Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for Adalimumab

Proprietary Product Name: Humira

Sponsor: AbbVie Pty Ltd

Date of CER: 28 March 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 the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

Contents

List of abbreviations

Abbreviation	Meaning
AAA	Anti-Adalimumab Antibody
ADA	Adalimumab
AE	Adverse Event
ALP	ALkaline Phosphatase
ALT	ALanine aminoTransferase
ANOVA	ANalysis Of VAriance
AS	Ankylosing Spondylitis
AST	ASpartate aminoTransferase
5-ASA	5-AminoSalicylic Acid
AZA	AZAthioprine
BMI	Body Mass Index
CD	Crohn's Disease
CER	Clinical Evaluation Report

Abbreviation	Meaning
CI	Confidence Interval
CL/F	apparent clearance
CMI	Consumer Medicines Information
CO	Clinical Overview
CR	Clinical Remission
CRESP	Clinical RESPonse
CRP	C-reactive protein
CS	CorticoSteroid(s)
CSR	Clinical Study Report
CV	Coefficient of Variation
CXR	Chest X-Ray
DB	Double-Blind
E/100 PY	Events per 100 Patient-Years
ECG	ElectroCardioGram
ELISA	Enzyme-Linked ImmunoSorbent Assay
EMA	European Medicines Authority
eow	Every other week
ET	Early Termination
EU	European Union
ew	Every week; weekly
FDA	Federal Drugs Administration (US)
GCP	Good Clinical Practice
HACA	Human Anti-Chimeric Antibody
IBD	Inflammatory Bowel Disease
IBDQ	Inflammatory Bowel Disease Questionnaire

Abbreviation	Meaning
IEC	Independent Ethics Committee
IgG1	human immunoglobulin
IMM	IMMunomodulator
IRB	Institutional Review Board
IS	Induction Set
ISSU	Integrated Summary of Safety Update
ITT	Intent-To-Treat
IVRS	Interactive Voice Response System
LLOQ	Lower Limit Of Quantification
LOCF	Last observation carried forward
MS	Maintenance Set
MedDRA	Medical Dictionary for Regulatory Activities
6-MP	6-MercaptoPurine
MTX	MethoTreXate
N	Number of subjects
N_{miss}	Number of non-missing observations
NMSC	Non-Melanoma Skin Cancer
NONMEM	NON-Linear Mixed Effect Modelling
NRI	Non-Responder Imputation
OL	Open-Label
PGA	Physician's Global Assessment
PI	Product Information
PK	PharmacoKinetic(s)
PM	Partial Mayo
Pop-PK	POPulation PharmacoKinetics

Abbreviation	Meaning
PPD	Purified Protein Derivative
PY	Patient-Years
RA	Rheumatoid Arthritis
RBC	Red Blood Cell
RBS	Rectal Bleeding Subscore
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	SubCutaneous; SubCutaneously
SCE	Summary of Clinical Efficacy
SCS	Summary of Clinical Safety
SD	Standard Deviation
SFS	Stool Frequency Subscore
TB	Tuberculosis
TGA	Therapeutic Goods Administration
TNF	Tumour Necrosis Factor
UC	Ulcerative Colitis
US	United States
UTI	Urinary Tract Infection
V/F	apparent volume of distribution
WBC	White Blood Cell

1. Introduction

Adalimumab (ADA) is a recombinant, fully human immunoglobulin (IgG1) monoclonal antibody that binds specifically and with high affinity to the soluble and transmembrane forms of tissue necrosis factor alpha (TNF-α; TNF used in this report means TNF-α), thereby inhibiting the binding of TNF-α with its receptors and neutralising the biological function of TNF.

Humira is approved for use in adults with rheumatoid arthritis (RA), psoriatic arthritis, psoriasis, ankylosing spondylitis (AS) and Crohn's disease (CD). Humira is approved in

polyarticular juvenile idiopathic arthritis in children over 4 years of age. The proposed additional 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.*

2. Clinical rationale

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

> Ulcerative colitis 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.

