups, respectively. Study CRD3002: 55.5%, 51.7% and 28.7%, respectively.

Indication	
	<p><u>Clinical remission at Week 8:</u> Study CRD3001: 20.9%, 15.9% and 7.3% in ustekinumab IV 6mg/kg, 130mg and placebo groups, respectively. Study CRD3002: 40.2%, 30.6% and 19.6%, respectively.</p> <p>95% CI were not provided in the CSRs of studies CRD3001 and CRD3002; only p-values were provided.</p>
Rapid improvement in signs and symptoms of moderate to severely active Crohn's disease following IV induction treatment with ustekinumab.	Statistically significant benefits compared to placebo observed after Week 3 following ustekinumab IV induction treatment.
In patients who responded to IV induction therapy, maintenance of efficacy shown up to 44 weeks following SC ustekinumab 90mg given every 8 weeks or 12 weeks.	<p>Clinical remission at Week 44 was 35.9%, 48.8% and 53.1% in the placebo, ustekinumab q12w and q8w groups, respectively.</p> <p>Clinical response at Week 44 was 44.3%, 58.1% and 59.4%, respectively.</p> <p>Corticosteroid free remission at Week 44 was 29.8%, 42.6% and 46.9%, respectively.</p>
Demonstrated consistent efficacy across the full spectrum of patients with moderately to severely active Crohn's disease, from those who had failed conventional therapies and were TNF-naïve to those who had failed TNF	<p>Statistically and clinically significant benefits with ustekinumab IV induction and SC maintenance treatment in all 3 pivotal Phase III studies (CRD3001, CRD3002 and CRD3003). Although response and remission rates were slightly lower in Study CRD3001 (patients failed TNF-antagonist treatment) compared to Study CRD3002 (failed conventional therapy), the difference compared with placebo were statistically and clinically significant in both studies.</p> <p>Benefit of maintenance therapy in patients unresponsive to TNF-antagonist therapy not statistically significant although still numerically better than placebo.</p>
Sustained clinical remission and clinical response observed in ustekinumab treatment groups.	Compared with placebo, patients treated with ustekinumab induction and maintenance treatment showed higher rates of sustained clinical remission (40.3%, 46.1% and 26% in 90mg q12w, 90mg q8w and placebo groups, respectively) and clinical response (53.5%, 53.1% and 38.2%, respectively).
Induction and maintenance treatment with ustekinumab reduces the need for concomitant corticosteroid treatment.	The proportion of patients in clinical remission and not receiving concomitant corticosteroids for at least 90 days (and 30 days) prior to Week 44 was significantly greater in ustekinumab groups compared with placebo.
Improved objective markers of	Biomarker analysis in the Phase II and Phase III

Indication	
inflammation including both laboratory and tissue-based biomarkers of inflammation	studies showed significant improvements with ustekinumab treatment.
Provided clinically meaningful improvement in both disease-specific and general health related quality of life measures such as IBDQ and SF-36.	Improvements in clinical response / remission, laboratory markers associated with relevant improvement in quality of life.
Evidence for endoscopic healing of the mucosa after ustekinumab induction therapy.	Among currently approved treatments for Crohn's disease, evidence of endoscopic improvement and mucosal healing has only been shown for TNF antagonists, but not for biologics with other mechanisms of action. However, there was insufficient evidence for endoscopic healing with ustekinumab maintenance therapy.
Evidence of fistula response over a year of therapy.	Draining fistulas are clinically important manifestations of Crohn's disease for which there remains a large unmet medical need for new therapies. At Week 44, 80.0% (n=12/15) of subjects in the combined ustekinumab groups had a fistula response compared with 45.5% (n=5/11) in the placebo group. However interpretation was limited by sample size.

First round assessment of risks

Risks	Strengths and Uncertainties
IV induction therapy associated with risks of anaphylaxis and/or serious infusion reactions.	However, there were no reports of anaphylaxis or serious infusion reactions in the 5 Crohn's disease studies.
Risks of malignancies and MACE.	There were no reports of MACE or malignancies in the placebo-controlled periods of the 5 Crohn's disease studies.
Risks of serious infections including opportunistic infections.	Proportion of subjects with serious infections was low and generally comparable across treatment groups with no evidence of a dose effect during the induction phase of the pooled Phase III studies (CRD3001 and CRD3002) and in randomised subjects in the Phase III maintenance study (CRD3003). In the 5 Crohn's disease studies, no single opportunistic infection occurred in more than 1 subject with the exception of cases of nonserious oesophageal candidiasis which occurred in 2 placebo-treated subjects and 3 ustekinumab-treated subjects
Review of Crohn's safety data identified four	These have been included in the proposed PI.

Risks	Strengths and Uncertainties
new ADRs of acne, asthenia, vulvovaginal mycotic infections and vomiting.	
Long-term safety in Crohn's disease only evaluated up to 1 year	The extension of the pivotal Phase III maintenance Study CRD3003 through to 272 weeks should provide data on long term efficacy and safety of ustekinumab in Crohn's disease.
No direct comparisons with other biologics approved for treatment of Crohn's such as infliximab, adalimumab, vedolimumab and certolimumab.	Overall, indirect comparisons to biologic therapies approved for moderate to severe Crohn's disease suggest that ustekinumab has efficacy that is at least comparable and in some instances appears better or has a more rapid onset than currently approved biologics with a favourable safety profile. Although cross-study comparisons with other approved biologic agents can provide insight into the relative efficacy and safety of ustekinumab and its potential place in the treatment of patients with moderate to severe Crohn's disease although such indirect comparisons are limited by differences in populations, timing and study designs.
Evidence to support efficacy of ustekinumab maintenance therapy in patients that are refractory to TNF-antagonist treatment was not unequivocal.	There was no significant difference in clinical remission rates at Week 44 in the subgroup of patients refractory to TNF-antagonists although the results were similar to those observed in the overall population. Interpretation may have been limited to lack of power to detect significant differences in this subgroup of TNF refractory patients. Furthermore, analysis of efficacy by induction study showed significant benefit of ustekinumab maintenance therapy only for subjects enrolled from Study CRD3002 (which did not include TNF-antagonist refractory patients).
The proposed CMI was not available for evaluation in the submitted dossier.	

First round assessment of benefit-risk balance

Ustekinumab is a fully human monoclonal antibody (mAb) with high specificity for the p40 subunit shared by the human IL-12 and IL-23 cytokines. It has a different mechanism of action to the currently approved biologics for treatment of Crohn's disease in Australia.

The 3 pivotal studies CRD3001/CRD3002/CRD3003 were part of a Phase III program to study the safety and efficacy of ustekinumab induction (CRD3001/CRD3002) and maintenance therapy (CRD3003) in subjects with moderately to severely active Crohn's Disease who have inadequate response to or have failed conventional therapies (CRD3002) and those who have failed or are intolerant to TNF antagonist therapy (CRD3001).

Both Phase III induction Studies CRD3001 and CRD3002 achieved the primary and all 4 major secondary endpoints for both IV induction doses (130mg and weight-based 6mg/kg). Both doses also showed consistent efficacy compared with placebo in additional efficacy measures, such as patient quality of life measures (such as IBDQ), significant reductions and normalisations in inflammatory markers. However, the magnitude of benefit seen with the lower 130 mg dose was generally less than that seen with the proposed weight-tiered approximately 6 mg/kg dose. Better efficacy, as illustrated by greater separation from IV placebo for approximately 6 mg/kg, was most notable in the CRD3002 study population where, for example, approximately 6 mg/kg induced 40.2% of subjects into the clinically important remission at Week 8, compared with 30.6% in the 130 mg group (versus 19.6% on IV placebo). This represents a clinically meaningful near-doubling of the treatment effect, from 11% with 130 mg to 20.6% with approximately 6 mg/kg. While remission differences in CRD3001 were more modest (5% difference between doses), they were still clinically meaningful in this difficult to treat population (refractory to TNF-antagonists) as they represent a >50% increase in the treatment effect in comparison to placebo. Clinical response differences at Week 8 showed a similar pattern, though differences in response rates between the dose groups were less than 5% in CRD3001.

The CRD3003 maintenance study and its randomised withdrawal study design represent the most appropriate dataset to examine persistence of efficacy as well as to consider any possible tolerance or tachyphylaxis that might be observed. Good overall persistence of efficacy with high rate of remission among responders was observed at the Week 44 primary endpoint. Among the responders to IV induction ustekinumab therapy at baseline of the maintenance study, 59.4% were in clinical response and 53.1% in clinical remission at Week 44. When considering remission rates over time in the overall populations, including both those subjects in remission and those only in response at study entry, the rate is consistent over time, having started only slightly higher at baseline (60%). When considering remission over time exclusively in the subset of responding subjects that were in remission upon entry to CRD3003 (that is, remission in remitters), there was a decline over time to 66.7% at Week 44 in the q8w group (with a lower proportion of 56.4% on q12w). This decline was gradual and even slowed over time. The early loss of remission may have been affected by mandatory steroid tapering and the study requirements for corticosteroid withdrawal in the primary population may have been a confounding factor when considering the ability of ustekinumab to maintain persistence of efficacy in the maintenance phase. Despite this, it is also important to note that there were subjects who were successfully tapered from steroids and had good clinical response to ustekinumab. Efficacy data beyond 1 year of treatment are currently not available in Crohn's disease although the 272 week long-term extension of Study CRD3003 should provide efficacy data of an additional 4 years.

