Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Adalimumab (rch)

Proprietary Product Name: Humira

Sponsor: AbbVie Pty Ltd

October 2013

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <http://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

I. Introduction to product submission

Submission details

Type of submission:	Extension of Indications
Decision:	Approved
Date of decision:	16 July 2013
Active ingredient:	Adalimumab (rch)
Product name:	Humira
Sponsor's name and address:	AbbVie Pty Ltd 32-34 Lord Street Botany NSW 2019
Dose form:	Solution for injection
Strengths:	20 mg and 40 mg
Containers:	Prefilled pen, prefilled syringe, and vial
Pack sizes:	1 x vial; 2 x prefilled syringe; 1, 2, 3, 4 or 6 x prefilled pen
New approved therapeutic use:	Ulcerative colitis Humira is indicated for the treatment of moderate to severe ulcerative colitis in adult patients who have had an inadequate response to conventional therapy or who are intolerant to or have medical contraindications for such therapies. Patients should show a clinical response within 8 weeks of treatment to continue treatment beyond that time (see CLINICAL TRIALS).
Route of administration:	Subcutaneous injection
Dosage (abbreviated):	For ulcerative colitis: *Induction*: 160 mg: initial dose (Day 0) as four injections OR as two injections on Day 0 and two injections on Day 1; 80 mg: second dose (Day 14) as two injections. *Maintenance:* 40 mg starting Day 28 and continuing fortnightly
ARTG numbers:	95779, 95780, 127116, 155315, 199410, 199411, 199412.

Product background

Adalimumab (rch[1]) is a recombinant, fully human immunoglobulin (IgG1) monoclonal antibody that binds specifically and with high affinity to the soluble and transmembrane

[1] rch: recombinant human

forms of tissue necrosis factor alpha (TNF-α), thereby inhibiting the binding of TNF-α with its receptors and neutralising the biological function of TNF.

Humira has been registered in Australia since 2003 and is approved for use in adults with rheumatoid arthritis (RA), psoriatic arthritis, psoriasis, ankylosing spondylitis (AS) and Crohn's disease (CD). Humira is also approved in polyarticular juvenile idiopathic arthritis in children over 4 years of age.

This AusPAR describes the application by AbbVie Pty Ltd (the sponsor[2]) to extend the indications for adalimumab to include the following:

> *Humira is indicated for the treatment of moderate to severe ulcerative colitis in patients who have had an inadequate response to conventional therapy or who are intolerant to or have medical contraindications for such therapies.*

Regulatory status

The product received initial registration on the Australian Register of Therapeutic Goods (ARTG) in December 2003.

At the time this application was considered by the TGA, a similar application had been approved in the European Union (EU, April 2012) and the USA (September 2012) and was undergoing review in Canada, Switzerland, New Zealand and Japan.

Product Information

The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality findings

There was no requirement for a quality evaluation in a submission of this type.

III. Nonclinical findings

There was no requirement for a nonclinical evaluation in a submission of this type.

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

Clinical rationale

The following clinical rationale was provided in the sponsor's covering letter and is considered acceptable:

[2] Sponsorship of the products in this application changed from 'Abbot Australasia Pty Ltd' to 'AbbVie Pty Ltd' during the evaluation phase.

Ulcerative colitis (UC) is a chronic, relapsing inflammatory disease of the rectum and/or large intestine characterised by inflammation and ulceration of the mucosal and submucosal intestinal layers. Clinical symptoms include bloody diarrhoea associated with rectal urgency and tenesmus. Disease of moderate or severe activity often may be associated with anorexia, nausea, weight loss and fever; as well as symptoms associated with anaemia and hypoalbuminaemia. Patients with UC are at an increased risk for certain malignancies such as colon cancer and lymphoma, and the risk of colon cancer increases with the duration of disease and the extent of colon affected by the disease.

The aim of medical treatment in UC is to induce and maintain remission. Conventional pharmaceutical therapies often do not completely abate the inflammatory process and have significant side effects. Infliximab has demonstrated efficacy in subjects with moderately to severely active UC and is approved in Australia for the treatment of subjects with moderate to severe UC.

However, infliximab is not a viable long-term treatment in all patients due to the development of intolerance or loss of response; and no other biologic treatment options have been approved for these patients. Patients receiving infliximab treatment are required to make regular hospital visits for treatment and for some Australian patients the time and travel involved in these visits is a huge burden. This is particularly problematic when there are few centres outside the metropolitan areas of Australia that are able to offer this service. Given the geographical challenges of enabling equity of access to therapy across Australia there appears to be a particularly strong unmet clinical need for an additional approved treatment option for UC that can be administered by the patient or care giver in a more convenient location.

Contents of the clinical dossier

The submission contained the following clinical information:

- 1 clinical pharmacology study provided pharmacokinetics (PK) data (derived from Study MO6-827, known as 'Study 827').
- 1 population PK (Pop-PK) analysis.
- 2 pivotal efficacy/safety, randomised, double-blind, placebo-controlled studies (both completed):
  - Study M06-826 known as 'Study 826' (induction of remission study).
  - Study M06-827 (induction and maintenance of remission study).
    - Including an Additional Analyses on Early Responders (Weeks 2 to 8) to Adalimumab report.
- 1 ongoing supportive open-label (OL) extension study (Study M10-223, known as 'Study 223') that provided interim efficacy and safety data (cut-off 16 December 2011).
- 1 integrated summary of safety (data cut-off 31 December 2009) report and updated integrated summary of safety (data cut-off 16 December 2011).

A clinical overview (CO), Summary of Clinical Efficacy (SCE), Summary of Clinical Safety (SCS), and literature references were also provided.

Paediatric data

The submission did not include paediatric data.

Good clinical practice

The sponsor declared all three studies included in this submission were conducted in accordance with their protocol, International Conference on Harmonisation (ICH) guidelines, applicable regulations and guidelines governing clinical study conduct and the ethical principles that have their origin in the Declaration of Helsinki. In addition, all local regulatory requirements were followed.

However, in Study 827, the sponsor found[3] significant non compliance with Good Clinical Practice (GCP) guidelines at three centres. The 24 trial subjects from these three sites were therefore excluded from the intent-to-treat (ITT) efficacy analyses in Study 827, but remained in the safety analyses. Several subjects from the non compliant sites entered the OL extension trial, Study 223, and were subsequently withdrawn. This issue is addressed further in the clinical evaluation report (CER; see Attachment 2 of this AusPAR). All other studies fully complied with GCP requirements.

Evaluator comment: This submission did not include a detailed description of non-GCP centres/subjects. Further details were requested (see *Second round evaluation of clinical data submitted in response to questions*, below).

Pharmacokinetics

Studies providing pharmacokinetics data

Pharmacokinetic (and immunogenicity) data were only collected in Study 827 (see Table 2 under *Efficacy* below for study details). A Pop-PK analysis was also conducted.

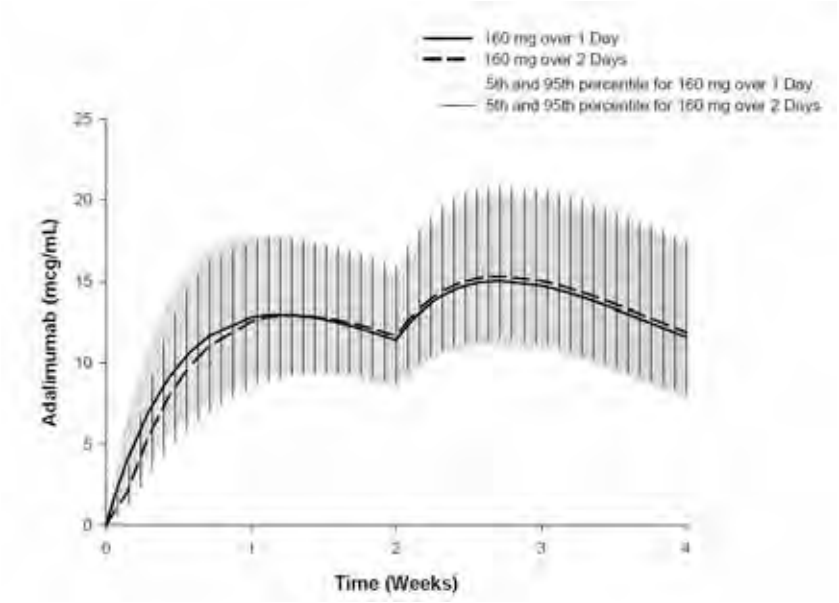
The clinical pharmacology of adalimumab has been well characterised in healthy subjects and in subjects with the approved indications (see the approved PI for Humira).

Summary of pharmacokinetics

Comparison of serum trough concentration instead of maximum serum concentration is standard practice with studies using monoclonal antibodies. Serum adalimumab trough concentrations appeared similar between anti-TNF naïve and anti-TNF experienced subjects in the induction period (Weeks 0 to 4, inclusive), but no further comparison was presented beyond Week 8.

[3] Note that the sponsor identified the non-compliance issues prior to the primary analysis and diligently dealt with those by excluding the subjects from the respective sites from the primary analysis.

Figure 1 Serum mean adalimumab concentrations for 160 mg adalimumab given over 1 or 2 days at Week 0, followed by 80 mg adalimumab over 1 day at Week 2



In contrast, anti-TNF naïve remitters consistently had higher mean serum adalimumab trough concentrations compared with anti-TNF experienced subjects. This suggests there is a reduction in serum levels during the maintenance phase of the study for anti-TNF experienced subjects. This may in turn translate into a negative effect on efficacy in these subjects. The higher clinical remission (CR) and Clinical RESPonse (CRESP) rates (as assessed by Mayo score, see Table 4 below) in the anti-TNF naïve group support this assertion. The percentage of subjects who achieved mucosal healing (MH, assessed by endoscopy) was also higher in anti-TNF naïve subjects. CRESP and MH in anti-TNF naïve subjects were statistically significantly superior to anti-TNF experienced groups at all time points recorded, although this trend was not evident in CR comparisons between these groups.

Clearance and volume of distribution (from the final Pop-PK model) are consistent with values obtained across the range of licensed indications for adalimumab, particularly Crohn's disease (CD). Furthermore, the estimated covariate effects of bodyweight, anti-adalimumab antibody positive (AAA+) status and albumin concentration, suggest no need for dosage adjustment. Similarly, no dosage adjustment was needed with co-administration of adalimumab with the immunosuppressant agents, methotrexate, azathioprine and 6-mercaptopurine.

The final Pop-PK model simulations support the proposed split-dose alternative induction regimen: 160 mg given over two days and then 80 mg at 14 days and 40 mg at 28 days. The effect on the PK profile of adalimumab was minimal and hence the effect of efficacy in UC should not be altered. This split-dose regimen is consistent with CD (see PI) and offers an alternative for patient convenience and acceptability.

Immunogenicity

Baseline human anti-chimeric antibody positive (HACA+) status appeared to result in lower mean serum adalimumab trough concentrations throughout the study duration (even with dose-escalation). The sponsor claims baseline HACA+ had minimal impact on efficacy following an analysis that compared anti-TNF experienced subjects irrespective of baseline HACA status against anti-TNF naïve subjects with HACA negative (HACA-) status. This comparison does not support the sponsor's conclusion as the comparative group contains both HACA+ and HACA- subjects. A more appropriate comparison is anti-TNF experienced HACA+ subjects versus anti-TNF experienced HACA- subjects. There is no

specific reference to previous anti-TNF treatment in the indication yet the PK data suggests, for HACA+ patients, exposure to drug is reduced. A subgroup efficacy analysis of those patients will be very important.[4]

Study 827 design quality is detailed in the CER (see Attachment 2 of this AusPAR). However, given 24 subjects (4.6%) had their data withdrawn from three centres secondary to GCP non-compliance and approximately 20% of subjects had missing baseline infliximab or HACA data such omissions have the potential to introduce significant selection bias into the study findings. Given the high cross-reactivity rate of the serum adalimumab enzyme-linked immunosorbent assay (ELISA) with previous infliximab treatment, as well as an apparent lag time between onset of development of AAA and a measurable level of AAA[5], significant measurement bias may have been introduced into the study. Furthermore, the true extent of antibody status (and hence the effect on efficacy and potentially, safety) may not be apparent until several months after trial cessation, in part due to the limitations on assay measurements and their sensitivity.

Anti-adalimumab antibody positive status appeared to have the greatest effect on efficacy but the rate reported in UC subjects was only 3.9% (n=19/487), of which six subjects had positive baseline HACA status.[6] While this rate is comparable with CD (2.6%), studies in other indications report much higher rates in monotherapy-treated subjects, ranging from 8% in psoriasis to 25.6% in polyarticular juvenile idiopathic arthritis. Most work has been undertaken in rheumatoid arthritis (RA), with much larger study numbers than the other approved indications, and these found an average rate of 12% AAA+ in adalimumab monotherapy. Given an apparent lag time between rapid reduction in serum adalimumab trough concentration and diagnostic confirmation of AAA+ status, it is possible many more subjects in Study 827 were AAA+ during the study but were not identified as such.

Evaluator's overall conclusions on pharmacokinetics and immunogenicity

Pharmacokinetics

Study 827 was generally well designed and conducted. Limitations included missing data and the use of the specific adalimumab ELISA assay. In particular, the assay could not detect AAA above 2 µg/L, potentially resulting in under-reporting of cases. Furthermore, assay cross-reactivity with infliximab was demonstrated, which could give rise to erroneous results such as false positives.

The Pop-PK analysis model was justified and considered appropriate. In particular, the covariate modelling approach emphasised parameter estimation rather than stepwise hypothesis testing. Pre-defined parameter relationships were identified and then a full model constructed. The model provided a good description of the data.

The mean serum adalimumab trough concentrations from Study 827 had a good relationship to the administered adalimumab dose. The PK parameters presented for UC in this submission were consistent with other licensed adalimumab indications, particularly CD (induction and maintenance).