3. Contents of the clinical dossier

3.1. Scope of the clinical dossier

The submission contained the following clinical information:

Module 5

- 1 clinical pharmacology study provided PK data (described in document R&D/10/462, dated 10/12/2010 and derived from Study MO6-827 known as 'Study 827').
- 1 population PK (Pop-PK) analysis.
- 2 pivotal efficacy/safety, randomised, double-blind (DB), 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 Additional Analyses on Early Responders (Weeks 2 to 8) to Adalimumab report (R&D/12/180).

· 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 (ISS; data cut-off 31 December 2009) report and updated ISS (ISSU; data cut-off 16 December 2011).

Module 1

· Application letter, application form, draft Australian PI and consumer medicines information (CMI), FDA-approved product label, European Summary of Product Characteristics.

Module 2

· Clinical Overview (CO), Summary of Clinical Efficacy (SCE), Summary of Clinical Safety (SCS) and literature references.

Comment: The SCE contained integrated efficacy analyses from Studies 826 and 827, but no separate report was included in the Module 5 data set provided in this application.

3.2. Guidance

No pre-submission meeting occurred with the Therapeutic Goods Administration (TGA) regarding this application. The TGA referred the Sponsor to the European Medicines Agency (EMA) "Guideline on the Development of New Medicinal Products for the Treatment of Ulcerative Colitis" (CHMP/EWP/18463/2006).

3.3. Paediatric data

The submission did not include paediatric data. The Sponsor has a paediatric development plan that consists of three clinical studies (in children aged 4 to 18 years with moderately to severely active UC) that are anticipated to be conducted in Canada, Europe and the US. Humira is approved in polyarticular juvenile idiopathic arthritis in children over 4 years of age.

3.4. Good clinical practice

The Sponsor declared all three studies included in this submission were conducted in accordance with their protocol, International Conference on Harmonization 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, significant non compliance with GCP guidelines were found at three centres (22635, 36809 and 27010). The 24 trial subjects from these three sites were excluded from the intent-to-treat (ITT) efficacy analyses in Study 827, but remained in the safety analyses. Several non compliant subjects entered the OL extension trial, Study 223, and were subsequently withdrawn. This issue is addressed further in Section 7 of this clinical evaluation report (CER). All other studies fully complied with GCP requirements.

> **Comment:** This submission did not include a detailed description of non-GCP centres/subjects. Further details are to be requested.

4. Pharmacokinetics

4.1. Studies providing PK data

PK (and immunogenicity) data were only collected in Study 827.

4.2. PK overview

The clinical pharmacology of ADA has been well characterised in healthy subjects and in subjects with the approved indications.

From the approved PI:

> Following subcutaneous (SC) administration absorption was slow with mean peak serum concentration reached around five days. The average absolute bioavailability of adalimumab was 64% following a single 40mg SC dose. The PK of adalimumab was linear over the dose range 0.5 to 10mg/kg following a single intravenous dose. The volume of distribution ranged from 4.7 to 6.0L following single intravenous doses in RA. AdalimumabW2 is slowly eliminated, with clearances typically under 12 mL/h (range 11-18). The mean terminal phase half-life was approximately two weeks (range 10 to 20 days) across RA studies. Mean steady-state trough concentrations following SC administration in RA without methotrexate administration was 5microgram/mL. The serum adalimumab trough levels at steady state increased approximately proportionally with dose between 20 to 80mg given weekly and fortnightly. Pop-PK analyses from over 1200 RA patients revealed a trend toward higher apparent clearance of adalimumab with increasing bodyweight and doubled in patients who developed the presence of anti-adalimumab antibodies (AAA). Concomitant methotrexate (MTX) may decrease clearance by 44%.
>
> In patients with CD: The loading dose of 160mg Humira on Week 0 followed by 80mg Humira on Week 2 achieved serum adalimumab trough concentrations of approximately 12μg/mL at Weeks 2 and 4. The mean steady state trough concentration at Weeks 24 and 56 were 6.6 μg/mL and 7.2 μg/mL, respectively. The range of trough concentrations in patients who received a maintenance dose of 40mg Humira every fortnight was 0-21.7 μg/mL.