Results from the Ustekinumab Endoscopy Substudy provided evidence to support efficacy of ustekinumab for induction of endoscopic healing of the mucosa, based on significant improvements in endoscopic disease activity in the ustekinumab group that were corroborated by improvements in histologic disease activity. However, this endoscopic substudy failed to provide definitive evidence to support efficacy of ustekinumab maintenance treatment on endoscopic activity. Among currently approved therapies for Crohn's disease, evidence of endoscopic improvement and healing of the mucosa has been reported for TNF antagonists²⁰ but not for biologics with other mechanisms of action.

The proportion of subjects developing antibodies to ustekinumab, utilising a drug tolerant assay, was low (2.3% and 3.0% in the q8w and q12w groups, respectively). Furthermore, presence of these antibodies did not preclude clinical response, with similar rates of clinical remission in those with antibodies (4/7, 57.1%) compared to those negative for antibodies (59.0%). However, interpretation was limited due to very small number of patients with positive antibodies. Antibody rates were slightly higher in the group of

subjects randomised to placebo who were later re-treated after ustekinumab induction (5.3%).

No direct comparator studies have been performed. Indirect comparisons to biologic therapies approved for moderate to severe Crohn's disease suggest that ustekinumab has efficacy that is at least comparable and in some instances appears better or has a more rapid onset than currently approved biologics with a favourable safety profile. Although, cross-study comparisons with other approved biologic agents can provide insight into the relative efficacy and safety of ustekinumab and its potential place in the treatment of patients with moderate to severe Crohn's disease, it is important to note that such indirect comparisons are limited by differences in populations, timing and study designs.

Ustekinumab was well tolerated in Crohn's disease, including subjects who received the proposed induction and maintenance dosages (that is, 6 mg/kg IV followed by 90 mg SC q8w). There were no meaningful differences between ustekinumab treatment groups and placebo treatment groups in the overall safety profile for both induction treatment (ustekinumab 130 mg IV and 6 mg/kg IV) and maintenance treatment (ustekinumab 90 mg SC q8w and q12w) through 1 year. No apparent dose effect between ustekinumab treatment groups was seen. Safety data from the Crohn's disease studies were consistent with those from the approved indications of psoriasis and PsA. With the exception of the new nonserious ADRs of acne, asthenia, vomiting, and vulvovaginal mycotic infections, there were no new types or patterns of AEs identified. There is no clear impact of ustekinumab on the safety events of serious infection, malignancy, infusion reactions and serious MACE. The comprehensive safety analyses presented in the Crohn's disease population, in 5 studies with 1,749 ustekinumab-treated subjects with up to 1 year of follow-up, combined with data from the psoriatic indications, support the safety of ustekinumab in the treatment of patients with moderately to severely active Crohn's disease.

The ustekinumab development program in Crohn's disease through 1 year demonstrated that ustekinumab therapy, administered as a single IV induction dose to rapidly gain control of inflammation and symptoms followed by a convenient SC maintenance regimen administered every 8 or 12 weeks, provides a new treatment option with a new mechanism of action for patients living with moderately to severely active Crohn's disease who have either failed conventional therapies or have failed or are intolerant to TNF antagonists.

Overall, the benefit-risk profile of ustekinumab for the proposed usage in Crohn's disease is favourable.

First round recommendation regarding authorisation

Approval is recommended for ustekinumab for the proposed indication of

Crohn's Disease: Stelara is indicated for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response, lost response, were intolerant to conventional therapy or a TNF α antagonist or have medical contraindications to such therapies.

However, approval is subject to incorporation of suggested changes to the proposed PI and satisfactory response to Clinical questions raised in this evaluation report.

Second round evaluation of clinical data submitted in response to questions

For details of the Clinical questions and sponsor's responses and the evaluation of these responses please see Attachment 2.

Second round benefit-risk assessment

Second round assessment of benefits

After consideration of responses to the clinical questions, the benefits of Stelara (ustekinumab) in the proposed usage are unchanged from those identified in the first round.

Second round assessment of risks

After consideration of responses to the clinical questions, the risks of Stelara (ustekinumab) in the proposed usage are unchanged from those identified in the first round.

Second round assessment of benefit-risk balance

The benefit-risk balance of Stelara (ustekinumab), given the proposed usage is favourable.

Second round recommendation regarding authorisation

Approval is recommended for ustekinumab for the proposed indication of

Crohn's Disease: Stelara is indicated for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response, lost response, were intolerant to conventional therapy or a TNF α antagonist or have medical contraindications to such therapies.

V. Pharmacovigilance findings

Risk management plan

Summary

- The sponsor has submitted EU-RMP version 13.2 (dated 7 September 2016; DLP 8 July 2015) and ASA version 3.2 (dated 19 October 2016) in support of this application, incorporating recommendations made in the first round evaluation.
- The proposed Summary of Safety Concerns and their associated risk monitoring and mitigation strategies are summarised below in Table 5.

Table 5: Summary of safety concerns

R=routine and A=Additional

Summary of safety concerns (EU-RMP v13.2 + ASA v3.2)		Pharmacovigilance		Risk Minimisation	
		R	A	R	A
Important identified risks	Serious systemic hypersensitivity reactions	Ü*	Ü	Ü	Ü
	Facial palsy	Ü*	Ü	-	-
	Pustular psoriasis	Ü*	Ü	Ü	-
	Erythrodermic psoriasis	Ü*	Ü	Ü	-
Important potential risks	Serious infections including mycobacterial and salmonella infections	Ü*	Ü	Ü	Ü
	Malignancy	Ü*	Ü	Ü	Ü
	Cardiovascular events	Ü*	Ü	Ü	-
	Serious depression including suicidality	Ü	Ü	Ü	-
	Reversible Posterior Leukoencephalopathy Syndrome	Ü*	Ü	Ü	-
	<u>Venous thromboembolism</u> (EU-RMP only)	€	€	-	-
	Exposure during pregnancy	Ü*	Ü	Ü	-
Missing information	<u>Use in paediatric patients†</u>	Ü	Ü	Ü	-
	Use in patients with renal impairment	Ü	Ü	Ü	-
	Use in patients with hepatic impairment	Ü	Ü	Ü	-
	Use in patients with a history of latent TB or TB	Ü	Ü	Ü	-
	Use in patients with concurrent malignancy or a history of malignancy	Ü	Ü	Ü	-
	Use after recent vaccination with live bacterial or live viral vaccines	Ü	-	Ü	-

Summary of safety concerns (EU-RMP v13.2 + ASA v3.2)		Pharmacovigilance		Risk Minimisation	
	Use in patients with active infections (e.g. TB, HIV, Hepatitis B, Hepatitis C)	ü	ü	ü	-
	Use in patients with recent or concomitant use of immunosuppressive therapy other than MTX, 6-MP, AZA, 5-ASA and corticosteroids	ü	ü	ü	-
	Use in patients with other forms of psoriasis	ü	ü	-	-
	Use in patients who have undergone allergy immunotherapy	ü	-	ü	-
	Long-term safety in adult patients with moderately to severely active Crohn's disease	ü	ü	-	-

Highlighted text indicates changes to the summary of safety concerns compared to EU-RMP v13.0 with ASA v3.1: Additions are underlined, explanatory text is *italicised*.

Targeted follow-up questionnaires to be used for enhanced routine pharmacovigilance

€ EU-RMP only, this safety concern is omitted in the ASA and not considered applicable for Australia.

† Multiple paediatric missing information categories have been consolidated into one: 'Use in Paediatric patients', as per recommendation 2.

The ongoing or proposed additional pharmacovigilance activities are:

- Ongoing clinical trials and registries
 - CNT01275CRD30003 Long term extension study (Crohn's disease)
 - PSOLAR observational registry (plaque psoriasis)
 - Nordic Database Initiative registry study (any form psoriasis)
 - Pregnancy research initiative
- Paediatric investigation plans
 - Psoriasis (one outstanding study in patients 6-12 yrs old)
 - Crohn's disease (study approved)
 - Juvenile idiopathic arthritis (study approved)
- Proposed studies
 - Postmarketing registry/prospective cohort observational study to monitor the long-term safety profile of ustekinumab use in adult patients with moderately to severely active Crohn's disease
 - Post market registry/prospective cohort observational study to further characterise the long-term safety profile of ustekinumab in the paediatric population 12 years and older and to explore any potential effect on growth and development, in-line with the consideration in the Stelara PIP

The additional risk minimisation activities proposed are:

- HCP Educational program
- Patient educational materials

The following risk minimisation activities are proposed in the sponsor's response but are not considered to be additional risk minimisation for a specific safety concern:

- Stelara patient app
- Optional Patient support program that provides home visits from a qualified nurse for self-injection support and an injection reminder service via SMS, telephone or email

New recommendations second round

The recommendations made in the first round RMP Evaluation (Recommendations 1 – 8) were adequately addressed by the sponsor. A new minor recommendation is made in this report as follows:

Minor recommendations

Recommendation 9: The sponsor is recommended to describe the patient app, patient support program and any other newly proposed risk minimisation tools in the ASA as 'stated' risk minimisation activities.