Administration of the first dose of the induction regimen, 160 mg over one or two days, had minimal impact on the PK of adalimumab during the induction period and is therefore

[4] After this application was finalised, the sponsor provided analyses which was claimed to show that, overall, baseline HACA status does not appear to impact adalimumab efficacy to a clinically relevant extent.
[5] Sponsor comment: The impact of infliximab interference would be expected to diminish from Week 8 onward (median elimination half-life is 7.7 to 9.5 days), reducing the measurement bias due to cross-reactivity. The apparent lag time between onset and measurable level of AAA should not play a role specifically for the Week 52 results. Also, subjects were found AAA+ as early as Week 8 which supports the minimal impact of the lag time. The "bias" is mainly due to the AAA classifying criteria (which has been standard across the indications).
[6] Sponsor comment: 3 of 19 AAA+ subjects were in remission, equalling about 16%, which is comparable with the overall efficacy results (16–17% at Weeks 8 and 52).

acceptable. Furthermore, the Pop-PK analysis results suggest no routine dosage adjustment is necessary based on bodyweight, AAA status, serum albumin levels or with co-administration of methotrexate, azathioprine or 6-mercaptopurine immunosuppressant therapy.

Overall, the data supports the proposed PI amendment to the *Clinical Pharmacology* section.

Immunogenicity

While overall AAA positivity was similar between CD and UC in this study, any effect of prior anti-TNF exposure, baseline HACA status and the development of AAA on efficacy (and safety) of adalimumab is unclear from the study results presented in this submission. The sponsor was asked to clarify these issues under specific clinical questions (see *Second round evaluation of clinical data submitted in response to questions*, below).

Pharmacodynamics

No data.

Efficacy

Dosage selection for the pivotal studies

The sponsor advises that doses for the Phase III clinical studies (Studies 826 and 827) were selected based on a combination of expert clinical advice, clinical data from the adalimumab development program in CD, and extensive PK data accumulated in the adalimumab RA and CD development programs, along with PK modelling.

In August 2007, the study design for Study 826 was amended (under Amendment 3) to incorporate an additional adalimumab induction dosing arm of 80/40 mg (80/40). Earlier that year, both 160/80/40 mg (160/80/40) and 80/40 induction regimens had been approved in the EU as induction treatment for CD. The adalimumab induction dosing regimen of 80/40 was therefore included upon agency request so both of these approved induction regimens would be evaluated for the induction of remission of UC.

The adalimumab 160/80/40 and 80/40 dosing induction regimens were in accordance with the CD dosage recommendations in the current US Package Insert (USPI) (160/80/40 mg), Company Core Data Sheet (CCDS), and the EU Summary of Product Characteristics (EU SPC) (80/40 mg or 160/80/40 mg if a rapid response is required).

In clinical studies conducted in subjects with CD, induction regimens comprising 160 mg adalimumab at Week 0 and 80 mg adalimumab at Week 2 (160/80/40 regimen) or 80 mg adalimumab at Week 0 and 40 mg adalimumab at Week 2 (80/40 regimen) produced higher rates of CR at Week 4 than placebo (35.5% and 24.0% versus 12.2%, respectively). In addition, statistically significantly greater proportions of subjects in the 160/80/40 and 80/40 adalimumab induction regimens experienced CR-70 (CD activity index [CDAI] decrease from baseline ≥ 70 points) clinical response at Week 4 than subjects on placebo (57.9% and 56.2% versus 36.1%, respectively). A statistically significantly greater proportion of subjects in the 160/80/40 mg adalimumab induction regimen compared with subjects on placebo experienced CR-100 (CDAI decrease from baseline ≥ 100 points) clinical response at Week 4 (48.7% versus 23.6%, respectively). Subjects in the 80/40 mg adalimumab induction regimen also experienced CR-100 clinical response at Week 4 at a higher rate than placebo (38.4%), but the difference was not statistically significant. With regard to the 40 mg adalimumab every other week (eow) dosing maintenance regimen (following the 160/80 mg adalimumab induction regimen), at Week 12, no statistically

significant difference between treatment groups was observed for clinical response CR-70 or clinical response CR-100. However, at Week 52, a statistically significantly greater proportion of subjects in the adalimumab group demonstrated clinical response when compared to subjects in the placebo group (CR-70: 40.6% versus 13.8%, respectively; p< 0.001 and CR-100: 35.9% versus 13.8%, respectively; P = 0.004).

Evaluator comment: Inclusion of the 80/40 mg adalimumab regimen into Study 826 appeared logical based on its acceptance as an induction regimen in CD. When Amendment 3 came into existence, 185 subjects had already received randomised treatment into the DB induction period (92 placebo and 93 adalimumab 160/80/40) and were effectively excluded from the primary analysis (intent-to-treat-A3 (ITT-A3)). Given the proposed induction regimen is adalimumab 160/80/40 mg, it is unfortunate the data for the pre-Amendment 3 subjects are only considered as part of a sensitivity analysis set, ITT-E.[7]

Studies providing efficacy data

Summaries of the two pivotal studies (826 and 827) and the supportive study (M10-223) provided for this application are shown in Table 1, Table 2 and Table 3, respectively.

[7] Sponsor comment: The sponsor considers that conducting the primary analysis on the post-amendment 3 study population was diligent, given that amendment 3 comprised changes other than adding the 80/40 mg arm, such as pertaining to exclusion criteria for prior medication. Because of these reasons the ITT-A3 population was more homogenous than the ITT-E population, and was consistently used throughout the analyses. It should also be noted that the proposed induction dosing regimen, although pre-amendment 3 subjects were excluded from the primary analysis, was still adequately studied post-amendment 3.

Table 1. Pivotal efficacy Study 826

Study ID/ No. of Centers/ Locations/ Duration	Study Start Enrollment Status, Date Total Enrollment	Design Control Type	Study and Control Drugs Dose, Route and Regimen	Study Objective	No. of Subjects by Arm Entered/ Completed	Sex M/F Median Age (Range)	Diagnosis Inclusion Criteria	Primary Endpoints
M06-826 80 centers AUS, BEL, CAN, CZ, GER, HU, IT, NL, POL, PR, SK, SWE, US 52 weeks	13 Nov 2006 Completed 05 Mar 2010 576 subjects	Randomized, DB, placebo-controlled period followed by OL period	During DB period Adalimumab SC eow • 160 mg at Week 0, 80 mg at Week 2, and 40 mg eow thereafter • 80 mg at Week 0 and 40 mg eow thereafter Placebo SC eow During OL period Adalimumab SC eow For subjects randomized to placebo: • Prior to Amendment 3: 160 mg at Week 8, 80 mg at Week 10, and 40 mg eow thereafter, with escalation to 40 mg ew allowed starting at Week 14[a] • After Amendment 3: 40 mg eow beginning at Week 8, with escalation to 40 mg ew allowed starting at Week 12[a]	Assess the efficacy and safety of 2 dosing regimens of adalimumab for the induction of clinical remission in subjects with moderately to severely active UC.	Adalimumab 160/80/40 223/143 Adalimumab 80/40 130/86 Placebo 223/153	356 M/220 F 38.5 yrs (18 – 75)	Adult subjects with moderate to severe active UC (Mayo score of 6 to 12 points with endoscopy subscore of 2 to 3 points), confirmed by colonoscopy with biopsy or by flexible sigmoidoscopy with biopsy.	Clinical remission per Mayo score at Week 8

Table 2. Pivotal efficacy Study 827

Study ID/ No. of Centers/ Locations/ Duration	Study Start Enrollment Status, Date Total Enrollment	Design Control Type	Study and Control Drugs Dose, Route and Regimen	Study Objective	No. of Subjects by Arm Entered/ Completed	Sex M/F Median Age (Range)	Diagnosis Inclusion Criteria	Primary Endpoints
M06-827 103 centers AUS, AUST, BEL, CAN, CZ, DEN, FR, GER, HU, ISR, NOR, NZ, POL, POR, SP, SWI, and US 52 weeks	20 Nov 2006 Completed 02 Mar 2010 518[b] subjects	Randomized, DB, placebo-controlled study	Adalimumab SC eow • 160 mg at Week 0, 80 mg at Week 2, and 40 mg eow thereafter Placebo SC eow Switch to OL adalimumab allowed starting at Week 12 and subsequent escalation to 40 mg ew	Assess the efficacy and safety of adalimumab for the induction and maintenance of clinical remission in subjects with moderately to severely active UC.	Adalimumab 258[b]/161 Placebo 260/135	305 M/212 F 40.6 yrs (18 – 79)	Adult subjects with moderate to severe active UC (Mayo score of 6 to 12 points with endoscopy subscore of 2 to 3 points), confirmed by colonoscopy with biopsy or by flexible sigmoidoscopy with biopsy.	Clinical remission per Mayo score at Week 8 and at Week 52

AUS = Austria; AUST = Australia; BEL = Belgium; CAN = Canada; CZ = Czech Republic; DEN = Denmark; FR = France; GER = Germany; HU = Hungary; ISR = Israel; IT = Italy; NL = The Netherlands; NOR = Norway; NZ = New Zealand; POL = Poland; POR = Portugal; PR = Puerto Rico; SK = Slovakia; SP = Spain; SWE = Sweden; SWI = Switzerland; US = United States; DB = double-blind; eow = every other week; OL = open-label; SC = subcutaneous

a. Study M06-826 Amendment 3 added the adalimumab 80/40 treatment group and modified the eligibility criteria and study design (Study M06-826 CSR Section 9.1).

b. In Study M06-827, 517 subjects received study drug; 1 additional subject was randomized but did not receive study drug.

Table 3. Non-pivotal efficacy Study M10-223

Study ID/ No. of Centers/ Locations/ Duration	Study Start Enrollment Status, Date Total Enrollment	Design Control Type	Study and Control Drugs Dose, Route and Regimen	Study Objective	No. of Subjects by Arm Entered/ Completed	Sex M/F Median Age (Range)	Diagnosis Inclusion Criteria	Primary Endpoints
M10-223 120 sites AUS, AUST, BEL, CAN, CZ, FR, GER, HU, IT, NL, NZ, POL, PR, SK, SP, SWE, SWI, US Up to 240 weeks	28 Nov 2007 Enrollment complete, study ongoing 592 subjects[a]	OL extension study of Study M06-826 and Study M06-827	Adalimumab SC eow • If receiving DB treatment in previous study, 40 mg eow with escalation to 40 mg ew allowed • If receiving OL treatment in previous study, continuation of previous regimen with escalation to 40 mg ew allowed	Assess efficacy and safety of long-term use of adalimumab as maintenance therapy	592/ ongoing[b]	373 M/219 F 41.6 yrs (19 – 76)	Successful enrollment in and completion of either Study M06-826 or Study M06-827	Long-term maintenance of response, safety, and tolerability of repeated administration of adalimumab in subjects with UC who participated in and successfully completed Study M06-826 or Study M06-827

AUS = Austria; AUST = Australia; BEL = Belgium; CAN = Canada; CZ = Czech Republic; FR = France; GER = Germany; HU = Hungary; IT = Italy; NL = The Netherlands; NZ = New Zealand; POL = Poland; PR = Puerto Rico; SK = Slovakia; SP = Spain; SWE = Sweden; SWI = Switzerland; US = United States; eow = every other week; ew = weekly; SC = subcutaneous

a. At the time of the safety data cutoff date (16 December 2011), enrollment in Study M10-223 was complete, with 592 subjects enrolled from 133 sites from Study M06-826 or Study M06-827.

b. As of 16 December 2011, 464 subjects (78.4%) had completed Week 60 of open-label treatment.

In addition, as part of the integrated summary of efficacy, efficacy data were provided from pooled analyses conducted across studies.

A description of the Mayo scoring system, used to assess clinical response, is shown in Table 4. (extracted from protocol for Study 827), whereby the worst score from the past 3 days was used in the study as opposed to the average score used in several other trials:

Table 4. Mayo Scoring System

The Mayo Score is a composite of the following subscores: Stool Frequency Subscore, Rectal Bleeding Subscore, Endoscopy Subscore, and Physician's Global Assessment Subscore.
Stool frequency Subscore*
0 = Normal number of stools for this subject
1 = 1-2 stools more than normal
2 = 3-4 stools more than normal
3 = 5 or more stools more than normal
*Each patient serves as his or her own control to establish normal stool frequency and the degree of abnormal stool frequency.
Rectal bleeding Subscore **
0 = No blood seen
1 = Streaks of blood with stool less than half the time
2 = Obvious blood with stool most of the time
3 = Blood alone passed
** The daily bleeding score represents the most severe bleeding of the day.
Endoscopy Subscore: Findings of flexible sigmoidoscopy
0 = Normal or inactive disease
1 = Mild disease (erythema, decreased vascular pattern, mild friability)
2 = Moderate disease (marked erythema, absent vascular pattern, friability, erosions)
3 = Severe disease (spontaneous bleeding, ulceration)

The Mayo Score is a composite of the following subscores: Stool Frequency Subscore, Rectal Bleeding Subscore, Endoscopy Subscore, and Physician's Global Assessment Subscore.
Physician's Global Assessment Subscore* **
0 = Normal (Subscores are 0)
1 = Mild disease (Subscores are mostly 1's)
2 = Moderate disease (Subscores are 1 to 2)
3 = Severe disease (Subscores are 2 to 3)
*** The physician's global assessment acknowledges the three other subscores, the subject's daily record of abdominal discomfort and functional assessment, and other observations such as physical findings, and the subject's performance status.

Evaluator's conclusions on clinical efficacy for ulcerative colitis

For adalimumab treatment in moderately to severely active UC, the clinical development program included one pivotal induction study (M06-826) that compared two induction regimens [adalimumab 160/80/40 and adalimumab 80/40] against placebo, one pivotal induction and maintenance study (M06-827) that compared adalimumab 160/80/40 against placebo and one ongoing open-label supportive extension study (M10-223). In response to questions by the European Medicines Agency (EMA) and FDA, early responder analyses (during the 8 week double-blind phase) were undertaken in Study 827 to identify subjects most likely to benefit from adalimumab treatment. Data from these studies form the basis for all efficacy data to support the proposed indication. This program is consistent with the TGA-adopted *Guideline on the development of new medicinal products for the treatment of ulcerative colitis* (CHMP/EWP/18463/2006, January 2008).