4.3. Study 827

See Section 7 for detailed study description. The secondary study objective assessed the PK of SC ADA administration.

Adult subjects (n=518) with moderate to severe UC (Mayo Score of 6 to 12 points with endoscopy subscore of 2 to 3; see Section 7.1.1.2.2) confirmed by colonoscopy with biopsy or flexible sigmoidoscopy with biopsy were enrolled at 103 sites worldwide. Subjects were stratified by prior exposure to infliximab and/or other anti-TNF agents, and randomised 1:1 to receive ADA or placebo by SC injection. Subjects assigned to the ADA treatment arm received 160mg at Week 0, 80mg at Week 2, and 40mg every other week (eow) between Weeks 4 and 52. Subjects assigned to the placebo treatment arm received matching placebo during the same period. At or after Week 10, subjects were evaluated and switched to OL ADA 40mg eow at Week 12 if they met the criteria for inadequate response. Subjects who demonstrated inadequate response at two consecutive visits at least 14 days apart while on OL ADA 40mg eow were dose-escalated to ADA 40mg once a week (ew).

Blood samples for ADA trough serum concentration assay, AAA, infliximab and human anti-chimeric antibody (HACA) assays were obtained immediately prior to dosing at time points indicated in the protocol. Abbott (Germany) analysed all serum samples using validated assay

methods. ADA serum concentrations were determined using a validated enzyme-linked immunosorbent assay (ELISA) method based on a double-antigen (capture and detector) technique.

PK analysis included 487 subjects (n=245 DB ADA 160/80/40 eow treatment group and n=242 DB placebo group). Twenty-four subjects (10 in the DB ADA 160/80/40 eow and 14 in DB placebo groups) were excluded due to GCP non-compliance. Table 1 and Figure 1 summarise the mean serum ADA trough concentrations by dose in UC subjects.

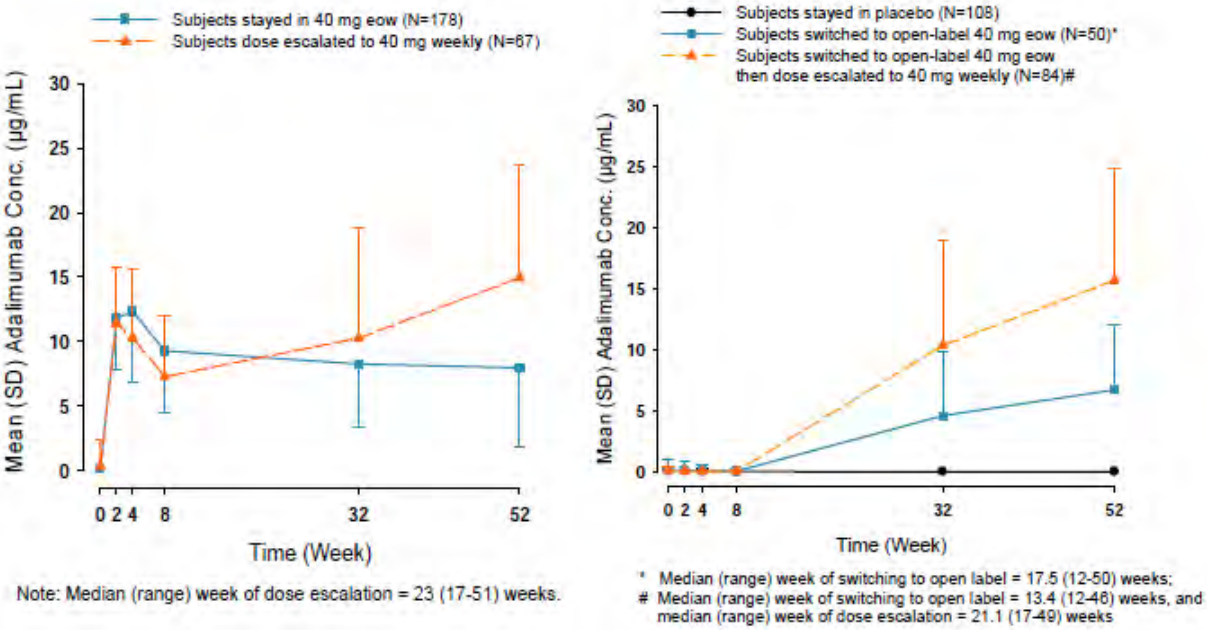
At the end of the induction period (Week 4) the mean (±SD) serum concentration in the DB ADA 160/80/40 eow treatment group, who remained in the eow group (n=160), was 12.3 µg/mL (±5.45). At the end of the maintenance period (Week 52), 101 subjects from this group had a mean (±SD) serum ADA trough concentration of 7.97 µg/mL (±6.09). These results are comparable to those found in CD (12 µg/mL at Week 4 and 7.2 µg/mL at Week 56, respectively).