It is acceptable for the sponsor to address this recommendation in the next update to the ASA.

Commitments to be included in a revised ASA

The sponsor has committed to maintaining the ASA to include a complete list of current studies and when the planned studies commence (including the proposed long term safety study in Crohn's disease).

The sponsor has committed to updating the HCP and patient educational materials and tools with information on Crohn's disease if approval for this indication is granted.

Wording for conditions of registration

Any changes to which the sponsor has agreed should be included in a revised RMP and ASA. However, irrespective of whether or not they are included in the currently available version of the RMP document, the agreed changes become part of the risk management system.

The suggested wording is:

The Stelara EU-RMP version 13.2 (dated 7 September 2016; data lock point 8 July 2015) with Australian Specific Annex version 3.2 (dated 19 October 2016), submitted with application PM-2015-04746-1-1, must be implemented.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

The evaluators have raised no objections, quality or microbial- wise, to the approval of the application to register ustekinumab 5.0 mg/1 mL solution for IV infusion injection vial.

Nonclinical

No nonclinical local tolerance studies of the new formulation diluted in an IV infusion solution and administered by the IV route, as proposed in this submission, have been submitted with this application. The local tolerance of the new IV product will therefore require clinical assessment. (It is noted that anaphylaxis or other serious infusion reactions have not been reported in Crohn's disease induction studies).

There are no systemic toxicological concerns regarding the presence of the excipients methionine and disodium edetate at the specified concentrations and the proposed clinical MRHD.

The following comments refer to the proposed PI document for Stelara:

Pharmacology

Mechanism of action

The following text is proposed by the sponsor:

'In patients with Crohn's disease, IL-12 and IL-23 are elevated in the intestines and lymph nodes. This is accompanied by increases in serum IFN γ and IL-17A levels, suggesting that IL-12 and IL-23 promote Th1 and Th17 activation in Crohn's disease. Both IL-12 and IL-23 can also stimulate TNF α production by T cells, resulting in chronic intestinal inflammation and epithelial cell injury. Significant associations have been found between Crohn's disease and genetic polymorphisms in the IL23R and IL12B genes, suggesting a potential causal role for IL-12/23 signalling in the disease. This is supported by pre-clinical data demonstrating that IL-12/23 signalling is required for intestinal injury in mouse models of inflammatory bowel disease.'

The proposal is acceptable by the nonclinical evaluator.

There are no further nonclinical comments.

Clinical

On pharmacokinetics

- This submission provided data to examine the pharmacokinetics of ustekinumab for the proposed initial single IV dose of approximately 6 mg/kg as well as the higher (90 mg every 8 weeks) SC dose regimen of ustekinumab.
- The recommended dose regimen for the plaque psoriasis and psoriatic arthritis indications is 45 mg SC at Weeks 0 and 4, then every 12 weeks thereafter. An alternative regimen of 90 mg at the above time points may be used for patients with body weight >100 mg. For patients with plaque psoriasis consideration may be given to treating as often as every 8 weeks.
- PopPK modelling predicted that the bioavailability of ustekinumab following SC dosing relative to IV dosing was 78.3% in subjects with moderately to severely active CD.
- The current PI notes the median volume of distribution during the terminal phase (V_z) following a single IV administration to patients with psoriasis, ranged from 57 to 83 mL/kg. This is consistent with the calculation from study NAP1002 in healthy volunteers in this submission where mean V_d was estimated to be 4.7L after infusion of 6 mg/kg of 90 mg/5 mL ustekinumab (with mean body weight 70.6 kg, V_d was 66.6 mL/kg). Based on these findings, it appears that plasma protein binding is high in both

healthy subjects and patients with CD and little to no ustekinumab is distributed to the tissues.

- Following the recommended IV induction dose, median peak serum ustekinumab concentration was 126.1 µg/mL. The pharmacokinetics of ustekinumab are linear with both IV and SC administration within the assessed dose range of 1, 3 and 6 mg/kg.
- Starting at Week 8, SC maintenance dosing of 90 mg ustekinumab was administered every 8 or 12 weeks. Steady state ustekinumab concentration was achieved by the start of the second maintenance dose i.e. at approximately 8 or 12 weeks after subjects began receiving ustekinumab 90 mg SC q8w, or ustekinumab 90 mg SC q12w, respectively.
- Median steady-state trough concentrations ranged from 1.97 µg/mL to 2.24 µg/mL and from 0.61 µg/mL to 0.76 µg/mL for 90 mg ustekinumab every 8 weeks or every 12 weeks respectively i.e. approximately 3 fold higher with the q8w dose cf. the q12 w dose.
- Ustekinumab was eliminated following SC administration with a median $t_{1/2}$ of approximately 23 to 25 days and following IV administration with a median $t_{1/2}$ of approximately 17 to 23 days.
- PopPK modelling predicted a %CV for between-subject variability for CL of 29.1%. PopPK modelling also predicted that CL would be 13.0% higher in subjects positive for antibodies to ustekinumab. This latter prediction was assessed from the 1.8% (n=30) of subjects in the pooled PopPK analysis set who developed antibodies to ustekinumab.
- Age, within the range of 18 to 76 years, had no meaningful impact on the PK of ustekinumab. CL was 14% higher in Asian subjects than in the other race categories. The metabolic pathway for ustekinumab has not been elucidated.

On pharmacodynamics

- Study C0379T07, a Phase IIa study is described in the CER. This study allowed for a placebo controlled evaluation of serum biomarker changes in response to either a single IV administration or multiple SC treatments with ustekinumab in subjects with moderately to severely active CD or fistulising CD. Patients received either SC or IV doses of ustekinumab. The IV dose was 4.5 mg/kg rather than the proposed dose which approximates 6 mg/kg. PD assessments were made throughout the first 8 weeks of the study.
- In summary, these figures showed that:
 - ustekinumab was associated with significant increases in IL-12p40 (up 600% from baseline), decreases in TNF alpha (approximately 20%), reductions in IL-6 (40 to 80%), reductions in VEGF (approximately 30% at week 8 for IV dosing) and smaller and/ or inconsistent changes in RANTES, interferon-gamma inducible protein 10(IP-10), monocyte chemotactic protein 1(MCP-1), epithelial-derived neutrophil-activating peptide (ENA-78), Epidermal growth factor (EGF), matrix metalloproteinase-3 (MMP-3), MMP-9 and Tropomyosin alpha-1 (TPM-1). The IL-12p40 was complexed with ustekinumab and was therefore inactive.
- A second Phase II study, C0743T26 also examined various serum markers following an IV induction dose of either 1, 3 or 6 mg/kg ustekinumab followed by SC doses starting at Week 8 in patients with CD:
 - Initial tests established that IL-17A was significantly up-regulated in patients with CD compared to healthy controls (p<0.0001).

- Then following 22 weeks of ustekinumab treatment, IL-17A was significantly down-regulated among patients who demonstrated consistent responses during both induction and maintenance, whereas, there were marginal effects on IL-17F expression.
 - By contrast, no significant modulation was observed among placebo treated subjects, or ustekinumab non-responders.
 - This study also showed a correlation between levels of IL-17A for the CD subtypes defined by different levels of the inflammatory markers (CRP, fCP and fLF) and for IL-17F levels and CD phenotypes defined by disease duration, CRP, fCP and the presence of fistula.
- An attempt was made to identify serum markers which were predictive of subsequent response or nonresponse to ustekinumab treatment in the Phase III studies. However, none of the markers examined could be used to consistently identify or distinguish between patients who would be responders or non-responders to ustekinumab.

On efficacy

There were two induction studies:

- CRD3001: A Phase III, randomised, double-blind, placebo-controlled, parallel-group, multicentre study to evaluate the safety and efficacy of Ustekinumab Induction Therapy in subjects with Moderately to Severely Active Crohn's Disease Who Have Failed or Are Intolerant to TNF Antagonist Therapy (UNITI-1)
- CRD3002: A Phase III, randomised, double-blind, placebo-controlled, parallel-group, multicentre study to evaluate the safety and efficacy of Ustekinumab Induction Therapy in subjects with Moderately to Severely Active Crohn's Disease (UNITI-2)

Studies 3001 and CRD3002 had the same design, differing only in inclusion criteria. In both studies, subjects were assigned in a 1:1:1 ratio to receive a single IV dose of placebo, ustekinumab 130 mg or ustekinumab approximating 6 mg/kg at Week 0.