Induction

In Study 827, a statistically significantly greater proportion of adalimumab subjects demonstrated clinical remission at Week 8 compared with placebo subjects, assessed by Mayo score (16.5% versus 9.3%, respectively, p=0.019). The clinical significance of a difference <10% is unclear. The secondary efficacy analyses are consistent with the primary analysis in terms of the magnitude of effect and the effect difference compared with placebo.

In Study 826, a statistically significantly greater proportion of adalimumab 160/80/40 subjects demonstrated CR at Week 8 compared with placebo subjects in the primary (ITT-A3 non-responder imputation (NRI)) analysis (18.5% versus 9.2%, p=0.031). The magnitude of the effect and difference compared with placebo is similar to the result in Study 827. While the third and fourth ranked secondary endpoints demonstrated statistical separation of adalimumab 160/80/40 against placebo (and most other ranked secondary endpoints for adalimumab 160/80/40 were numerically greater than placebo), the first ranked secondary endpoint (clinical response per Mayo score at Week 8 in the adalimumab 160/80/40 treatment group versus placebo) did not meet the criteria for statistical significance.

The adalimumab 80/40 induction regimen in Study 826 did not demonstrate statistical superiority against placebo for the primary and ranked secondary endpoints.

Maintenance

In Study 827, a statistically significantly greater proportion of adalimumab subjects demonstrated CR at Week 52 compared with placebo subjects, assessed by Mayo score (17.3% versus 8.5%, respectively, p=0.004). Again the difference is <10%. The secondary efficacy analyses are consistent with the primary analysis in terms of the magnitude of effect and the net difference compared with placebo.

In Study 827, the first ranked secondary endpoint, sustained CR per Mayo score at both Weeks 8 and 52, provides a robust estimate of adalimumab ability to maintain efficacy over 44 weeks from the induction period. In the adalimumab treatment group, 21 subjects (8.5%) maintained remission throughout the maintenance period compared with 10 subjects (4.1%) in the placebo group (p=0.047). Approximately half the subjects who remitted at Week 8 had sustained CR at Week 52 (51.2% (n=21/41) adalimumab subjects and 43.5% (n=10/23) placebo subjects). In terms of those subjects who completed DB treatment, 25.6% (n=21/82) adalimumab subjects had sustained CR and 17.9% (n=10/56) placebo subjects had sustained CR. Again, the differences between active and placebo treatment are <10%, which is modest.

In Study 827, early responder analyses suggested there is a consistent favourable effect over the total adalimumab treatment group (at each time point) through to Week 52 of adalimumab treatment for Weeks 2, 4, and 8 PM responders and Week 8 full Mayo (FM) responders, in terms of CR and CRESP rates, baseline reductions in FM score, MH and baseline reductions in endoscopy subscore. In early responders to adalimumab, the magnitude of the differences measured, compared with placebo, consistently exceeded 10% and was consistently higher on every parameter measured against the total adalimumab 160/80/40 group results.

In Study 826, maintenance was assessed in an OL manner and hence was not a true maintenance study. At Week 52 approximately 24% of the ITT-E (NRI) actively-treated population were in CR as per Mayo score. Additional quality of life (QoL) endpoints, such as inflammatory bowel disease questionnaire (IBDQ) and Short form 36-item health survey (SF-36) scores, provided supportive evidence of adalimumab 160/80/40 efficacy. The lack of control within the OL study design and the eow/ew dosing regimens means the results from this study are of limited usefulness.

Similarly, Study 223 is an OL extension trial and lends support to longer term use of adalimumab but is of limited usefulness in the assessment of maintenance of treatment. Disease activity (based on Mayo and partial Mayo (PM) scores) remained stable for 60 weeks in a subset of the adalimumab population, indicating some benefit in a selected population of responders. Conversely, approximately 23% subjects discontinued the study due to lack of efficacy (even allowing for periods of dose escalation to once weekly treatment).

Anti-TNF status

Subjects in Study 827 were stratified and analysed by prior anti-TNF exposure (for primary and ranked secondary endpoints). Among anti-TNF naïve subjects, a statistically significantly higher proportion of those treated with adalimumab achieved the primary endpoints compared with placebo in CR per Mayo score at both Weeks 8 (21.3% versus 11.0%, respectively, p=0.017) and 52 (22.0% versus 12.4%, respectively, p=0.029). Although statistical significance was not achieved in the first ranked secondary end-point (observed difference 4.5% for naïve and 4% for experienced), most other ranked secondary end-points statistically significantly favoured adalimumab treatment over placebo for anti-TNF naïve subjects.

Among anti-TNF experienced subjects, adalimumab did not achieve statistical separation against placebo at the first primary end-point, that is, CR per Mayo score at Week 8 (9.2%

versus 6.9%, respectively, p=0.559). Statistical significance was achieved at the second primary endpoint and several secondary endpoints.

The early responder analyses did not demonstrate statistically significant differences between early responders who had prior anti-TNF exposure and those who did not. The numbers of early responders who had prior anti-TNF exposure are small and therefore these post hoc analyses, undertaken on the adalimumab treated subjects only (not placebo responders), are of limited usefulness. The early responder analyses are only regarded as supportive as selection for a subgroup of subjects does not allow for comparisons between randomised treatment groups.

However, overall, the analyses presented in this submission suggest subjects who respond early to adalimumab treatment are the most likely to benefit from treatment and achieve/sustain remission.

Overall conclusions

The pivotal efficacy study, Study 827, was generally well designed and conducted (although three centres in Study 827 were found by the sponsor to be non-GCP compliant). The original design of Study 826 was changed upon agency request after 185 subjects had entered the study proper, with the introduction of an additional treatment arm (namely addition of a lower induction dose of 80/40 mg), which is different from the proposed dosage regimen in UC. The primary analysis set (ITT-A3) therefore did not include the 185 subjects (including 93 subjects who had received the proposed 160/80/40 adalimumab induction dosage regimen).

The most notable issues with the efficacy studies were the number of protocol deviations and violations, as well as the large number of subjects who switched to open-label treatment from lack of efficacy or worsening UC.

The adalimumab 160/80/40 induction regimen demonstrated statistical superiority over placebo treatment in the primary endpoints, that is, adalimumab is clinically effective in inducing CR in subjects with moderately to severely active UC. However, the overall difference compared with placebo was modest irrespective of analysis set (<10%).

The beneficial effects of adalimumab treatment were consistently observed across the ranked secondary endpoints, although statistical significance was not wholly achieved in all. Of note, the magnitude of effect in UC was approximately half that observed with this adalimumab induction regimen in CD.

The adalimumab 80/40 induction regimen did not demonstrate statistical superiority or sizeable numerical difference over placebo for the primary endpoint of CR.

The evidence for maintenance of remission is less convincing than the induction data. The proportion of subjects who achieved and maintained CR was modest (a 4.4% positive difference compared with placebo; p=0.047). This effect is supported by statistically superior results of adalimumab over placebo in the first eight ranked secondary endpoints. Steroid-free remission is an important clinical endpoint in practice and while positive differences of adalimumab over placebo occurred numerically, these findings are descriptive.[8]

The early responder analyses lend support for the benefit for those subjects who responded early to adalimumab treatment to gain a longer-term benefit. However, the analyses were exploratory and lacked a randomised comparison, and did not form part of

[8] Sponsor comment: The difference between adalimumab and placebo was statistically significant at Week 52.

the original statistical plan. Furthermore, the early responder analyses did not identify subjects who were most likely to respond to early treatment.[9]

Efficacy was not demonstrated in subjects with prior anti-TNF-α exposure.[10]

Overall, the evaluator concluded that there are issues of internal validity within Studies 826 and 827 (with several potential sources of bias). The studies were externally valid (extrapolation to the general UC population with moderately to severely active UC), with statistically significantly favourable results for adalimumab in the primary and many ranked secondary efficacy endpoints for the induction and maintenance periods, but the difference in actual percentage of subjects who achieved these endpoints (especially sustained remission throughout the study) was consistently <10% and therefore are of questionable clinical significance. Early responder analyses, hospitalisation rates and QoL parameters also tend to favour adalimumab treatment. However, the clinical evaluator considered that, on balance, the efficacy results [in the overall population] are not compelling, particularly in terms of maintenance treatment (beyond 8 weeks).

Safety

Studies providing evaluable safety data

The safety of adalimumab in UC was determined using data from three clinical studies: two completed multicentre, multinational, double-blind, placebo-controlled, Phase III pivotal studies (Study 826 and Study 827), which assessed safety as a primary outcome, and one ongoing OL extension trial, Study 223.

The pivotal studies were conducted in adult subjects with moderately to severely active UC, defined as a Mayo score of 6 to 12 points and endoscopy subscore of 2 to 3 points, despite treatment with oral corticosteroids, immunomodulators or both (or having failed to respond to or been unable to tolerate these treatments), and confirmed by colonoscopy with biopsy or by flexible sigmoidoscopy with biopsy.

The original cut-off date for the integrated summary of safety (ISS) report for Study 223 was 31 December 2009, but this was extended to 16 December 2011 to form the Integrated Summary of Safety Update (ISSU) report. On 16 December 2011, 133 sites had enrolled 592 subjects into Study 223. Three hundred and eighty four subjects (64.8%) were ongoing in the study, with 464 (78.3%) had completed the Week 60 visit. The sponsor based its safety conclusions on the integrated safety population, but the focus of this safety evaluation is on data from the pivotal studies.

The ISSU included safety data for an ongoing Phase II/III, randomised, three-arm, placebo-controlled, 52 week double-blind, efficacy and safety study in Japanese subjects with moderately to severely active UC (Study M10-447). No study protocol or clinical study report (CSR) was provided in the submission and so only comments on serious adverse events and deaths were noted by the clinical evaluator as it was beyond the scope of the application to evaluate Study M10-447.

Safety of adalimumab throughout the studies was monitored and assessed by adverse events (AEs,) physical examination, laboratory data and vital signs. The ISS and ISSU

[9] Sponsor comment: The identification of subjects who were most likely to respond to early treatment would require the identification of a biomarker. The objectives of this clinical program did not include the identification of a biomarker

[10] Sponsor comment: subjects met 3 clinically meaningful maintenance endpoints, i.e., clinical remission per Mayo score at Week 52 (placebo 3.0% versus adalimumab 10.2%, p=0.039), clinical response per Mayo score at Week 52 (placebo 9.9% versus adalimumab 20.4%, p=0.038), and sustained clinical response per Mayo score at Week 8 and at Week 52 (placebo 5.9% versus adalimumab 15.3%, p=0.032). However, the study was not powered for statistical significance in this subgroup.

analyses focused on treatment-emergent adverse events (TEAEs), deaths, serious adverse events (SAEs), premature discontinuations due to AEs, TEAEs of special interest (including infection and hepatic AEs), clinical laboratory evaluations (including analysis of subjects meeting criteria for laboratory values of potential clinical significance) and analysis of TEAEs by intrinsic and extrinsic factors.

Comment: The ISSU provides more safety data than the original ISS and hence is more useful in the assessment of risk of adalimumab administration in UC patients. Generally the TEAE rates in the ISS and ISSU were comparable across treatment groups with no new safety signal identified.

Patient exposure

Four integrated analysis sets were examined:

- Induction Set (IS; n = 1093*): subjects who received at least one dose of randomised DB placebo or DB adalimumab (160/80/40 and 80/40) treatment between Weeks 0 and 8. The IS included 576 randomised subjects from Study 826 and 518 randomised subjects from Study 827;
- Maintenance Set (MS; n = 457): subjects who received at least one dose of randomised DB placebo or DB adalimumab 160/80/40 treatment between Weeks 8 and 52 in Study 827;
- All Adalimumab Set (AAS; n = 1010): subjects who received at least one dose of randomised DB or OL treatment with adalimumab in Studies 826, 827 and 223, through to 16 December 2011. The AAS includes 610 subjects randomised to adalimumab in Studies 826 or 827 and 400 subjects randomised to placebo in Studies 826 or 827 who switched to OL adalimumab treatment in Studies 826, 827 or 223;
- Placebo Set (PS; n = 483): subjects who received at least one dose of randomised DB placebo (between Weeks 0 and 8 in Study 826, and between Weeks 0 and 52 in Study 827).

*One subject in Study 827 did not receive study drug.

Notes:

The IS represents the total number of subjects exposed to study drug (adalimumab or placebo) in the UC clinical program.

Study drug exposure for each analysis set reflects the different study designs and treatment regimens within each analysis set. The median exposure in the AAS was 646 days (range: 14 to 1814 days; Table 5). More subjects randomised to DB placebo switched to OL adalimumab treatment during the maintenance period because of an inadequate response, hence the lower median exposure observed in placebo subjects.

Table 5. Extent of study drug exposure in the Induction, Maintenance and All Adalimumab Sets

	Induction Set		Maintenance Set		All Adalimumab Set[a]
	Placebo N = 483	Adalimumab N = 610	Placebo N = 223	Adalimumab N = 234	Adalimumab N = 1010
Duration of treatment (days)					
Mean ± SD	53.3 ± 9.79	54.2 ± 8.14	134.8 ± 118.12	168.2 ± 120.56	684.1 ± 512.50
Median (range)	56.0 (14 – 69)	56.0 (14 – 69)	70.0 (14 – 323)	142.5 (14 – 315)	646.0 (14 – 1814)
Total number of injections					
Mean ± SD	7.7 ± 0.84	7.8 ± 0.68	9.6 ± 8.41	12.0 ± 8.62	63.4 ± 49.75
Median (range)	8.0 (4 – 8)	8.0 (3 – 8)	5.0 (1 – 22)	10.0 (1 – 22)	53.0 (1 – 228)
Average monthly number of injections					
Mean ± SD	4.52 ± 0.905	4.43 ± 0.717	2.12 ± 0.139	2.13 ± 0.107	3.08 ± 1.138
Median (range)	4.29 (3.3 – 8.6)	4.29 (3.2 – 8.6)	2.14 (1.1 – 2.7)	2.14 (1.3 – 2.6)	2.71 (1.6 – 8.6)
PYs	70.5	90.5	82.3	107.8	1891.7

a. The All Adalimumab Set includes subjects randomized to adalimumab in Study M06-826 or Study M06-827 (N = 610), as well as those subjects randomized to placebo in Study M06-826 or M06-827 who switched to OL adalimumab treatment in Studies M06-826, M06-827, or M10-223 (N = 400).

Across the three studies a total of 1010 subjects with UC were exposed to at least one dose of adalimumab as of 16 December 2011 (that is, the AAS), for a cumulative exposure of 1891.7 patient years (PYs). Of these subjects, 622 (61.6%) had >12 months of adalimumab exposure; 530 (52.5%) had >18 months of adalimumab exposure, 459 (45.4%) had >24 months of adalimumab exposure, 291 (28.8%) had >36 months of adalimumab exposure and 75 (7.4%) had >48 months of adalimumab exposure.

Comment: adalimumab exposure was sufficient to identify new safety issues in this patient group.

Evaluator's overall conclusions on clinical safety

Overall, adalimumab treatment was well tolerated in the Phase III controlled studies for subjects with moderately to severely active UC. Safety data were generated using appropriate methods with particular focus on the AEs of special interest. The AE profile of adalimumab was consistent with the known profile established in other indications, including CD, with the exception of a higher lymphoma rate [but see below]. No new safety signals were identified in the UC program.

The three cases of B-cell lymphoma were complicated by confounding factors that could give rise to lymphoma independently of study drug (such as smoking history, and prior azathioprine/immunomodulator treatment). Lymphoma will continue to be monitored in pharmacovigilance activities detailed in the risk management plan (RMP)/long-term registry. No case of colon cancer was identified in this submission and again this will be closely monitored in Study M10-223 and post-marketing surveillance/RMP activities because of the recognised association between UC and colon dysplasia/carcinoma.[11]

Subjects who received prior anti-TNF treatment tended to have higher rates of some TEAEs such as SAEs and study discontinuations. Ulcerative colitis worsening/flare (most common AE) rates were higher in anti-TNF experienced subjects compared with naïve subjects, probably indicative of reduced efficacy in this subgroup.

The four deaths in this submission (and two in the ongoing Japanese Phase III study) do not appear to be related to adalimumab treatment, although autopsy reports are not available for at least two of the subjects in the ISSU) and so causality remains uncertain in these cases.

[11] Sponsor comment: One case of colon cancer was identified in the open-label extension study M10-223. Colon cancer will continue to be closely monitored in this study and post-marketing surveillance/RMP activities.

Adalimumab treatment consistently demonstrated higher rates of injection site reactions compared with placebo treatment, and the effect of long-term adalimumab immunogenicity on safety (and efficacy) remains unknown.

First round benefit-risk assessment

First round assessment of benefits

The benefits of adalimumab in the proposed usage, as stated by the clinical evaluator, are:

- An alternative to infliximab in terms of medication and route of administration (SC versus intravenous (IV));
- If approved, adalimumab would be the only self-administered monoclonal antibody therapy for UC (and hence hospitalisation is not required);
- The PK of adalimumab in UC is very similar to other adalimumab indications, particularly CD;
- The alternative 160/80/40 adalimumab regimen (160 mg given over the first two days instead of one day) is acceptable with a similar exposure-concentration profile, which may provide improved adherence to treatment;
- The primary efficacy end-points were achieved in Studies 826 and 827 for the DB adalimumab 160/80/40 regimen for induction with a modest difference (<10%) compared with DB placebo;
- The first eight ranked secondary efficacy end-points in Study 827 supported the primary end-point results for the DB adalimumab 160/80/40 group, adding robustness to the results;
- Subjects who were anti-TNF naïve tended to benefit more than those subjects who had prior anti-TNF exposure;
- Early responders to adalimumab treatment appeared to derive the greatest benefit of treatment;
- Most endpoints/parameters examined tended to favour adalimumab treatment over placebo treatment, including steroid-free remission rates, all-cause hospitalisation rates, although many of the analyses were either exploratory or did not attain statistical superiority over placebo;
- No new safety signals were identified;
- No death was attributed to adalimumab treatment (but no autopsy reports were available);
- No case of colon carcinoma was identified in this submission[12];
- In the ongoing extension trial, Study M10-223, disease activity was reduced at baseline and remained stable while on treatment (eow or ew dosing for up to 60 weeks);
- A thorough RMP and post-marketing surveillance program (including a recently established safety registry for adalimumab in UC);
- Study M10-223 and the ongoing controlled Japanese study (DB for 52 weeks) using two adalimumab induction regimens (160/80/40 and 80/40) will provide much more efficacy data (particularly for maintenance treatment) and safety data.

[12] Sponsor comment: One case of colon cancer was identified in the open-label extension study M10-223.

First round assessment of risks

The risks of adalimumab in the proposed usage, as stated by the clinical evaluator, are:

- The first ranked secondary efficacy endpoint in Study 826 for DB adalimumab 160/80/40 was not achieved. This suggests the study power (and participant numbers) were insufficient, as supported by the sample size calculations;
- The ITT-A3 analysis set in Study 826 did not include 93 DB adalimumab 160/80/40 subjects (and 92 DB placebo subjects), yet this is the very group upon which the proposed indication relies. While this population was considered in the ITT-E group, this was regarded as a 'sensitivity analysis' only;
- The numbers of subject withdrawals from the DB adalimumab 160/80/40 regimen prior to implementation of Amendment 3 in Study 826, is in the order of twice the number for AEs, lack of efficacy and withdrawal of consent, compared with the same group post-Amendment 3. This suggests a difference in baseline disease and/or medical history between those subjects recruited pre- and post-Amendment 3[13];
- Only modest efficacy (<10% difference compared to placebo) for complete response was demonstrated in the induction period in both pivotal studies;
- Efficacy was not established in those subjects previously exposed to anti-TNF treatment;
- Although early responders to adalimumab treatment appeared to gain the most benefit, the overall success rates of sustained remission remained low and the characteristics of those subjects most likely to benefit from adalimumab treatment remain unknown;
- Maintenance effect was not adequately demonstrated [in the overall population] (less than 10% of DB randomised achieved sustained remission with <5% difference compared those who achieved clinical remission in the DB placebo group in Study 827);
- Dose-escalation to once weekly adalimumab treatment was not associated with greater efficacy;
- Autopsy reports were not provided by the investigators for at least two subject deaths so no assessment could be made;
- Adverse events related to worsening UC/flare (overall and SAEs) were frequently reported in placebo and adalimumab-treated subjects (placebo > adalimumab), as well as the most common AE leading to premature discontinuation from the studies, which suggests adalimumab dosing may be sub-optimal in subjects with moderately severe to severely active UC;
- Due to the small numbers of subjects [with events of colectomy] in the pivotal studies it remains unknown whether adalimumab can delay or prevent colectomy in UC patients, albeit monitoring will occur in the UC registry described in the RMP;
- The long-term immunogenicity of adalimumab [in UC] is unknown;
- Development of AAA, leading to loss of response to treatment, is a recognised phenomenon but it is unclear what the incidence is in UC because there may be a significant lag time to identify cases and the sensitivity and specificity of the

[13] Sponsor comment: UC history at baseline was: Duration of UC: ITT-A3: Placebo 7.48 years, ADA 160/80 8.11 years; ITT-E: Placebo 7.89 years, ADA 160/80 8.41 years Mayo score: ITT-A3: Placebo 8.7, ADA 160/80 8.8 ITT-E: Placebo 8.8, ADA 160/80 8.9. During Week 0-8, only 'withdrew consent' seems to be a little bit higher in pre-A3 compared to ITT-A3.

adalimumab ELISA assay may be inadequate in detecting those subjects who develop AAA.

First round assessment of benefit-risk balance

While the safety profile of adalimumab in UC was consistent with the established safety profile for this agent and no new safety signals were identified in this submission, the efficacy results do not provide compelling evidence for a clinical benefit, as the adalimumab 160/80/40 induction regimen achieved <10% difference compared with placebo (a modest clinical benefit) and a 4.4% greater difference than placebo in sustaining clinical remission does not provide confidence in the ability of adalimumab to maintain remission. Furthermore, few subjects who had prior anti-TNF exposure achieved a benefit from adalimumab treatment in this submission.

Many of the serious risks associated with adalimumab [and other TNF antagonists] are rare (such as demyelination) or take many years to develop (for example, lymphoproliferative disorders or malignancies such as hepatosplenic T-cell lymphoma, dysplasia and colorectal carcinoma) and would be expected to be identified on long-term monitoring rather than in relatively short-term clinical studies. The information contained in the PI and RMP adequately address the safety aspects at this juncture.

The adalimumab 80/40 induction regimen did not demonstrate efficacy over placebo. Given this induction regimen is approved for CD in Europe and the US and the modest efficacy demonstrated in the adalimumab 160/80/40 regimen in UC compared with CD (in the order of a two-fold difference), these findings suggest the induction dose of 160/80/40 is sub-optimal in the treatment of moderately severe to severely active UC. Furthermore, the high rates of UC worsening/flare across studies for adalimumab (and placebo), including SAEs and premature discontinuations secondary to these events, provides additional evidence that the adalimumab 160/80/40 induction regimen/and possibly maintenance dose are sub-optimal in the treatment of moderately severe to severely active UC.

Overall, despite the favourable PK and safety data for adalimumab in UC provided in this application, the efficacy results are not compelling to recommend full approval. With <5% difference compared with placebo in sustaining clinical remission over 44 weeks of adalimumab treatment, the benefit in treating so many patients in the knowledge few will derive long-term benefit is not acceptable clinical practice, especially given the known toxicity of TNF-antagonists. The recommendation to cease treatment after 8 weeks if inadequate response to adalimumab treatment occurs will result in a more favourable benefit-risk balance.

The provisional benefit-risk balance is only favourable for anti-TNF naïve subjects but would become more favourable if early responders to adalimumab treatment can be identified prior to commencement of treatment.

First round recommendation regarding authorisation

The clinical evaluator's provisional recommendation was to approve adalimumab in UC only for anti-TNF naïve patients.

Second round evaluation of clinical data submitted in response to questions

The TGA List of Questions[14] on clinical data and the clinical evaluator's evaluation of the sponsor's responses appear in this section:

Pharmacokinetics

What are the mean serum adalimumab trough concentrations for the anti-TNF naïve and anti-TNF experienced groups at Weeks 32 and 52 (by randomised treatment group and by weekly or fortnightly Humira 40 mg regimen) as cited in Table 6 in document R&D/10/462 that pertains to Study M06-827?

Evaluator comment on response:

For those subjects who completed DB adalimumab eow treatment there was an 11% difference in mean serum adalimumab concentration at Week 52, which favoured anti-TNF naïve subjects. A similar trend is noted for those subjects who dose-escalated to once weekly treatment, with an 18% difference at Week 52 that favoured anti-TNF naïve subjects. These results suggest prior anti-TNF exposure may lower the mean serum adalimumab concentration, and potentially adversely affect efficacy for this group.

Immunogenicity

While it is not apparent from the Study M10-223 clinical study report, were AAA and/or HACA status measured and/or monitored for participants who entered this study from Study M06-827? If so, please provide further details by randomised treatment group and anti-TNF status, as well as remitter/non-remitter status.

Evaluator comment on response:

The effect of AAA status on efficacy (and safety) in ulcerative colitis remains uncertain. While a similar proportion of development of AAA to Crohn's Disease might be expected (2.6% in the PI), this cannot be assumed. The sponsor should submit the AAA data to the TGA for evaluation when it becomes available.

Efficacy

Question 1: In Section 2.7.3.3 of the Summary of Clinical Efficacy reference is made to integrated efficacy analyses that relate to Studies M06-826 and M06-827. Where in this application is the Module 5 data set for the integrated efficacy analyses?

Evaluator comment on response:

The sponsor's response is satisfactory.

Question 2: What proportion of subjects screened at a) the pre-Amendment 3 period and b) post-Amendment 3 periods failed screening and therefore did not enter the DB randomisation phase? What are the reasons for screening failure in both the pre-Amendment 3 and post-Amendment 3 periods?

Evaluator comment on response:

The proportions of subjects who failed screening pre- and post-amendment 3 were similar, as were the reasons except there was proportionately more *C. difficile* positive failures in the pre-amendment 3 group compared with the post-amendment 3 group (12.7% versus 5.2%, respectively). This finding is unlikely to be clinically significant.

Question 3: What proportion of subjects screened to enter Study M06-827 failed screening? What reasons are given for screening failure?

[14] Note: Questions and evaluation of responses regarding the PI are beyond the scope of the AusPAR.

Evaluator comment on response:

The sponsor's response is satisfactory. The main reasons for screen failure, and their proportions, were similar to those listed in Table 2 of the sponsor's response.

Question 4: Where in this submission is the baseline data (particularly baseline demographics, disease history and disease activity data) for the pre-Amendment 3 population in Study M06-826 (that is, for the 93 subjects receiving adalimumab 160/80/40 and 92 placebo subjects)?

Evaluator comment on response:

While the pre-Amendment 3 and post-Amendment 3 (ITT-A3) populations were generally similar in terms of baseline demographics, comparison of disease characteristics in the adalimumab 160/80 groups revealed more severely ill subjects in the pre-Amendment 3 adalimumab group (higher mean Mayo score, higher Mayo subscore [10-12], higher proportion of subjects with pancolitis, C-reactive protein (CRP) and those who used corticosteroid at baseline). While untested, omission of this more severe group of subjects from the primary efficacy analysis has the potential to skew the overall findings towards a positive effect of adalimumab treatment versus placebo treatment in ulcerative colitis.[15]

Question 5: What are the results of the primary efficacy analyses (that is, at Week 8) for subjects recruited into Study M06-826 prior to Amendment 3 (by randomised treatment group)?