Study agents were to be given over at least 1 hour with infusions completed within 5 hours of preparation. Subjects were permitted to receive oral 5-ASA compounds, the immune-modulators AZA, 6-MP, and MTX, oral corticosteroids, and/or antibiotics or the treatment of Crohn's disease during the study, provided that the subject was on a stable dose for a specified period before baseline.

Efficacy was primarily assessed using the CDAI. This is a tool to quantify CD symptoms based on 8 factors: *number of stools daily; abdominal pain; presence of complications; diarrhoea; management medication; presence of abdominal mass; haematocrit; and body weight*. Severe CD is generally defined as a CDAI >450 and remission as <150. In these studies, subjects required a CDAI ≥ 220 and ≤ 450 for study entry.

Primary efficacy endpoint

- clinical response at Week 6 defined as a reduction from baseline in the CDAI of ≥ 100 points.
- subjects with a baseline CDAI of ≥ 220 to ≤ 248 points were considered to be in clinical response if a CDAI <150 was attained
- subjects who had any of the following events before the Week 6 visit were considered to not be in clinical response at Week 6, regardless of the actual CDAI score: a Crohn's disease-related surgery (with the exception of drainage of an abscess or seton placement) that was thought to be a result of lack of efficacy of study agent
- specified changes in concomitant Crohn's disease medications

- if the CDAI score could not be calculated (that is, <4 components available) at a visit, the CDAI score was considered missing. Subjects with a missing CDAI at Week 6 were considered to not have achieved clinical response at Week 6.

Major secondary endpoints in order of importance:

- clinical remission at Week 8, defined as a CDAI score <150 points
- clinical response at Week 8
- 70-point response at Week 6, defined as a reduction from baseline in the CDAI score of ≥ 70 points
- 70-point response at Week 3.

Other outcomes assessed included:

- mucosal healing (in an endoscopy substudy)
- fistula closure
- serum CRP
- faecal lactoferrin and faecal calprotectin markers
- the Inflammatory Bowel Disease Questionnaire (IBDQ)
- the 36-Item Short-Form Health Survey (SF-36); and Health economics analyses.

The primary endpoint (proportion of subjects in clinical response at Week 6) analysis was based on comparison between each of the ustekinumab treatment groups and the placebo group, using a 2-sided Cochran-Mantel-Haenszel chi-square test, stratified by study region (Asia, Eastern Europe, or rest of world), CDAI score (≤ 300 or >300), and initial response to TNF antagonist therapy (yes or no), at a significance level of 0.05. A fixed-sequence testing procedure was used to control the overall Type 1 error rate at the 0.05 level of significance. Each study was considered positive if the ustekinumab high-dose group was significantly different from the placebo group for the primary endpoint.

The robustness of the primary endpoint analysis was examined by sensitivity analyses of the primary endpoint using the observed case; last observation carried forward, multiple imputations and the worst case missing data methods. The consistency of the efficacy of the primary endpoint was evaluated in subgroups based on demographic, baseline disease characteristics, Crohn's disease medication history, concomitant Crohn's disease medication use at baseline, centre location and initial response to TNF antagonist therapy.

The major inclusion criteria were: age ≥ 18 years, moderately to severely active Crohn's disease or fistulising Crohn's disease of at least 3 months' duration, with colitis, ileitis or ileocolitis, confirmed by radiography, histology, and/or endoscopy (Crohn's Disease Activity Index [CDAI] score ≥ 220 but ≤ 450).

The major exclusion criteria were: complications of CD that might require surgery or preclude the use of the CDAI to assess response; abscess; bowel resection or diversion or any other intra-abdominal surgery within specified time periods before screening; draining (that is, functioning) stoma or ostomy; stool culture or other examination that was positive for an enteric pathogen within a specified time period; treatment with an IL-12 or IL-23 antagonist; non-autologous stem cell therapy; IV corticosteroid; immunomodulatory agents (other than azathioprine [AZA], 6-mercaptopurine [6-MP], or methotrexate [MTX]), biologic agents, investigational drugs, and treatment with apheresis or total parenteral nutrition (TPN) were prohibited within specific time periods before screening.

Recent live vaccinations, serious infection, herpes zoster infection; nontuberculous mycobacterial infection, serious opportunistic infection, recurrent infections, or infection

with HIV, hepatitis B, or hepatitis C or malignancy; receipt of allergy immunotherapy for prevention of anaphylactic reactions; diagnosis or history of lymphoproliferative disease; or the presence of severe, progressive, or uncontrolled renal, hepatic, hematologic, endocrine, pulmonary, cardiac, neurologic, cerebral, or psychiatric disease and any history of tuberculosis were also exclusion criteria.

The studies differed in their inclusion of subjects with a history of exposure to TNF antagonists.

In Study 3001 subjects had received infliximab, adalimumab, or certolizumab pegol at a dose approved for the treatment of Crohn's disease and either did not respond initially, responded initially but then lost response, or were intolerant to the medication. In Study CRD3002 subjects had failed conventional therapy (immune-modulators and/or corticosteroids; including subjects who were corticosteroid dependent). Subjects in Study CRD3002 could have previously received TNF antagonist therapy but could not have met the failure criteria specified for Study 3001.

In Study 3001, there were 769 subjects randomised but the efficacy analysis only included the 741 subjects who were randomised after the study was restarted. The restart was due to a stability issue with an early formulation of the 130 mg ustekinumab in 26 mL [5 mg/mL] developed to facilitate IV administration. Subjects assessed for efficacy received the commercially available 90 mg/mL liquid in vial formulation (with 45 or 90 mg/vial). Most subjects were women (57%) and Caucasian (84.1%). Median age was 36 years and median weight was 67 kg. The median duration of disease at baseline was 10.14 years and median CDAI score was 317 (consistent with moderate severity of CD). Clinically apparent fistula was present at baseline in 19.3% of subjects and 47.5% had a history of current or prior fistulising disease. 72.5% of subjects were receiving 1 or more concomitant medications for Crohn's disease, with 340 (45.9%) were receiving corticosteroids and 233 (31.4%) were receiving immune-modulators (AZA, 6-MP or MTX). All subjects had failed at least 1 TNF antagonist, 29.1% due to an inadequate initial response, 69.4% had response followed by loss of response. 40.8% of subjects had failed 2 TNF antagonists and 10.4% had failed 3.

Table 6: Primary (Key) endpoints for clinical outcomes (3001)

	Placebo	Ustekinumab 130 mg 6 mg/kg	
Number randomised	247	245	249
Primary endpoint Clinical response Week 6	21.5%	34.3%*	33.7%*
Secondary endpoints			
Clinical remission Week 8	7.3%	15.9%*	20.9%*
Clinical response Week 8	20.2%	33.5%*	37.8%*
70-point response Week 6	30.4%	46.1%*	43.8%*
70-point response Week 3	27.1%	38.4%*	46.6%*

- the absolute difference in clinical response at 6 weeks between placebo and the proposed dose of ustekinumab was 12.2% (number needed to treat (NNT) approximately 8).
- statistical significance in each of the major secondary endpoints was also demonstrated for both the 130 mg ustekinumab dose and the 6 mg/kg dose.

- results for various subgroup analyses for the primary efficacy endpoint are shown in the CER.
- of particular note:
 - subjects who were non-responders to the initial TNF antagonist therapy (representing approximately 25% of the total subjects per group), who were given 130 mg ustekinumab had a clinical response rate which was similar to placebo (24.1% versus 25%, OR=0.9, 95% CI: =0.4, 2.2; p=0.833).
 - non-responders to TNF antagonist therapy given 6 mg/kg ustekinumab had a clinical response rate at 6 weeks of 18.6% versus 25% for placebo, OR=0.7, 95% CI: 0.3, 1.7; p=0.376).

In Study CRD3002, there were 628 subjects randomised with 627 included in the efficacy analysis. Of these 52.9% were female and 83.8% were Caucasian. The median age was 37.0 years and the median weight was 70.8 kg. The median duration of CD at baseline was 8.28 years in the placebo group compared with the 5.61 years and 6.21 years in 130 mg and approximately 6 mg/kg ustekinumab groups respectively. The median CDAI score was 292.5. 15.6% of subjects had clinically apparent fistulas at baseline and 35% had current or prior fistulising disease. 77.9% of subjects were receiving one or more concomitant medications for CD with 247 (39.3%) receiving corticosteroids and 219 (34.9%) receiving immune-modulators (AZA, 6-MP or MTX).