Evaluator comment on response:

The adalimumab 160/80 group did not demonstrate statistical separation from placebo at Week 8 (unlike the ITT-A3 analysis). The sponsor also provided pooled efficacy data from Studies 826 and 827 in support of its response, but this information was not useful except to emphasis the higher clinical remission rates achieved in anti-TNF naïve subjects (versus anti-TNF experienced subjects).

Question 6

No question 6 was submitted to the sponsor.

Question 7: Subjects randomised to receive adalimumab 160/80/40 mg in Study M06-826 had markedly higher withdrawal rates (approximately two-fold greater) in the pre-Amendment 3 group than the comparative post-Amendment 3 group in terms of adverse events, lack of efficacy and withdrawn consent. How does the sponsor reconcile this difference in withdrawal rate?

Evaluator comment on response:

Pre-Amendment 3 adalimumab 160/80 mg subjects had proportionately higher rates of 'withdrew consent' than the subjects in the corresponding post-Amendment 3 group. Pre-Amendment 3 subjects (placebo and adalimumab groups) had proportionately higher withdrawals secondary to AEs. These differences are not expected to greatly affect the overall efficacy results.

Question 8: How does the sponsor explain the lack of efficacy of the 80/40 mg adalimumab induction regimen in Study M06-826?

Evaluator comment on response:

The sponsor's response* is satisfactory.

[*In the response, the sponsor provided a detailed explanation in terms of biologic activity of the adalimumab 80/40 induction regimen, lower hospitalisation rates of adalimumab

[15] Sponsor comment: ITT-E analyses including all subjects were provided and the results were consistent with those for the ITT-A3 data set.

compared with placebo and simulations based on population PK model developed for adult UC patients in Study MO6-827. The sponsor determined the predicted mean adalimumab trough concentrations for the 80/40 ADA regimen were two-fold lower at Weeks 2 and 4 (i.e. the induction phase in UC) compared with the 160/80 ADA regimen. Hence the lack of Mayo-based efficacy of the 80/40 ADA induction regimen is explained by the lower ADA exposures achieved at this dose in the induction phase.]

Question 9: In respect of the early responder analyses, and to place these results in a more meaningful clinical context, the evaluator would like more information on the baseline characteristics of those subjects who responded early to adalimumab treatment in Study M06-827. In particular:

Was there a difference in baseline FM and PM scores between responders and non-responders?

Was the primary location of UC (pancolitis, descending colon etc) different between responders and non-responders?

Did the early responders receive more concomitant corticosteroids or immunomodulatory agents than non-responders?

Was there a marked difference in terms of gender or age distribution between early responders and non-responders?

In subjects who had prior anti-TNF exposure, were the early responders predominantly subjects who failed prior anti-TNF treatment due to 'lack of efficacy' or those who were 'intolerant' of such treatment?

Evaluator comment on response:

On the information provided, there were no meaningful differences between early responders to adalimumab treatment and non-responders in terms of full and partial Mayo scores, gender or age distribution or reasons for discontinuation of anti-TNF treatment prior to study entry. However, early responders were noted to have lower baseline CRP values (possibly indicative of less active disease), higher rates of pancolitis (and lower rates of descending colon disease) and greater use of corticosteroid at baseline. Furthermore, 71% anti-TNF naïve subjects achieved early response. Further investigation to identify the early responder group is required but anti-TNF naïve subjects appear to have a greater chance of a response to adalimumab treatment than those with prior anti-TNF exposure.

Safety

No questions.

GCP compliance

Question 1: Where in this submission are the detailed explanations why Sites 22635, 36809 and 27010 failed GCP requirements in Study M06-827?

Evaluator comment on response:

The sponsor's response is satisfactory.

Question 2: What are the mean serum adalimumab trough concentrations at Weeks 0, 2, 4, 8, 32 and 52 in Study M06-827 when the 24 non-GCP compliant subjects are included in the analyses (by randomised treatment group and dose)?

Evaluator comment to response:

Inclusion of the 24 non-GCP compliant subjects in the analyses did not affect the mean adalimumab trough concentration through the 52 week study period.

Question 3: What are the results of the primary efficacy endpoints and first ranked secondary endpoint when the 24 non-GCP compliant subjects are included in the primary analysis (ITT) set in Study M06-827?

Evaluator comment on response:

The results were consistent with the primary and secondary efficacy analyses in Study MO6-827.

Question 4: What was the baseline AAA, HACA and anti-TNF status for the non-GCP subjects (by randomised treatment group)?

Evaluator comment to response:

The 24 non-GCP subjects generally had lower rates in all three parameters compared with the ITT population and therefore their exclusion from the primary ITT population is unlikely to adversely affect the overall efficacy results.

Conclusion

The sponsor's responses to the Clinical Questions are generally considered satisfactory. There were no further clinical questions relating to this submission.

Final round benefit-risk assessment

Final round assessment of benefits

The clinical information submitted in the sponsor's response to the TGA request for further information does not change the assessment of benefits as described in the *First round assessment of benefits*, above.

Final round assessment of risks

The clinical information submitted in the sponsor's response to the TGA request for further information does not change the assessment of risks as described in the *First round assessment of risks*, above.

Final round assessment of benefit-risk balance

The clinical information submitted in the sponsor's response to the TGA request for further information does not change the assessment of the benefit-risk balance as described in the *First round assessment of benefit-risk balance*, above.

The benefit-risk balance for adalimumab, given the proposed usage, is only favourable for patients who have not had prior exposure to anti-TNF treatment and for those who respond early to adalimumab treatment.

Final round recommendation regarding authorisation

The clinical information submitted in the response to the TGA clinical questions does not change the assessment recommendation. Efficacy has not been clearly demonstrated in subjects who have had prior exposure to anti-TNF treatment and so approval is only recommended in ulcerative colitis for anti-TNF naïve subjects.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan (RMP) for adalimumab (Edition 10.0, November 2011) + Australian Specific Annex which was reviewed by the TGA's Office of Product Review (OPR).

A summary of ongoing safety concerns (all indications) is shown in Table 6.

Table 6. Summary of ongoing safety concerns (all indications)

Important identified risks	Serious infections including opportunistic infections, e.g., invasive fungal infections, parasitic infections, legionellosis, and TB Reactivation of hepatitis B Pancreatitis Lymphoma Hepatosplenic T-cell Lymphoma Leukemia Non-melanoma Skin Cancer Melanoma Demyelinating disorders (including MS, GBS, and optic neuritis) Immune reactions (including lupus-like reactions and allergic reactions) Sarcoidosis Congestive Heart Failure Myocardial Infarction Cerebrovascular Accident Interstitial Lung Disease Pulmonary embolism Cutaneous vasculitis SJS and erythema multiforme Worsening and new onset of Ps Haematologic disorders Intestinal perforation Intestinal strictures in CD Liver failure Elevated ALT levels Medication errors and maladministration

Important potential risks	Other malignancies (except lymphoma, HSTCL, leukemia, NMSC, and melanoma) Vasculitis (non-cutaneous) Progressive Multifocal Leukoencephalopathy Reversible Posterior Leukoencephalopathy Syndrome Amyotropic Lateral Sclerosis Colon cancer in UC patients Infections in infants exposed to adalimumab *in utero* Medication errors with paediatric vial Off-label use

Important missing information	Subjects with immune-compromised conditions (that is, subjects with HIV, post-chemotherapy, organ transplant) Subjects with a history of clinically significant drug or alcohol abuse Subjects with poorly controlled medical conditions such as uncontrolled diabetes or documented history of recurrent infections, unstable ischemic heart disease, CHF, recent cerebrovascular accidents; Subjects with history of listeriosis, history of histoplasmosis, active TB, persistent chronic or active infections requiring treatment with antibiotics, antivirals, or antifungals, history of viral hepatitis; Subjects with history of cancer, lymphoma, leukaemia, or lymphoproliferative disease; Subjects with history of neurologic symptoms suggestive of demyelinating disorders; Children < 18 years of age for PsA, AS, Ps, UC, SpA, HS, ERA, and uveitis indications; Children < 4 years of age for JIA and pedPs; Children < 6 years of age for pedCD and pedERA; Pregnant and lactating women; Subjects with renal or liver impairment; Patients taking concomitant biologic therapy; Long-term RA data beyond 5 years; Long-term JIA data beyond 7.5 years; Episodic treatment in JIA; Long-term AS data beyond 5 years; Short- and long-term SpA data; Short- and long-term pedERA data; Long-term PsA data beyond 3 years; Long-term Ps data beyond 6 years; Episodic treatment in Ps; Short- and long-term HS data; Long-term CD data beyond 5 years; Episodic treatment in CD; Long-term ped CD data beyond 2 years; Long-term UC data; Episodic treatment in UC; Short- and long-term uveitis data.

RA Rheumatoid Arthritis; JIA Polyarticular juvenile idiopathic arthritis; PsA Psoriatic arthritis; AS Ankylosing spondylitis; CD Crohn's disease; Ps Psoriasis; pedERA Paediatric Enthesitis-related Arthritis; SpA Spondyloarthritis; UC Ulcerative Colitis

Pharmacovigilance plan

Routine pharmacovigilance is planned for all important identified and potential risks. Routine activities, as described by the sponsor include monitoring through long-term clinical studies, registries and post-marketing surveillance activities.

Risk minimisation activities

Risk minimisation activities comprise routine activities, patient education and Healthcare Professional education.

Evaluator's assessment of the RMP

Table 7 summarises the issues raised during the OPR's evaluation of the RMP, the sponsor's responses to these issues and the second round evaluation of the sponsor's responses to questions raised by the RMP evaluator.

Table 7. Summary evaluation of RMP issues

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
1. Safety considerations may be raised by the clinical and non-clinical evaluators through the consolidated section 31 requests and/or the nonclinical and clinical Evaluation Reports respectively. It is important to ensure that the information provided in response to these includes consideration of the relevance for the Risk Management Plan, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, please provide information that is relevant and necessary to address the issue in the RMP.	*The safety profile of adalimumab is well established and no safety issues requiring further consideration were raised in the consolidated section 31 request. AbbVie has not yet received a copy of the clinical evaluation report.*	This is acceptable.
2. The induction and maintenance regimen for the proposed indication appears to be identical to the Crohn's disease indication which is presented in a table in the Pl. For ease of interpretation and for consistency it is recommended that the regimen for the proposed indication should also be presented in a table.	*The sponsor agrees to add a table for the induction and maintenance regimen for the proposed indication.*	This is acceptable.
3. Annex 3 of the RMP provides information on a further study regarding use of adalimumab in UC. Study Ml0-447 is a randomised, double-blind, placebo-controlled study to assess the efficacy and safety of two dosing regimens of adalimumab in Japanese subjects with moderately to severely active UC. However this study does not appear to	*It is correct that M10-447 is not in the Pharmacovigilance Plan of the RMP. The study is, however, listed in Annex 3 as one of the ongoing or completed clinical trial programs. Study M10-447 was conducted at Japanese sites in Japanese subjects as part of PMDA´s regulatory requirements to bridge clinical trial results from a local study in Japan to the*	This is acceptable.

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
be described in the Pharmacovigilance Plan. The sponsor should confirm the status of this study including if it is part of the Pharmacovigilance Plan or not.	*global clinical development results. The controlled portion of this study is completed and reported:* *<http://www.clinicaltrials.gov/ct2/show/NCT00853099?term=m10-447&rank=1>* *The open label continuation period is still ongoing and pharmacovigilance activities for this study are conducted at the Japanese affiliate level.*	
4. In their s31 response the sponsor should provide further detail of the education programme for Australia including whether it is already in use, draft education materials and a distribution plan.	The sponsor has provided further detail and draft versions of the educational materials.	The current and planned activities as outlined in the s31 response are acceptable from a RMP standpoint. Such detail should be included in the Australian-specific annex when it is next updated.
5. The RMP states that "affiliates are implementing country-specific evaluations". The sponsor should provide more detail on the Australian-specific evaluation of the effectiveness of the education programme.	*Abbvie is currently developing an evaluation tool to assess the effectiveness of the Australian educational programme. An online survey will be conducted by an independent third party vendor each year for 2 years after approval of new indications. Participants will be a representative cross section of potential Humira prescribers. Further evaluation will be conducted as appropriate and the educational programme modified as necessary.*	This approach is considered acceptable. Once developed, further detail of this assessment should be included in an update to the risk minimisation section of the Australian-specific annex.

Summary and recommendations

There are no outstanding issues in relation to the RMP for this submission.

Suggested condition of registration:

- Implement RMP for adalimumab (edition 10.0, November 2011) + Australian-specific Annex (undated) and any future updates as a condition of registration.
- Provide Periodic Safety Update Reports (PSURs) in accordance with current regulatory requirements.

VI. Overall conclusion and risk/benefit assessment

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

Background

The sponsor has applied to extend the indications for Humira (adalimumab) 40 mg solution for injection in vial, pen and prefilled syringe and 20 mg solution for injection in pre-filled syringe.

Note: While the 20 mg presentation is used in a paediatric population, it is approved for the same indications as the 40 mg presentations.

The proposed new indication is:

> *Humira is indicated for the treatment of moderate to severe ulcerative colitis in patients who have had an inadequate response to conventional therapy or who are intolerant to or have medical contraindications for such therapies.*

Humira (adalimumab) is a recombinant human immunoglobulin (IgG1) monoclonal antibody containing only human peptide sequences. Adalimumab binds to TNF and neutralises the biological function of TNF by blocking its interaction with the p55 and p75 cell surface TNF receptors. Adalimumab also modulates biological responses that are induced or regulated by TNF.