Subjects in the study were allowed to have previously received TNF antagonists but they were not to have demonstrated inadequate response or intolerance to them. A total of 197 (31.4%) subjects had previously received TNF antagonists and 98.5% of these subjects had not demonstrated failure or intolerance to them, per study entry criteria, 431 (68.6%) subjects were therefore anti-TNF naïve.

Table 7: Primary (Key) endpoints for clinical outcomes (3002):

	Placebo	Ustekinumab 130 mg 6 mg/kg	
Number randomised	209	209	209
Primary endpoint Clinical response Week 6	28.7%	51.7%*	55.5%*
Secondary endpoints			
Clinical remission Week 8	19.6%	30.6%*	40.2%*
Clinical response Week 8	32.1%	47.4%*	57.9%*
70-point response Week 6	38.8%	58.9%*	64.6%*
70-point response Week 3	31.6%	49.3%*	50.7%*

- the absolute difference in clinical response at 6 weeks between placebo and the proposed dose of ustekinumab was 26.8% (NNT approximately 3.7).
- statistical significance in each of the major secondary endpoints was also demonstrated for both the 130 mg ustekinumab dose and the 6 mg/ kg dose.
- the various subgroup analyses were also supportive of each of the dose regimens of ustekinumab.

Maintenance study

- CRD3003 was a randomised, double-blind, placebo-controlled, parallel group, multicentre study. Subjects with a clinical response at Week 8 to either dose regimen of ustekinumab in the induction studies (3001 or CRD3002) were randomised in a 1:1:1 ratio at Week 0 to receive a SC administration of either placebo or 1 of 2 maintenance regimens of ustekinumab (ustekinumab 90 mg every 12 weeks [q12w] through Week 36 or ustekinumab 90 mg every 8 weeks [q8w] through Week 40). This population of subjects was the primary population for assessment of efficacy and is also referred to as the randomised population. The long-term extension is planned to continue through Week 272. This submission contained data to Week 44.

- For the primary population:

The primary efficacy endpoint:

- clinical remission (CDAI score of <150) at Week 44.

The major secondary efficacy endpoints, in hierarchical order:

- clinical response at Week 44 (reduction from Week 0 of induction Study 3001 or CRD3002 in the CDAI score of ≥ 100 points)
- clinical remission at Week 44 in subjects who were in clinical remission to ustekinumab at Week 0 of maintenance; Corticosteroid-free remission at Week 44
- clinical remission at Week 44 in the subset of subjects who were refractory or intolerant to TNF antagonist therapy (subjects from Study 3001).

Subjects in the primary population receiving corticosteroids at Week 0 who were in clinical response were to initiate corticosteroid tapering at Week 0. This tapering was mandatory and was to follow a recommended schedule. Subjects were not permitted to initiate any of the following prohibited medications: Immunomodulatory agents other than 6-MP/AZA or MTX (including but not limited to 6-TG, cyclosporine, tacrolimus, sirolimus, mycophenolate mofetil); Immunomodulatory biologic agents (including but not limited to TNF antagonists, natalizumab, and abatacept); Experimental Crohn's disease medications. If initiated at any time during the study, subjects were discontinued from study agent.

A single dose adjustment to ustekinumab 90 mg q8w was permitted for subjects in the primary population who met loss of response criteria. Clinical response was assessed 16 weeks after adjustment and subjects were discontinued from study agent if not in clinical response.

A total of 1,281 subjects who completed the ustekinumab induction studies were enrolled in this study. Out of these, 397 had received induction therapy with ustekinumab and achieved a clinical response. Of these, 133 received placebo, 132 ustekinumab q12w and 132 ustekinumab q8w.

In the primary population, 56.4% were women and 84.9% were Caucasian. Median age was 36 years and median weight was 69 kg. The median duration of disease at baseline was 7.57 years and median CDAI score was 311. Overall, 95.5% (n=379/397) of primary population had previously received corticosteroids. Of those, 44.3% had previously failed to respond, 10.8% had become intolerant or developed a medical contraindication to these agents, and 47.2% had been corticosteroid dependent. 83.1% of subjects (n=330/397) had previously received immune-modulators. Of those, 62.7% had previously failed to respond and 45.2% had become intolerant or developed a medical contraindication to these agents. 44.8% were TNF antagonist refractory, 15.6% had received TNF antagonists and had not demonstrated failure or intolerance and 39.5% had not received any TNF antagonist therapy prior to study participation.

At commencement of Study CRD3003, 79.3% of subjects were receiving 1 or more concomitant medications for CD, 181 (45.6%) corticosteroids and 143 (36.0%) immunomodulators. Dose adjustment occurred in 51 (38.3%) subjects given placebo initially, 29 (22%) subjects given ustekinumab q12w initially and in 29 (22%) given ustekinumab q8w initially.

Primary efficacy endpoint outcome

- At Week 44, clinical remission was present in 48.8% of the ustekinumab q12w and 53.1% of the q8w groups compared with 35.9% for the placebo group.
- These differences were statistically significant. The absolute difference between the proposed maintenance dose group and placebo was 17.2% (NNT 5.8).

Primary and major secondary endpoint results are tabulated below (Table 8).

Table 8: Maintenance of clinical response and remission Study CRD3003 at Week 44 (randomised subjects)

	Placebo	Ustekinumab 90 mg q12w	Ustekinumab 90 mg q8w
Subjects randomized*	131	129	128
Clinical remission	36%	49% ^b	53% ^a
Clinical response	44%	58% ^b	59% ^b
Corticosteroid-free clinical remission	30%	43% ^c	47% ^a
Sustained clinical remission	26%	40% ^c	46% ^c
Clinical remission in patients: in remission at the start of maintenance therapy	46% (36/79)	56% (44/78)	67% (52/78) ^a
who are TNF-antagonist- refractory/intolerant	26% (16/61)	39% (22/57)	41% (23/56)
who failed conventional therapy	44% (31/70)	57% (41/72)	63% (45/72) ^c
who are TNF-antagonist-naïve	49% (25/51)	57% (30/53)	65% (34/52)

a: p<0.01; b: p<0.05; c: nominally significant (p<0.05)

Among patients who achieved a clinical response with either induction regimen of ustekinumab, *the maintenance of that response was achieved by an additional 15% of patients (given the proposed ustekinumab maintenance regimen) compared with placebo.*

Most patients who were taking concomitant corticosteroids or immunomodulatory agents continued these agents while taking maintenance ustekinumab.

Overall, 29 subjects in the ustekinumab 90 mg q12w group had a dose adjustment to 90 mg q8w after meeting Loss Of Response (LOR) criteria. When assessed 16 weeks after dose adjustment: *41.4% of these subjects were in clinical remission, 55.2% of these subjects had regained clinical response and the median change in CDAI score from time of dose adjustment was -141.0.*

Overall, 28 subjects in the ustekinumab 90 mg q8w group met LOR criteria for dose adjustment but continued to receive ustekinumab 90 mg q8w (per protocol). When

assessed 16 weeks after meeting LOR criteria for dose adjustment: 32.1% of these subjects were in clinical remission, 46.4% of these subjects had regained clinical response and the median change in CDAI score from time of dose adjustment was -78.5.

A post hoc analysis of the dose-adjustment data, which preserved the initial randomisation and with the LOR treatment failure criteria suspended and the rest of the analysis rules were kept the same, was performed. *That analysis showed no consistent difference in clinical remission or clinical response rates between the q8w and the q12w groups. The induction dose of the clinical responders did not significantly affect the subsequent response to maintenance treatment.*

The non-randomised population included subjects who were not in clinical response to ustekinumab at Week 8 of the induction studies and subjects, who initially received placebo (both in clinical response and not in clinical response). Subjects in clinical response to placebo induction continued to receive SC placebo throughout the maintenance study. Subjects not in clinical response to IV placebo induction received ustekinumab 130 mg IV administration at Week 0. Subjects who were not in clinical response to ustekinumab IV induction received ustekinumab 90 mg SC at Week 0 of the maintenance study. Subjects who achieved clinical response at Week 8 (of the maintenance study) continued to receive ustekinumab 90 mg SC q8w through Week 40; otherwise they were discontinued from further study agent administration.

There were 884 non-randomised subjects. Within the non-randomised group, 123 subjects who had received placebo and reached clinical response continued to receive placebo. The remaining subjects received ustekinumab at either q12w or q8w. *No statistical testing was performed in the non-randomised population and corticosteroid tapering was not required.*

Among the non-randomised subjects in the maintenance study, there were 467 who were ustekinumab induction non-responders (that is, at the Week 8 clinical response assessment in either Study 3001 or CRD3002). At Week 8 after being given an additional SC dose of ustekinumab 90 mg (that is, Week 16 from the initial IV induction dose), 50.5% of these subjects had achieved clinical response and 28.9% were in clinical remission. The median change from baseline in CDAI score was -66.0. Of these 467 subjects, 251 continued dosing at Week 8 of Study CRD3003 (subsequently received ustekinumab 90 mg SC q8w. , 68.1% maintained clinical response and 50.2% were in clinical remission at Week 44 (median change from baseline in CDAI score for these subjects was -115.0).