Ulcerative colitis is a chronic, relapsing, immune-mediated, inflammatory disease of the colon that always affects the rectum, extends proximally to a variable extent, and is characterized by a relapsing and remitting course. As noted in *Therapeutic Guidelines (Gastroenterology)*[16], the aims of treatment are to change the natural history of the disease and its long-term outcomes, rather than simply to achieve symptomatic control. Currently treatments for severe UC include: cyclosporine, azathioprine, mercaptopurine, methotrexate and infliximab (Remicade). At the time this overview was written, infliximab was the only TNF inhibitor currently approved for management of UC.

Quality

There was no requirement for a quality evaluation in a submission of this type.

[16] Gastrointestinal Expert Group. Therapeutic guidelines: gastrointestinal. Version 5. Melbourne: Therapeutic Guidelines Limited; 2011.

Nonclinical

There was no requirement for a nonclinical evaluation in a submission of this type.

Clinical

Pharmacology

The PK of adalimumab are known. In this submission mean serum trough levels of adalimumab in subjects enrolled in the pivotal efficacy and safety study for UC (Study 827) were compared with those seen in subjects with Crohn's disease given the same dose regimen. The results were similar at the end of the induction period (Week 4) and the maintenance period (Week 52). In both populations the mean trough concentration of adalimumab reduced from Week 4 to Week 52. At the end of Week 4 the mean (±SD) serum concentration in the DB adalimumab 160/80/40 eow treatment group, who remained in the eow group (n=160), was 12.3 µg/mL (±5.45). At the end of the maintenance period (Week 52), 101 subjects from this group had a mean (±SD) serum adalimumab trough concentration of 7.97 µg/mL (±6.09).

Trough results were also assessed by prior exposure to anti-TNF agents. The mean trough concentration of adalimumab was similar for anti-TNF naïve and anti-TNF experienced subjects at the end of the induction period (Week 4) however at Week 8 the mean adalimumab trough concentration was 9.6% higher in the anti-TNF naïve group. No comparative results at Week 52 were provided. Trough levels of adalimumab were also compared by presence/absence of measurable HACA. Results strongly suggest the presence of HACA is associated with reduced adalimumab concentration.

In Study 827 there were 19 subjects (3.9%) assessed as anti-adalimumab antibody + (AAA+) during the entire study (3.7% [n=8] in anti-TNF experienced subjects and 4.1% [n=11] in anti-TNF naïve subjects, respectively). However adalimumab interferes in the assay by binding to AAA and prevents AAA from binding to capture and detection antibody. Therefore, samples with adalimumab levels above 2 µg/ mL) were not analysed for AAA. The assessment may therefore not reflect the real level of antibody development to adalimumab.

In those subjects who achieved clinical remission in Study 827 in the DB adalimumab 160/80/40 treatment group, mean serum adalimumab concentrations were consistently higher than non-remitters at all time points, despite lower baseline levels (Table 8).

Table 8. Summary of serum adalimumab trough concentrations (µg/mL) by remission status at Week 52 in subjects with ulcerative colitis in DB ADA 160/80/40 eow treatment group

	Mean ± SD (Min-Max), N_{nmiss}					
	Week					
Treatment Groups	0	2	4	8	32	52
40 mg eow Subjects Who were Remitters (N = 43)	0.168 ± 0.953 (0.000 – 6.02), 40	13.2 ± 4.30 (4.05 – 23.1), 41	14.1 ± 6.03 (0.000 – 25.6), 43	11.4 ± 5.15 (0.000 – 22.8), 41	10.6 ± 5.64 (0.000 – 26.9), 39	10.8 ± 7.45 (0.000 – 39.3), 39
40 mg eow Subjects Who were Non-Remitters (N = 153)	0.181 ± 1.68 (0.000 – 18.8), 126	11.4 ± 3.75 (0.000 – 19.9), 126	11.7 ± 5.08 (0.000 – 26.2), 117	8.49 ± 4.35 (0.000 – 21.8), 110	6.95 ± 3.98 (0.000 – 18.1), 70	6.18 ± 4.22 (0.000 – 16.1), 62

N_{nmiss} = number of non-missing observations

Clearance and volume of distribution of adalimumab are consistent with that seen with adalimumab when used for other indications. The clinical evaluator has stated that there is no need for dose adjustment based on bodyweight, AAA positive status and albumin concentration, or co-administration of adalimumab with the immunosuppressant agents, methotrexate, azathioprine and 6-mercaptopurine. Population-PK modelling supported

the proposed split-dose alternative induction regimen of 160 mg given over two days and then 80 mg at 14 Days and 40 mg at 28 Days.

Efficacy

Two pivotal studies were included in the submission: Study 826 (induction of remission study) and Study 827 (induction and maintenance of remission study). Study 223, an open-label extension study is ongoing.

Study 827 was a 52 week, Phase III randomised, DB, placebo-controlled trial with a 21 day screening period prior to randomisation (baseline), followed by an 8 week induction period, a 44 week maintenance period and a 70 day follow-up period. Rescue open-label adalimumab was permitted and on study completion patients could enrol in the extension study. The primary objective was to assess the efficacy and safety of adalimumab for the induction and maintenance of clinical remission in subjects with moderate to severely active UC.

The major inclusion criteria were that subjects be aged ≥ 18 years and have active UC with a Mayo score of 6 to 12 points and endoscopy subscore of 2 to 3 points, despite concurrent treatment with at least one of the following (oral corticosteroids or immunosuppressants or both as defined below):

- Stable oral corticosteroid dose (prednisone ≥20 mg/day or equivalent) for at least 14 days prior to baseline or stable oral corticosteroid dose (prednisone <20 mg/day) for at least 40 days prior to baseline and/or
- At least a consecutive 90 day course of azathioprine or 6-mercaptopurine prior to baseline, with a dose of azathioprine ≥1.5mg/kg/day or 6-mercaptopurine ≥1mg/kg/day (rounded to the nearest available tablet formulation), or a dose that is the highest tolerated by the subject (for example, due to leukopenia, elevated liver enzymes, nausea) during that time. Subject must have been on a stable dose for at least 28 days prior to baseline.

Previous use of anti-TNF agents other than adalimumab was permitted if the subject had discontinued its use due to a loss of response or intolerance to the agent. Subjects continued taking aminosalicylates, azathioprine or 6-mercaptopurine, but doses remained unchanged throughout the study. No dose adjustments of UC-related concomitant treatments were allowed, except for corticosteroid taper between Weeks 8 and 52 and a dose decrease of other UC-related concomitant treatments in the event of treatment-related toxicities (for example, leukopenia or elevated liver enzymes) considered moderate to severe in the opinion of the Investigator.

During the induction phase, subjects were randomised to receive either adalimumab 160/80/40 or placebo by SC injection. Each adalimumab subject received 160 mg at Week 0 and 80 mg at Week 2, and 40 mg eow thereafter, starting at Week 4. Subjects assigned to placebo treatment received matching placebo. At or after Week 10, subjects who met the criteria for inadequate response could switch to open-label adalimumab 40 mg eow beginning at Week 12. Inadequate response was defined as:

- Partial Mayo (PM) score ≥ their baseline score on two consecutive visits at least 14 days apart (for subjects with a PM score of 4 to 7 at baseline);
- PM score ≥7 on two consecutive visits at least 14 days apart (for subjects with a PM score of 8 or 9 at baseline).

Subjects who demonstrated an inadequate response at two consecutive visits at least 14 days apart while on open-label adalimumab 40 mg eow were permitted to dose escalate to adalimumab 40 mg ew. Subjects with persistent inadequate response while on adalimumab 40 mg ew could discontinue from the study at the Investigator's discretion.

Clinical response was assessed using the Mayo scoring system as shown in Table 4, above.

This system scores severity of UC on a scale from 0 to 12 with higher scores equating to more severe disease. The primary efficacy endpoints were 1) the proportion of subjects who achieved clinical remission at Week 8 and 2) the proportion of subjects who achieved clinical remission at Week 52. Clinical remission required a Mayo score of ≤ 2 with no subscore >1. Sustained remission (from Weeks 8 to 52) and clinical response at Week 8 and Week 52 were secondary endpoints. Clinical response was defined as a reduction in Mayo score of ≥3 points and ≥ 30% from baseline plus a reduction in rectal bleeding subscore of ≥1 or an absolute rectal bleeding subscore of 0 or 1.

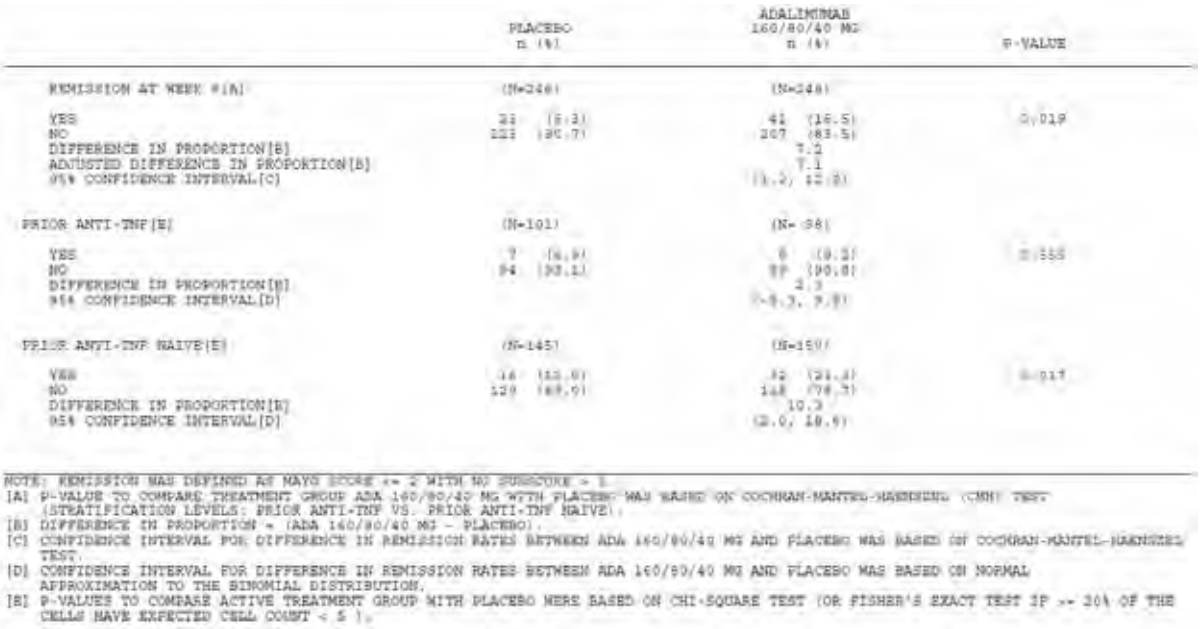
A total of 494 subjects were included in the ITT analysis with 248 receiving adalimumab and 246 placebo. Prior to Week 8, 11.9% subjects in the ITT analysis set discontinued treatment (9.3% in the adalimumab group and 14.6% in the placebo group, respectively). At Week 52, 37.9% (n=94) subjects in the adalimumab group and 46.7% (n=115) in the placebo group had discontinued prematurely. Only 82 (33%) subjects given DB adalimumab continued with 40 mg eow to Week 52 and 56 (23%) subjects given placebo continued with blinded placebo to Week 52.

All subjects had inflammatory bowel disease, with subjects in the ITT analysis set having a mean duration of UC of 8.3 years, with the primary disease site pancolitis (48.6%). The mean baseline Mayo score was 8.9, indicative of moderate to severe disease activity. Subscores were similar between groups. Most subjects were anti-TNF naïve (59.7%) with similar treatment histories in the active and placebo groups.

At Week 8 clinical remission was reported for 16.5% of subjects given adalimumab versus 9.3% given placebo (p=0.019; NNT = 14). At Week 52 clinical remission was reported for 17.3% given adalimumab versus 8.5% given placebo (p=0.004; NNT = 11).

Clinical remission rates were reduced in subjects with prior exposure to anti-TNF agents at both Week 8 and Week 52 in the placebo and adalimumab treatment groups. Statistical significance for difference in remission rates between adalimumab and placebo was not achieved for the anti-TNF experienced subgroup at either Week 8 or Week 52 (see Table 9 and Table 10, below). For subjects with no prior experience of anti-TNF agents clinical remission at Week 8 was achieved in 21.3% of subjects given adalimumab and 11.0% given placebo, compared with 9.2% given adalimumab and 6.9% given placebo who were anti-TNF experienced. At Week 52 subjects with no prior experience of anti-TNF agents clinical remission was achieved in 22% of subjects given adalimumab and 12.4% given placebo, compared with 10.2% given adalimumab and 3.0% given placebo who were anti-TNF experienced.

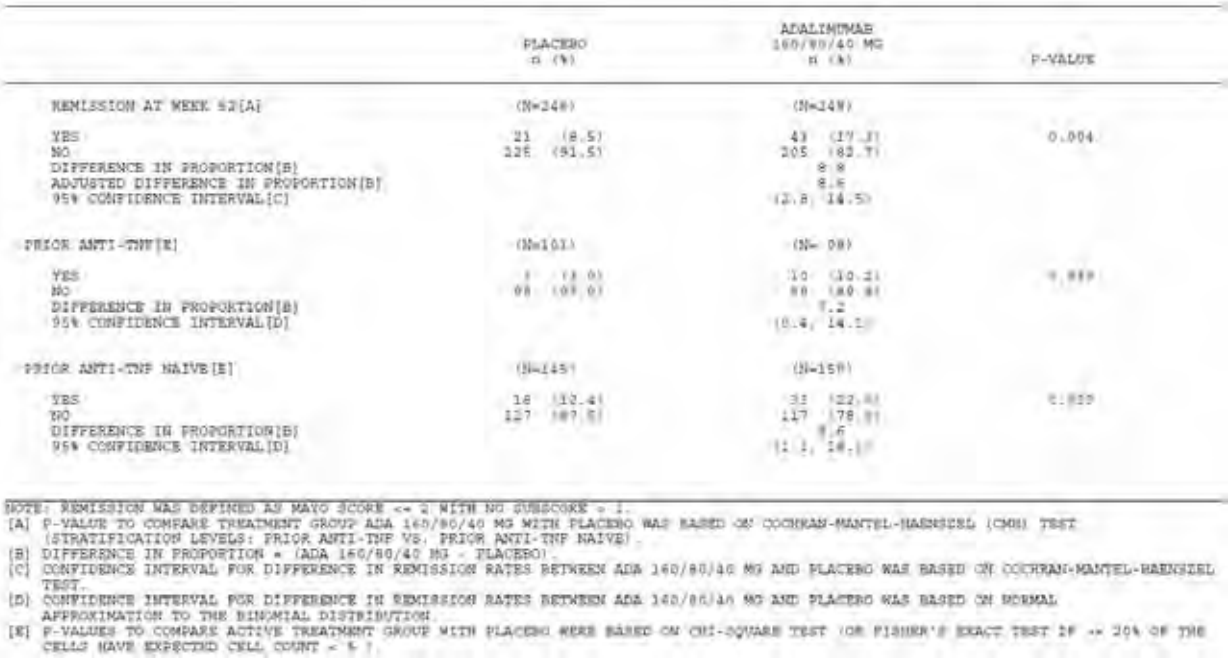
Table 9. Subjects in remission per Mayo Score at Week 8 (NRI; ITT Analysis Set)



	PLACEBO n (%)	ADALIMUMAB 160/80/40 MG n (%)	P-VALUE
REMISSION AT WEEK 8[A]	(N=248)	(N=248)	
YES	21 (8.5)	41 (16.5)	0.019
NO	227 (91.5)	207 (83.5)	
DIFFERENCE IN PROPORTION[B]		7.9	
ADJUSTED DIFFERENCE IN PROPORTION[B]		7.1	
95% CONFIDENCE INTERVAL[C]		(1.2, 12.8)	
PRIOR ANTI-TNF[E]	(N=101)	(N= 98)	
YES	7 (6.9)	6 (6.1)	0.555
NO	94 (93.1)	92 (93.9)	
DIFFERENCE IN PROPORTION[B]		-0.8	
95% CONFIDENCE INTERVAL[D]		(-8.3, 7.0)	
PRIOR ANTI-TNF NAIVE[E]	(N=145)	(N=150)	
YES	14 (13.0)	35 (23.3)	0.017
NO	129 (89.0)	115 (76.7)	
DIFFERENCE IN PROPORTION[B]		10.3	
95% CONFIDENCE INTERVAL[D]		(2.0, 18.6)	

NOTE: REMISSION WAS DEFINED AS MAYO SCORE <= 2 WITH NO SUBSCORE > 1.
[A] P-VALUE TO COMPARE TREATMENT GROUP ADA 160/80/40 MG WITH PLACEBO WAS BASED ON COCHRAN-MANTEL-HAENSZEL (CMH) TEST (STRATIFICATION LEVELS: PRIOR ANTI-TNF VS. PRIOR ANTI-TNF NAIVE).
[B] DIFFERENCE IN PROPORTION = (ADA 160/80/40 MG - PLACEBO).
[C] CONFIDENCE INTERVAL FOR DIFFERENCE IN REMISSION RATES BETWEEN ADA 160/80/40 MG AND PLACEBO WAS BASED ON COCHRAN-MANTEL-HAENSZEL TEST.
[D] CONFIDENCE INTERVAL FOR DIFFERENCE IN REMISSION RATES BETWEEN ADA 160/80/40 MG AND PLACEBO WAS BASED ON NORMAL APPROXIMATION TO THE BINOMIAL DISTRIBUTION.
[E] P-VALUES TO COMPARE ACTIVE TREATMENT GROUP WITH PLACEBO WERE BASED ON CHI-SQUARE TEST (OR FISHER'S EXACT TEST IF >= 20% OF THE CELLS HAVE EXPECTED CELL COUNT < 5).

Table 10: Subjects in remission per Mayo Score at Week 52 (NRI; ITT Analysis Set)



	PLACEBO n (%)	ADALIMUMAB 160/80/40 MG n (%)	P-VALUE
REMISSION AT WEEK 52[A]	(N=248)	(N=248)	
YES	21 (8.5)	43 (17.3)	0.004
NO	226 (91.5)	205 (82.7)	
DIFFERENCE IN PROPORTION[B]		8.9	
ADJUSTED DIFFERENCE IN PROPORTION[B]		8.6	
95% CONFIDENCE INTERVAL[C]		(2.8, 14.5)	
PRIOR ANTI-TNF[E]	(N=101)	(N= 98)	
YES	1 (1.0)	10 (10.2)	0.009
NO	98 (99.0)	88 (89.8)	
DIFFERENCE IN PROPORTION[B]		9.2	
95% CONFIDENCE INTERVAL[D]		(3.4, 14.1)	
PRIOR ANTI-TNF NAIVE[E]	(N=145)	(N=150)	
YES	20 (13.8)	33 (22.0)	0.059
NO	125 (86.2)	117 (78.0)	
DIFFERENCE IN PROPORTION[B]		8.2	
95% CONFIDENCE INTERVAL[D]		(1.1, 16.1)	

NOTE: REMISSION WAS DEFINED AS MAYO SCORE <= 2 WITH NO SUBSCORE > 1.
[A] P-VALUE TO COMPARE TREATMENT GROUP ADA 160/80/40 MG WITH PLACEBO WAS BASED ON COCHRAN-MANTEL-HAENSZEL (CMH) TEST (STRATIFICATION LEVELS: PRIOR ANTI-TNF VS. PRIOR ANTI-TNF NAIVE).
[B] DIFFERENCE IN PROPORTION = (ADA 160/80/40 MG - PLACEBO).
[C] CONFIDENCE INTERVAL FOR DIFFERENCE IN REMISSION RATES BETWEEN ADA 160/80/40 MG AND PLACEBO WAS BASED ON COCHRAN-MANTEL-HAENSZEL TEST.
[D] CONFIDENCE INTERVAL FOR DIFFERENCE IN REMISSION RATES BETWEEN ADA 160/80/40 MG AND PLACEBO WAS BASED ON NORMAL APPROXIMATION TO THE BINOMIAL DISTRIBUTION.
[E] P-VALUES TO COMPARE ACTIVE TREATMENT GROUP WITH PLACEBO WERE BASED ON CHI-SQUARE TEST (OR FISHER'S EXACT TEST IF >= 20% OF THE CELLS HAVE EXPECTED CELL COUNT < 5).

21 subjects (8.5%) maintained remission throughout the maintenance period, compared with 10 subjects (4.1%) in the placebo group (p=0.047). Approximately half the subjects who remitted at Week 8 had sustained clinical remission at Week 52 (51.2% (n=21/41) adalimumab subjects and 43.5% (n=10/23) placebo subjects). Of those subjects who completed DB treatment, 25.6% (n=21/82) adalimumab subjects had sustained clinical remission compared with 17.9% (n=10/56) placebo subjects.

At Week 12, 54.9% (n=135/246) and 46.8% (n=116/248) subjects in the DB placebo and DB adalimumab groups, respectively, had inadequate clinical response and switched to open-label adalimumab, that is, approximately half the study population required rescue treatment by Week 12. Of these 251 subjects, 34.1% (n=84) and 27.4% (n=68) in the placebo and adalimumab groups, respectively, dose escalated from 40 mg eow to 40 mg ew, that is, approximately one quarter of adalimumab-treated subjects required dose-escalation.

In subjects who dose-escalated to open-label adalimumab 40 mg ew, a greater proportion of subjects previously randomised to the placebo group achieved complete remission at Week 52 compared with the adalimumab group (34.1% versus 12.2%, respectively) however, 47.6% (n=40/84) of randomised placebo subjects and 39.7% (n=27/68) of randomised adalimumab subjects had missing data. Hence, meaningful conclusions could not be made from that comparison.

Clinical response assessments were included as secondary endpoints with results as shown below:

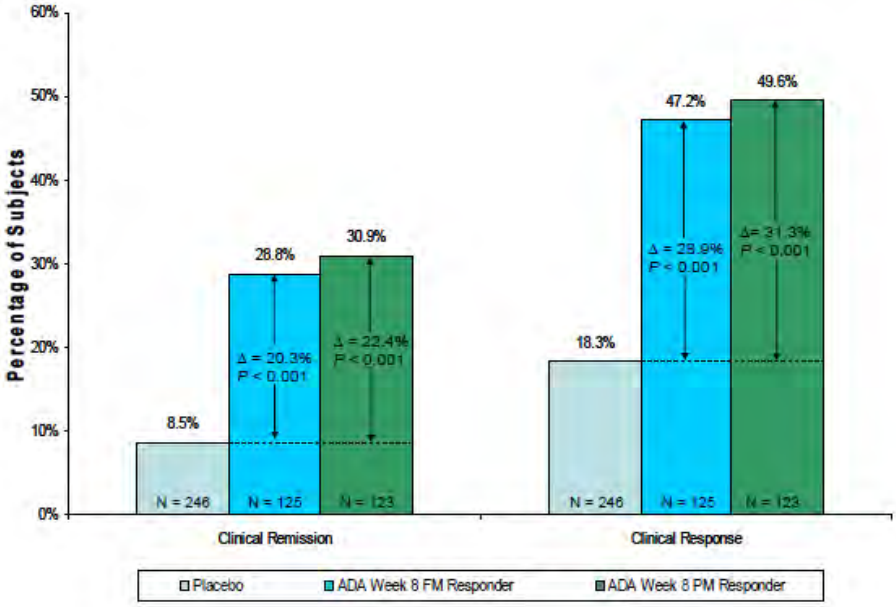
Table 11. Clinical response assessments

	Placebo	Adalimumab	p
Clinical response Week 8	34.6%	50.4%	<0.001
Clinical response Week 52	18.3%	30.2%	0.002
Sustained clinical response Week 8-52	12.2%	23.8%	<0.001

Subjects without prior anti-TNF experience had higher clinical responses for both the placebo (naïve versus experienced) and adalimumab (naïve versus experienced) comparisons.

Post-hoc analyses to determine whether early clinical response was predictive of clinical remission or response at Week 52 is discussed in the CER (see Attachment 2 of this AusPAR). The sponsor undertook an early responder analysis and the inclusion in the proposed indication to discontinue adalimumab treatment in patients who fail to respond before 8 weeks is based on this early responder report. Among subjects given adalimumab who had a clinical response at Week 8, by Week 52 around 48% of these subjects met the criteria for clinical response and 30% met the criteria for clinical remission (Figure 2).

Figure 2. Clinical remission and response per Full Mayo score at week 52 among subjects randomised to adalimumab who achieved CRESP per FM and PM score at Week 8 versus all subjects randomised to placebo (ITT NRI)



Note: According to the NRI method, all missing remission and response values were considered to be nonremission and nonresponse. Subjects who switched to OL adalimumab were considered to be nonremitters and nonresponders at and after the time of the switch.

Study 826 was a double-blind, randomised, placebo-controlled study. After the induction period maintenance treatment was open-label adalimumab for all subjects to Week 52. The primary objective was to assess the efficacy and safety of the two dosing regimens of adalimumab for the induction of clinical remission in subjects with moderate to severely active UC. The secondary objective was to provide supportive information on the maintenance of CR during the open-label phase of the study. The protocol was amended after commencement of the study to include a lower dose (80/40) induction regimen so that for the primary analysis there were 3 induction groups 160/80/40, 80/40 and placebo. The study used the same efficacy measures as Study 827. All subjects were anti-TNF naïve. The primary efficacy measure was the proportion of subjects in clinical remission at Week 8 and the primary comparisons was of the adalimumab 160/80/40 versus placebo. In efficacy analyses, the NRI method was used for missing or incomplete data. Efficacy analyses for sensitivity were performed with missing or incomplete data handled as observed case and LOCF method.

A total of 390 subjects were included in the primary ITT population (130 each to adalimumab 160/80/40; adalimumab 80/40; and placebo). The adalimumab 160/80/40 regimen demonstrated statistically significantly higher remission rates against placebo in the primary ITT analysis (18.5% versus 9.2%, p=0.031), with similar findings in the sensitivity analyses. Adalimumab 80/40 regimen consistently failed to demonstrate statistical superiority against placebo with clinical remission at Week-8 of 10.0%. Fewer subjects in the adalimumab 160/80/40 treatment group required dose escalation (from 40 mg eow to 40 mg weekly) as compared to the adalimumab 80/40 or placebo groups (22.9% versus 30.0% and 31.1%, respectively).

Sustained clinical remission from Weeks 8–52 was assessed and results are shown in Table 12. During this open-label period all treatment groups received adalimumab and tended to have higher clinical remission rates at Week 52 compared with Week 8. Sustained remission rates were <10% in all groups. The study report also showed sustained clinical response Week 8 to 52 (an unranked secondary endpoint) and this was

achieved by approximately 30% of subjects, similar to that achieved in anti-TNF naïve subjects in Study 827.

Table 12. Subjects with remission per Mayo Score at Weeks 8 & 52 (ITT-E NRI and Dose Escalation set)

	Number (%) of Subjects by Randomization Group				
	Placebo[a]				
Analysis Set Visit	Adalimumab 40	Adalimumab 160/80/40	All Placebo	Adalimumab 80/40	Adalimumab 160/80/40
ITT-E (NRI)[b]	**N = 130**	**N = 92**	**N = 222**	**N = 130**	**N = 223**
Week 8	12 (9.2)	4 (4.3)	16 (7.2)	13 (10.0)	35 (15.7)
Week 52	34 (26.2)	24 (26.1)	58 (26.1)	26 (20.0)	55 (24.7)
Weeks 8 and 52	7 (5.4)	3 (3.3)	10 (4.5)	7 (5.4)	21 (9.4)
ITT-E (mNRI)[c]	**N = 130**	**N = 92**	**N = 222**	**N = 130**	**N = 223**
Week 52	41 (31.5)	25 (27.2)	66 (29.7)	30 (23.1)	62 (27.8)
Dose escalators (NRI)[d]	**N = 49**	**N = 20**	**N = 69**	**N = 39**	**N = 51**
Week 52	7 (14.3)	1 (5.0)	8 (11.6)	4 (10.3)	7 (13.7)

a. Subjects randomized to placebo switched to OL adalimumab at Week 8 or Week 12 after visit evaluations were performed.

b. According to the NRI analysis method, all missing response (or remission) values and values after dose escalation were imputed as non-response (or non-remission).

c. According to the mNRI method, only missing values were imputed as non-response (or non-remission).

d. According to the NRI analysis method, for dose escalators, only subjects who increased dosing to adalimumab 40 mg weekly were included and missing values were imputed as non-response (or non-remission).