Risk management plan

ACSOM advice was not requested for this application.

For details of the recommendations see Pharmacovigilance findings above.

Risk-benefit analysis

Delegate's considerations

In assessing the PK of ustekinumab using the proposed dose regimen for Crohn's disease, the sponsor has concentrated on the initial IV dose, which in addition to being IV rather than SC is approximately 8.67 fold higher than the current initial dose of 45 mg for Plaque psoriasis (PP) and Psoriatic arthritis (PA)

The dosing interval is also different from that of PP and PA, with the proposed subsequent doses at 8 week intervals {via SC injection} rather than doses at Weeks 0 and 4 and then every 12 weeks thereafter. The recommended maintenance regimen for CD is the same as

the maintenance regimen for patients with body weight > 100 kg with either plaque psoriasis or psoriatic arthritis. PK data for CD patients in the maintenance phase of treatment was available only from the PK analysis. The proposed exposure to ustekinumab for patients with CD is substantially higher than for the currently approved indications of PP and PA. Safety data obtained from other patient groups, apart from CD patients, may therefore provide false reassurance given the higher exposures required to treat for CD.

Response rates in individuals who were either TNF antagonist naïve or who had previously responded to a TNF antagonist were substantially better than for those who failed prior TNF antagonist therapy. It is not possible to perform a reliable statistical comparison of CD response rates between patients who were naïve to TNF antagonists and given a first course of infliximab and patients who were TNF antagonist naïve and given ustekinumab, due to differences in (a) study design and (b) response rates in the placebo groups across the infliximab and ustekinumab studies. While CD patients who have failed TNF antagonist treatment and those who have not, have both been shown to benefit from ustekinumab, it is clear that those who have not failed prior TNF antagonist treatment are likely to do better on ustekinumab, in the short term.

Response rates separated from placebo in both induction studies at the Week 3 assessment (for the 70-point reduction in CDAI). It appears that for many patients with CD, ustekinumab may be an adjunctive treatment and that, immunomodulatory therapy and/ or corticosteroids will continue to be required.

There was no statistical analysis of the differences in efficacy between the two dose regimens of ustekinumab assessed in either the induction studies or the maintenance study. However, the results generally showed higher response rates with the proposed dose regimen compared to the 130 mg induction dose and the q12w maintenance dose regimens. Various laboratory assessments also generally supported the higher doses. Given that only an additional 15% of patients who had an initial clinical response maintained that response on the proposed ustekinumab maintenance regimen, it is not clear whether patients should receive regular maintenance therapy or a repeat induction course on loss of clinical response. The effect of repeat induction treatment on an as-required basis has not been examined.

There no objections to the approval of the new ustekinumab dose strength (90 mg/mL) and new route (IV) of ustekinumab administration from the clinical, biochemical, microbiological, non-clinical and RMP evaluators from the efficacy and safety points of view.

Summary of issues

One pivotal study enrolled patients who failed or are intolerant to one or more TNF antagonist therapies and the other did not. Efficacy has been demonstrated in both patient groups. It is not clear whether ustekinumab should be limited to patients who have failed or who are intolerant of TNF antagonists. The sponsor has proposed that patients not be required to have demonstrated failure or intolerance to TNF antagonists as a condition of eligibility for ustekinumab.

Patients were screened for current active infection or a history of latent or active granulomatous infection (including TB), nontuberculous mycobacterial infection, serious opportunistic infection, recurrent infections, or infection with HIV, hepatitis B, or hepatitis C or malignancy; receipt of allergy immunotherapy for prevention of anaphylactic reactions; diagnosis or history of lymphoproliferative disease; or the presence of severe, progressive, or uncontrolled renal, hepatic, hematologic, endocrine, pulmonary, cardiac, neurologic, cerebral, or psychiatric disease. These were criteria for exclusion from the

studies. It is not clear if these criteria should be contraindications to receipt of ustekinumab.

There is a need to compare relative efficacy in prior TNF treated lack of response/intolerance patients group with other patients here. Non-TNF antagonists exposed, that is, naive patients had much better clinical responses than TNF antagonists experienced patients with previous intolerance or failure.

Poor dose response demonstrated, for both the selected induction dose and the maintenance dose interval, except for individuals in Study 001 who had failure with TNF antagonists, that group did better with the higher (6 mg/kg) dose of ustekinumab for induction of clinical response.

Proposed action

The Delegate had no reason to say, at this time, that the application to extend the indication of ustekinumab [Stelara] should not be approved for registration, subject to resolving issues arising from the ACM deliberations and finalisation of matters pertaining to the PI and RMP to the satisfaction of the TGA.

Request for ACPM advice

The committee is requested to provide advice on the following specific issues:

1. Given that:

- the enhanced therapeutic efficacy of ustekinumab (Stelara) appears to be via the inhibition of a parallel but pharmacologically different inflammatory pathway, such as the IL-12/23 cytokine pathway, from those of other immune-modifiers, such as adalimumab (Humira), infliximab and vedolizumab used in Crohn's disease (CD)
- the pivotal studies were restricted to patients who failed or are intolerant to one or more TNF antagonist therapies,

is there a clinical justification for specifically considering amendment to ustekinumab's proposed indication to: "as a rescue therapy where more than one TNF antagonists have failed i.e. anti-TNF- α -resistant CD cases and/ or intolerance thereof to one or more TNF antagonist therapies?"

The committee is (also) requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Response from Sponsor

A robust global clinical development program demonstrating the efficacy and safety of Stelara (ustekinumab) for the treatment of Crohn's Disease has been conducted. This comprised a Phase I study, two placebo-controlled Phase II studies, and three placebo-controlled Phase III studies. The patient population studied reflects the full-spectrum of biologic eligible patients with Crohn's Disease in Australia and, as such, the sponsor's proposed indication is:

Stelara is indicated for the treatment of adult patients with moderately to severely active Crohn's Disease who have had an inadequate response, lost response, were intolerant to conventional therapy or a TNF α antagonist or have medical contraindications to such therapies.

This proposed indication has been endorsed by the clinical evaluator. The Delegate is seeking advice from members of the Advisory Committee on Medicines (ACM) if there is

any clinical justification for amending this indication, on the stated basis that '*the pivotal studies were restricted to patients who failed or are intolerant to one or more TNF antagonist therapies*'.

Regrettably, this statement is incorrect and represents a significant factual error. Following receipt of the Delegate's Request for Advice from the ACM, a request from the sponsor for the document to be re-issued with the omission of the incorrect information was not granted. Therefore, the sponsor must address this statement now, and clarify for the committee members that the pivotal studies were not restricted in the manner outlined in the Delegate's Request for Advice from the ACM and thus no amendment to the proposed indication is warranted.

Patient Populations Studied in the Pivotal Phase III Studies Investigating Stelara for the Treatment of Crohn's Disease

The Phase III program encompassed a broad range of biologic-eligible patients with Crohn's Disease, from those who were TNF antagonist-naïve (having previously failed only steroids and/or immune-modulators), to those who had previously failed one or more TNF antagonists.

The program included two 8 week IV induction studies (known as CRD3001 and CRD3002) and one 44 week subcutaneous (SC) maintenance study (CRD3003). Studies CRD3001 and CRD3002 were the same design but targeted different, mutually exclusive patient populations:

CRD3001 enrolled patients with a history of inadequate response to, or intolerance to, at least one TNF antagonist.

CRD3002 enrolled patients with a history of inadequate response to or intolerance of corticosteroids or immune-modulators. These patients could either have never received treatment with a TNF antagonist (that is, TNF antagonist-naïve patients) or could have been treated with a TNF antagonist but not have a documented history of an inadequate response or intolerance to them.

Patients from Studies CRD3001 and CRD3002 who had been randomised to Stelara induction therapy at Week 0 and were in clinical response at Week 8 were eligible to enter the primary population of the 44 week maintenance study (CRD3003).

The sponsor reiterates that two of the three pivotal studies (CRD3002 and CRD3003) enrolled TNF antagonist-naïve patients, negating the factual error in the Delegate's Request for Advice from the ACM, which states '*the pivotal studies were restricted to patients who failed or are intolerant to one or more TNF antagonist therapies*'. Table 9 presents the Crohn's Disease-related medication history of the patients studied in the Phase III pivotal studies. 68.6% (n=431) of patients in CRD3002 were TNF antagonist-naïve and these patients went on to make up 39.5% (n=157) of the primary population of the maintenance Study CRD3003.