Cross reference: Table 14.2__11.1, Table 14.2__32.1, Table 14.2__40.1

Safety

As noted by the clinical evaluator, anti-TNF experienced subjects had higher rates of AEs of particular interest compared with anti-TNF naïve subjects, including higher rates of worsening UC/flare. This was consistent with reduced efficacy in this these subjects. Adalimumab was more toxic and less efficacious in anti-TNF experienced subjects compared with anti-TNF naïve subjects. However, these subjects may have had more treatment resistance or more severe disease at baseline (although there were no obvious differences in baseline disease characteristics). The safety and efficacy results may also, in part, reflect in the lower serum trough levels achieved in the anti-TNF experienced subjects.

Clinical evaluator's recommendation

The clinical evaluator recommendation that: efficacy has not been clearly demonstrated in subjects who have had prior exposure to anti-TNF treatment and so approval is only recommended in ulcerative colitis for anti-TNF naïve subjects.

Risk management plan

A satisfactory RMP has been agreed. The RMP reviewer recommended that the dosage and administration sub-section for UC be presented in tabular form, similar to the form used to present dosing information for the CD indication. The RMP reviewer recommended the following be a condition of registration:

- Implement RMP for Adalimumab (edition 10.0, November 2011) + Australian-specific Annex (undated) and any future updates as a condition of registration.

Risk-benefit analysis

Delegate considerations

The trough levels of adalimumab in adults with UC were similar to those seen in subjects with CD given the same dose regimen. PK sampling shows that over 12 months the mean trough levels of adalimumab decline, particularly in subjects who have HACA or AAA antibodies. Subjects with prior experience of an anti-TNF agent also had a reduction in mean trough adalimumab serum concentration. The assay for assessing AAA may not have given accurate results due to limitations in the trough levels of adalimumab that could be assessed for AAA.

In the pivotal efficacy studies the primary efficacy measures related to clinical remission rather than clinical response.[17] Clinical remission and clinical response were defined as in the clinical trials of infliximab in UC. However, the primary efficacy measure in the infliximab studies[18], as described in the PI for Remicade (infliximab), was clinical response at Week 8 rather than clinical remission at Week 8. While there are limitations in cross-study comparisons such as this, it is reasonable to note that with infliximab clinical response at Week 8 was achieved by 33.2% of subjects given placebo compared with 66.9% given the approved infliximab dose regimen. The corresponding clinical response rates for adalimumab in Study 827 were 34.6% for placebo and 50.4% for adalimumab. Clinical remission rates at Week 8 were 10.2% for placebo and 36.4% for infliximab compared with 9.3% for placebo and 16.5% for adalimumab.

From the above comparison it appears that adalimumab is somewhat less effective than infliximab in the treatment of UC. However, around 40% of subjects in the pivotal study for adalimumab had prior exposure to an anti-TNF agent. A better comparison may be with the anti-TNF naïve subgroup from Study 827 and with Study 826. Clinical remission at Week 8 for anti-TNF naïve subjects in Study 827 was 21.3%. This is still lower than the 36.4% achieved with infliximab. Sustained clinical response from Week 8 to 52 was achieved by around 30% of anti-TNF naïve subjects across the two adalimumab studies. Comparative data with infliximab is not available because efficacy was reported to Week 30 in the PI for Remicade.

The clinical evaluator has noted that statistical superiority over placebo for clinical remission at Week 8 was not met for the anti-TNF experienced subgroup. These subjects tended to have poorer outcomes for all efficacy assessments. Placebo recipients who were anti-TNF experienced also tended to do worse than placebo recipients who were anti-TNF naïve, suggesting part of the effect is due to more severe disease, making it less likely that clinical remission would be achieved.

The cessation of treatment in subjects who had not achieved a clinical response at Week 8 was strongly supported by the post-hoc analysis.

Conclusions

Efficacy of the proposed dose regimen of adalimumab for the treatment of UC in adults has been demonstrated. Limited cross-study comparisons suggest efficacy is not as great as with infliximab, the only other anti-TNF agent approved for treatment of UC. Adalimumab has an advantage in that it can be self-administered rather than requiring administration in a hospital or clinic. Adalimumab also has safety advantages over infliximab in that it has fewer serious hypersensitivity reactions.

[17] Sponsor comment: this is in accordance with the adopted guideline CHMP/EWP/18463/2006
[18] These studies were conducted before guideline CHMP/EWP/18463/2006 was in effect

The sponsor has not proposed limiting the UC indication to adults[19] or to anti-TNF naïve patients though the data suggest these restrictions should be considered. Restricting use beyond 8 weeks to subjects who attain a clinical response at Week 8 of treatment would result in many fewer individuals receiving long term treatment without a clinically significant benefit. This is particularly important given the toxicity associated with all anti-TNF agents including adalimumab.

The Delegate proposed to restrict the indication to adults and to restrict treatment beyond 8 weeks to patients who achieve either a full or partial clinical response according to the Mayo scoring system at Week 8 after commencing treatment.

The clinical evaluator noted that efficacy has not been clearly demonstrated in subjects who have had prior exposure to anti-TNF treatment and so recommended approval only for anti-TNF naïve subjects. In the USA the UC indication includes the following statement: *The effectiveness of HUMIRA has not been established in patients who have lost response to or were intolerant to TNF blockers.*

The Delegate considered the above information should be prominently displayed in the *Clinical trials* section of the PI rather than be included in the indication because the subgroup analysis of anti-TNF experienced subjects was a secondary analysis. The primary analysis for efficacy demonstrated statistical superiority of adalimumab over placebo for adults with moderate to severe ulcerative colitis. In addition, the early responder analysis supported efficacy in the subgroup with clinical response at Week 8 regardless of prior anti-TNF experience.

Proposed action

The Delegate proposed to approve the use of adalimumab (Humira) for the following indication:

> *Ulcerative Colitis:*
>
> *Humira is indicated for the treatment of moderate to severe ulcerative colitis in <u>adult</u> patients who have had an inadequate response to conventional therapy or who are intolerant to or have medical contraindications for such therapies.*
>
> *<u>Patients who have not shown a clinical response during 8 weeks of treatment should be withdrawn from treatment (see CLINICAL TRIALS).</u>*

The Delegate also proposed to implement several revisions to the PI. Details of these are beyond the scope of the AusPAR.

Request for ACPM advice

The Delegate sought general advice from the Advisory Committee on Prescription Medicines (ACPM) on the pharmacology, efficacy and safety issues that have become apparent from review of the submission. In addition, the Delegate requested the ACPM provide specific advice on the following:

1. Should the indication reflect the poor efficacy in anti-TNF experienced patients with ulcerative colitis?
2. Should the *Indications* or *Dosage and Administration* section of the PI qualify what is meant by "clinical response" that is, provide the criteria used to assess clinical response used in the clinical trials and recommend Mayo scoring system assessments at baseline and at 8 weeks after commencing treatment?

[19] Note: this application did not specifically request the inclusion of paediatric patients.

3. Does the Committee consider that the revised *Clinical Trials* section of the PI provides an adequate description of the efficacy results for anti-TNF experienced patients and patients who did not have a clinical response at the first 8 weeks of treatment?
4. The 20 mg presentation is intended for paediatric use and no dose recommendations are available for treatment of UC in a paediatric population. Should the 20 mg presentation be excluded from approval for this indication?

Response from sponsor

AbbVie Pty Ltd agreed with the Delegate's proposed action as stated in the Delegate's Overview (Above). The sponsor's responses to specific matters raised in the Overview are presented below.

1. The Delegate suggests the statement that efficacy has not been established in anti-TNF experienced patients should be "prominently displayed" in the Clinical Trials section rather than in the indication.

The sponsor agrees to include such a statement in the *Clinical Trials* section of the PI.

2. The Delegate suggests the statement that treatment should not be continued beyond 8 weeks if patients have not shown a clinical response by that time should be added to the indication.

As this is a dosing issue, the sponsor suggests that this statement be included in the dosing section of the PI. The indication should remain simple and globally consistent. Humira has also been shown to be effective with statistical superiority over placebo in the population of patients that included those who did not respond by Week 8 (Full ITT set); however, efficacy is greater in Week 8 responders. Hence the recommendation in the dosing section is suggested, so as to enhance the benefit-risk balance. Prominently adding this statement to the indication might even imply a safety issue. In addition, to maintain consistency within the Australian PI, the sponsor would like to point out that a similar statement also appears in the dosing recommendation for Crohn's disease without any addition to the indication (*"Patients usually respond within the induction phase. However, if a patient does not show any response, available data do not sufficiently support further Humira treatment"*).

3. A question posed to the ACPM is whether the PI should include a definition of "clinical response" and recommend applying the Mayo scoring system.

Of note, the Mayo scoring system includes clinical signs and symptoms (such as number of stools, rectal bleeding) that physicians would already be discussing with patients without the formal recommendation to apply a scoring system normally meant for use in clinical trials. Thus, this addition to the PI would not appear to provide useful information to the prescribing physician. In addition, this recommendation would create indications (for example, Crohn's Disease Activity Index (CDAI) for Crohn's disease, Psoriasis Severity and Area Index (PASI) for psoriasis, American College of Rheumatology (ACR) for rheumatoid arthritis). Thus, to maintain consistency with the other indications in the Humira PI, as well as to be consistent with other UC indications (for example, infliximab), the sponsor disagrees with this recommendation.

4. Another question posed to the ACPM is whether the 20 mg formulation should be excluded from approval.

This application is for adult patients with ulcerative colitis, and the 20 mg formulation is for use in another paediatric indication.

The sponsor's comments regarding proposed revisions to the PI are beyond the scope of the AusPAR.

Advisory committee considerations

The Advisory Committee on Prescription Medicines (ACPM) having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The ACPM, taking into account the submitted evidence of efficacy and safety, agreed with the Delegate and considered Humira (containing adalimumab) to have an overall positive benefit–risk profile for the Delegate's amended indication;

> *Humira is indicated for the treatment of moderate to severe ulcerative colitis in adult patients who have had an inadequate response to conventional therapy or who are intolerant to or have medical contraindications for such therapies.*
>
> *Patients who have not shown a clinical response during 8 weeks of treatment should be withdrawn from treatment (see CLINICAL TRIALS).*

The ACPM agreed with the Delegate that the indication should be restricted to adults given the lack of evidence submitted in the paediatric population.[20] The ACPM also agreed with the Delegate that efficacy in individual patients should be reviewed at 8 weeks. The ACPM advised that adalimumab should not be indicated in patients who have not shown a clinical response during 8 weeks of treatment because of the low likelihood of response with continuing treatment.

- **Proposed conditions of registration:**

The ACPM agreed with the Delegate on the proposed conditions of registration.

- **Proposed PI/CMI amendments:**

The ACPM agreed with the Delegate to the proposed amendments to the PI and Consumer Medicine Information (CMI).

The ACPM advised that the 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 these products.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Humira injection solution, containing adalimumab 20 or 40 mg, indicated for the following new indication:

> **Ulcerative colitis**
>
> *Humira is indicated for the treatment of moderate to severe ulcerative colitis in adult patients who have had an inadequate response to conventional therapy or who are intolerant to or have medical contraindications for such therapies. Patients should show a clinical response within 8 weeks of treatment to continue treatment beyond that time (see CLINICAL TRIALS).*

The full indications are now:

> **Rheumatoid arthritis**
>
> *Humira is indicated for reducing signs and symptoms, as well as inhibiting the progression of structural damage in adult patients with moderate to severely active*

[20] Note: This application did not specifically seek approval for use in a paediatric population.

rheumatoid arthritis. This includes the treatment of patients with recently diagnosed moderate to severely active disease who have not received methotrexate.

Humira can be used alone or in combination with methotrexate.

Polyarticular juvenile idiopathic arthritis

Humira in combination with methotrexate is indicated for reducing the signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis in patients aged 4 years of age and older. Humira can be given as monotherapy in case of intolerance or when continued treatment with methotrexate is inappropriate.

Psoriatic arthritis

Humira is indicated for the treatment of signs and symptoms, as well as inhibiting the progression of structural damage, of moderate to severely active psoriatic arthritis in adult patients where response to previous DMARDs has been inadequate.

Ankylosing spondylitis

Humira is indicated for reducing signs and symptoms in patients with active ankylosing spondylitis.

Crohn's disease

Humira is indicated for the treatment of moderate to severe Crohn's disease in adults to reduce the signs and symptoms of the disease and to induce and maintain clinical remission in patients who have had an inadequate response to conventional therapies, or who have lost response to or are intolerant of infliximab.

Ulcerative colitis

Humira is indicated for the treatment of moderate to severe ulcerative colitis in adult patients who have had an inadequate response to conventional therapy or who are intolerant to or have medical contraindications for such therapies. Patients should show a clinical response within 8 weeks of treatment to continue treatment beyond that time (see CLINICAL TRIALS).

Psoriasis

Humira is indicated for the treatment of moderate to severe chronic plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy.

Specific conditions applying to these therapeutic goods

- The Humira (adalimumab) Risk Management Plan (RMP), version 10.0, November 2011 with Australian-specific Annex (undated), included with submission PM-2012-01954-3-1, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

Attachment 1. Product Information

The Product Information approved at the time this AusPAR was published is at Attachment 1. For the most recent Product Information please refer to the TGA website at <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

Attachment 2. Extract from the Clinical Evaluation Report

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