Table 9: Summary of Crohn's Disease-Related Medication History of Randomised Subjects in the Phase III Clinical Development Program

	Induction ^a		Maintenance ^b
	CRD3001	CRD3002	CRD3003
Randomised Subjects	741	628	397
Crohn's Disease-related medication history, %			

	Induction ^a		Maintenance ^b
Previously treated with and failed full/adequate course of:			
Oral corticosteroids	70.3	80.9	77.7
Immuno-modulators	78.9	67.5	76.9
Corticosteroids or immuno-modulators	89.3	99.4	94.7
Inadequate initial response, loss of response, or intolerance to 1 or more TNF antagonists:	99.2	NA	44.6
1 TNF antagonist	48.0	NA	23.7
2 TNF antagonists	40.8	NA	17.1
3 TNF antagonists	10.4	NA	3.8
TNF antagonist-naïve	NA	68.6	39.5
Previously received but not failed a TNF antagonist	NA	31.4	15.6

^a Excludes subjects enrolled before study restart

^b Primary population, that is, subjects who were in clinical response to ustekinumab IV induction dosing; includes 9 subjects enrolled before study restart.

Discussion of Efficacy Outcomes in the Studied Patient Populations

Notwithstanding that one of the rationales for seeking advice on any justification to revise the indication is factually incorrect the remit of the TGA is to assess an application for quality, safety and efficacy. No concerns from these perspectives which could hinder approval have been raised in the evaluation of this application to date, and three appropriate and well controlled Phase III studies have demonstrated the efficacy and safety of Stelara in patients with Crohn's Disease.

The CRD3001 and CRD3002 induction studies demonstrated rapid, robust, statistically significant, clinically meaningful results across multiple endpoints for clinical outcomes, inflammatory biomarkers, and health-related quality of life outcomes in patients with moderately to severely active Crohn's Disease, including those who were refractory to conventional therapy and those who were refractory or intolerant to TNF antagonists (Table 10).

Table 10: Key endpoints for clinical outcomes: randomised subjects in Phase III induction studies in Crohn's Disease (CRD3001 and CRD3002)

CRD3001 (TNF antagonist failures)				CRD3002 (Conventional therapy failures)		
	Stelara			Stelara		
	Placebo (P)	130 mg	~6 mg/kg	P	130 mg	~ 6 mg/kg
Subjects randomised*	247	245	249	209	209	209
PRIMARY ENDPOINT (%)						
Clinical response at Week 6	21.5	34.3 ^b	33.7 ^b	28.7	51.7 ^a	55.5 ^a
MAJOR SECONDARY ENDPOINTS (%)						
Clinical remission at Week 8	7.3	15.9 ^b	20.9 ^a	19.6	30.6 ^b	40.2 ^a
Clinical response at Week 8	20.2	33.5 ^b	37.8 ^a	32.1	47.4 ^a	57.9 ^a
70-point response at Week 6	30.4	46.1 ^a	43.8 ^b	38.8	58.9 ^a	64.6 ^a
70-point response at Week 3	27.1	38.4 ^b	40.6 ^b	31.6	49.3 ^a	50.7 ^a

Clinical response=reduction in CDAI \geq 100 points or CDAI $<$ 150; clinical remission=CDAI score $<$ 150.

*Excludes subjects randomised before study restart and Site 1127.

^a p $<$ 0.001 versus placebo.

^b p $<$ 0.01 versus placebo.

In the CRD3003 maintenance study, subjects who responded to Stelara induction achieved long-term, significant, and clinically meaningful benefit with Stelara (Table 11). The primary endpoint was clinical remission at Week 44 (52 weeks of treatment) and significantly greater proportions of subjects in the Stelara 90 mg q8w and q12w groups were in clinical remission at Week 44 compared to placebo.

Table 11: Maintenance of Clinical Response and Remission in CRD3003 (Week 44; 52 weeks from initiation of the induction dose): randomised subjects

	Placebo	Stelara 90 mg q8w	Stelara 90 mg q12w
Subjects randomised*	131	128	129
Clinical Remission	36%	53% ^a	49% ^b
Clinical Response	44%	59% ^b	58% ^b
Corticosteroid-Free Clinical Remission	30%	47% ^a	43% ^c
Sustained Clinical Remission	26%	46% ^c	40% ^c
Clinical Remission in patients:			
in remission at the start of maintenance therapy	46% (36/79)	67% (52/78) ^a	56% (44/78)
who are TNF antagonist-refractory/intolerant	26% (16/61)	41% (23/56)	39% (22/57)
who failed conventional therapy	44% (31/70)	63% (45/72) ^c	57% (41/72)
who are TNF antagonist-naïve	49% (25/51)	65% (34/52) ^c	57% (30/53)

Clinical remission=CDAI score <150; clinical response=CDAI of at least 100 points or being in clinical remission; sustained clinical remission=clinical remission at weeks 36, 40 and 44

* Subjects who were in clinical response to ustekinumab induction dosing at start of maintenance therapy; excludes subjects randomised before study restart.

† Patients who achieved a clinical response to Stelara at start of maintenance therapy

^a p < 0.01

^b p < 0.05

^c nominally significant (p<0.05)

In summary, the sponsor has demonstrated that Stelara is significantly effective in inducing clinical remission of Crohn's Disease in patients who have failed or not tolerated conventional therapies, including azathioprine, 6-mercaptopurine, corticosteroids and methotrexate. Stelara is also significantly effective in inducing clinical remission of Crohn's Disease in patients who failed treatment with or did not tolerate one or more TNF antagonist.

Approved indications should reflect the data available in the patient populations studied, as is the case with the indications granted for the other biologic treatment options for Crohn's Disease in Australia (notably adalimumab, infliximab and vedolizumab). In support of the Sponsor's proposed indication, the clinical evaluator commented during the evaluation that '*...importantly, similar treatment effects were observed regardless of prior treatment history (i.e., in both conventional therapy failures, including those naïve to prior TNF antagonists and in TNF antagonist-refractory subjects)*'. Any restriction of access to Stelara to only patients who have failed or who are intolerant to one or more TNF antagonist therapies is not an accurate representation of the data submitted by the

sponsor, inconsistent with other biologic treatment options (despite equivalent data) and would serve only to deny Australian patients of a safe and efficacious treatment option.

It is well established in the medical community that biologic-naïve patients tend to show the most significant response or improvement with the first biologic agent they are treated with. This is also reflected in the data generated for Stelara and acknowledged by the Delegate who has stated '*naïve patients had much better clinical responses than TNF antagonists experienced patients with previous intolerance or failure*'. Given Stelara has demonstrated such significant efficacy in TNF antagonist naïve patients, there is essentially no clinical justification for amending the indication as per the advice being sought of ACM. It is in the interests of Crohn's Disease patients, and physicians to have access to Stelara as their first-line biologic treatment, which offers the opportunity for significant clinical improvements (response and remission) and improvements in quality of life.

The Delegate has also noted that 'the enhanced therapeutic efficacy of ustekinumab appears to be via the inhibition of a parallel but pharmacologically different inflammatory pathway'. Specifically, Stelara binds to the shared p40 protein subunit of the human cytokines interleukin (IL)-12 and IL-23. In patients with Crohn's Disease, IL-12 and IL-23 are elevated in the intestines and lymph nodes, and full details of the potential mechanism of action of Stelara in Crohn's Disease is provided in the Australian PI.

The sponsor views this observation from the Delegate on the mechanism of action and enhanced therapeutic efficacy of Stelara as positive in support of the Sponsor's proposed indication. With only two classes of biologic agents currently available for Crohn's Disease patients who have failed or are intolerant to conventional systemic therapies (the TNF antagonists and the integrin inhibitors), there is an unmet need for additional treatment options for a disease that largely affects younger patients during their most formative and productive years. Stelara can fulfil this need. As presented in detail in the submitted dossier, in the absence of direct comparator studies, cross-study comparisons with the other approved biologic treatments provides insight into the relative efficacy and safety of Stelara and its appropriate place in the treatment of patients with moderate to severe Crohn's Disease. Acknowledging the limitations of such comparisons, the sponsor's conclusions were reiterated by the clinical evaluator, who commented "Overall, indirect comparisons to biologic therapies approved for moderate to severe Crohn's Disease suggest that ustekinumab has efficacy that is at least comparable and in some instances appears better or has a more rapid onset than currently approved biologics with a favourable safety profile".

The safety profile of Stelara is well-established. Stelara has been approved in Australia for the treatment of psoriasis and psoriatic arthritis since July 2009 and February 2015 respectively, and the estimated cumulative worldwide exposure to Stelara from global launch to 31 December 2015 is 551,966 person-years. The safety profile in Crohn's Disease is similar to the established safety profile demonstrated in the existing large clinical trial and postmarketing database, which further supports the use of Stelara a treatment option for both biologic-naïve and biologic-refractory patients with moderately to severely active Crohn's Disease.

On the totality of evidence, Stelara has demonstrated acceptable safety and efficacy for approval for the treatment of Crohn's Disease in both biologic-refractory and biologic-naïve patients. For patients who have either exhausted existing treatment options or those who are relatively new to treatment, the lifelong course of Crohn's Disease and the lack of a single enduring treatment highlight the need for additional treatment options with durable efficacy, a favourable benefit-risk profile, and minimally invasive dosing and frequency. Stelara has these attributes and has demonstrated efficacy in both these areas of unmet need. The sponsor believes the indication proposed by the sponsor is appropriate and clinically justified to meet these areas of need in Australia.

Update on Stelara for Crohn's Disease in Australia and worldwide

There is experience among key opinion leaders in Australia with the use of Stelara in Crohn's Disease as Australian sites participated in the pivotal studies. 41 Australian patients were randomised into the induction studies CRD3001 or CRD3002. 38 of these patients entered the CRD3003 maintenance phase and 15 continued to the long-term extension phase (to 272 weeks), which is still ongoing.

The indication proposed by the sponsor would provide access that is in line with indications approved by other major regulatory authorities for Crohn's Disease patients.

Additional Comments on the Delegate's Request for Advice from the ACM

The Delegate has questioned if the exclusion criteria for the pivotal studies should be contraindications to receipt of Stelara. As discussed, Stelara has an established safety profile and the exclusion criteria reflects either already existing contraindications or precautions in the Stelara Australian PI or standard criteria which, if present, could possibly confound the ability to assess the effect of treatment with the investigational product. The current Stelara Australian PI is an appropriate tool for helping to ensure the right patients are treated with Stelara and no additional amendments are warranted.

The Delegate has commented about the dose response being poor for both the induction dose and the maintenance dose interval. Regarding induction, it is correct that both the 130 mg and the approximately 6 mg/kg dose provided rapid, meaningful clinical benefit across a range of endpoints in the broad Crohn's Disease population. However, the totality of the evidence across clinical outcomes, patient reported outcomes and inflammatory biomarkers confirmed that the approximately 6 mg/kg dose performed better than the 130 mg dose, especially in observations of clinical remission at Week 8 (the 130 mg dose group started to lose response between Weeks 6 and 8 while the approximately 6 mg/kg dose was stable or continued to improve). No meaningful differences in safety were observed. Regarding the maintenance dose, the totality of the clinical, patient reported, and objective inflammatory marker data presented demonstrates that dosing every 8 weeks (q8w) is the single best regimen to which all patients should have access, and equally safe compared with dosing every 12 weeks (q12w). Although the q12w regimen maintained clinical response and met the endpoint of clinical remission and corticosteroid-free remission, q8w performed better overall. Differences that were most notable in more stringent efficacy endpoints at Week 44 with q8w versus q12w included overall remission (especially in TNF antagonist-naïve patients), remission in subjects who entered maintenance in remission and sustained remission, as well as clinically meaningful improvements in quality-of-life measures. There was no apparent safety difference between the q8w and q12w regimens. Based on this, the induction dose based on weight and the q8w maintenance dose is the recommended dosage regimen.

The Delegate has also raised the possibility of, for example, a repeat induction course on loss of response. This was not studied but the results from the SC placebo group in the primary population of CRD3003 where subjects who lost response and received Stelara upon loss of response, indicate that most subjects are able to regain benefit upon reintroduction of Stelara by the SC route, without necessitating re-induction by the IV route, despite treatment interruptions of up to 32 weeks.

Conclusion

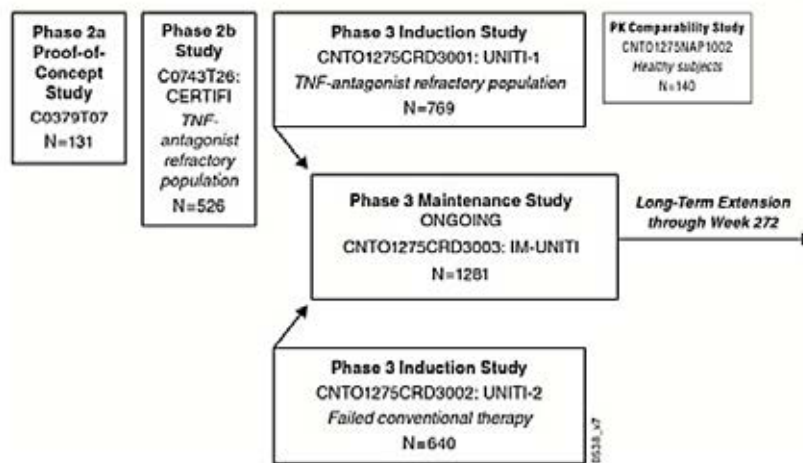
A broad range of biologic eligible patients with Crohn's Disease would benefit from treatment with Stelara, from those who are TNF antagonist-naïve and have previously failed only steroids or immune-modulators, to those who have previously failed two or more TNF antagonists. The clinical development program was designed with these patient populations in mind and data demonstrating safety and efficacy in both biologic refractory

and biologic naïve Crohn's Disease patients were submitted to support the approval of the following proposed indication:

Stelara is indicated for the treatment of adult patients with moderately to severely active Crohn's Disease who have had an inadequate response, lost response, were intolerant to conventional therapy or a TNF α antagonist or have medical contraindications to such therapies.

For patients who have either exhausted existing treatment options or those who are relatively new to treatment, the lifelong course of Crohn's Disease and the lack of a single enduring treatment highlight the inevitable need for additional treatment options with durable efficacy, a favourable benefit-risk profile, and minimally invasive dosing and frequency. Stelara has these attributes, and offers a new mechanism of action with comparable, if not better efficacy than existing treatment options. The indication proposed by the sponsor is appropriate and clinically justified to meet the areas of unmet need in Australia.

Figure 2: Development program for Stelara in Crohn's Disease



Advisory Committee Considerations

The ACM, taking into account the submitted evidence of efficacy, safety and quality, considered Stelara solution for IV containing 5 mg/mL of ustekinumab are of the opinion that there is an overall positive benefit–risk profile for the indication;

Stelara is indicated for the treatment of adult patients with moderately active Crohn's disease who have had an inadequate response, lost response to, or were intolerant to either conventional therapy or a TNF α antagonist or have medical contraindications to such therapy.

Proposed Product Information (PI)/Consumer Medicine Information (CMI) amendments

The ACM agreed with the Delegate to the proposed amendments to the Product Information (PI) and Consumer Medicine Information (CMI) and specifically advised on the inclusion of the following:

- A statement in the PI text discussing findings in tables of results indicating less ~~no~~ benefits for patients who have failed TNF antagonist compared to TNF α naïve patients.
- A statement in the PI similar to the EMA PI indication is acceptable but remove 'to severely' statement.
- A statement in the PI warning patients that facial palsy was a possible adverse effect.

- A statement in the CMI warning patients who are having vaccines to consult with their doctor about possible adverse drug reaction

Specific Advice

The ACM advised the following in response to the delegate's specific questions on this submission:

1. *Given that:*

- a. the enhanced therapeutic efficacy of ustekinumab (Stelara) appears to be via the inhibition of a parallel but pharmacologically different inflammatory pathway, such as the IL-12/23 cytokine pathway, from those of other immune-modifiers, such as adalimumab (Humira), infliximab and vedolizumab used in Crohn's disease (CD)*

The ACM advised that there was no enhanced therapeutic efficacy of Stelara.

- b. the pivotal studies were restricted to patients who failed or are intolerant to one or more TNF antagonist therapies*

Is there a clinical justification for specifically considering amendment to ustekinumab's proposed indication to: "as a rescue therapy where more than one TNF antagonists have failed i.e. anti-TNF- α -resistant CD cases and/or intolerance thereof to one or more TNF antagonist therapies?"

The ACM advised that one of the pivotal studies was so restricted and the other studies excluded such subjects. Results suggest ustekinumab is less effective after TNF antagonist failure or intolerance. It was agreed that there was no clinical justification for specifically considering amendments to ustekinumab's proposed indication as there was no justification to support this claim in the studies.

The ACM also advised that the sponsor be asked to provide any further evidence, if any, that might justify the dose choices made for the application. The ACM was of the view that the 'severe' indication was not supported by pivotal study data.

The ACM also advised that the sponsor be asked of any study data beyond 44 weeks and to be encouraged to generate paediatric study data.

The ACM advised that implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of this product.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of the registration of new strength Stelara ustekinumab 5.0 mg/1 mL solution for intravenous infusion injection vial, the extension of indications for Stelara ustekinumab solution for injection vial and pre-filled syringe indicated for:

Crohn's Disease

Stelara is indicated for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a TNF α antagonist or have medical contraindications to such therapies.

Specific conditions of registration applying to these goods

The Stelara (ustekinumab) EU Risk Management Plan (RMP) version 13.2, dated 7 September 2016 (data lock point 8 July 2015) with Australian specific annex 3.2, dated 19

October 2016, submitted with the application, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

Attachment 1. Product Information

The PI for Stelara approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <<https://www.tga.gov.au/product-information-pi>>.

Attachment 2. Extract from the Clinical Evaluation Report

Therapeutic Goods Administration

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