Table 1: Summary of Serum Adalimumab Trough Concentrations (µg/mL) by Dose in Subjects with Ulcerative Colitis

	Mean ± SD (Min-Max), N_{nmiss}					
	Week					
Treatment Groups	**0**	**2**	**4**	**8**	**32**	**52**
Double-blind 160/80/40 mg eow Subjects Who Stayed in 40 mg eow (N = 178)	0.178 ± 1.54 (0.000 – 18.8), 166	11.8 ± 3.95 (0.000 – 23.1), 167	12.3 ± 5.45 (0.000 – 26.2), 160	9.28 ±4.74 (0.000 – 22.8), 151	8.26 ± 4.94 (0.000 – 26.9), 109	7.97 ± 6.09 (0.000 – 39.3), 101
Double-blind 160/80/40 mg eow Subjects Who Dose Escalated to 40 mg Weekly (N = 67)	0.320 ± 2.09 (0.000 – 16.4), 62	11.4 ± 4.36 (0.923 – 25.7), 66	10.3 ± 5.41 (0.000 – 22.6), 64	7.28 ± 4.71 (0.000 – 18.5), 64	10.3 ± 8.54 (0.000 – 32.5), 47	15.0 ± 8.75 (0.000 – 38.0), 36
Double-blind Placebo Subjects Who Stayed in Placebo (N = 108)	0.035 ± 0.187 (0.000 – 1.60), 103	0.113 ± 0.713 (0.000 – 5.42), 98	0.024 ± 0.170 (0.000 – 1.52), 86	0.016 ± 0.134 (0.000 – 1.14), 72	0.000 ± 0.000 (0.000 – 0.000), 51	0.000 ± 0.000 (0.000 – 0.000), 47
Double-blind Placebo Subjects Who Switched to Open-Label 40 mg eow (N = 50)	0.139 ± 0.869 (0.000 – 6.01), 48	0.112 ± 0.736 (0.000 – 5.10), 48	0.076 ± 0.516 (0.000 – 3.61), 49	0.038 ± 0.263 (0.000 – 1.82), 48	4.58 ± 5.28 (0.000 – 20.2), 36	6.71 ± 5.29 (0.000 – 18.2), 31
Double-blind Placebo Subjects Who Switched to Open-Label 40 mg eow, Then Dose Escalated to 40 mg Weekly (N = 84)	0.071 ± 0.366 (0.000 – 2.92), 82	0.022 ± 0.145 (0.000 – 1.31), 84	0.007 ± 0.040 (0.000 – 0.320), 80	0.019 ± 0.158 (0.000 – 1.42), 81	10.3 ± 8.60 (0.000 – 27.3), 52	15.7 ± 9.19 (0.000 – 36.5), 42

N_{nmiss} = number of non-missing observations

Figure 1: Mean (SD) Serum Adalimumab Trough Concentrations versus Time by Dose in Subjects with Ulcerative Colitis (Left panel: DB 160/80/40; Right panel: DB placebo)



Note: Median (range) week of dose escalation = 23 (17-51) weeks.

* Median (range) week of switching to open label = 17.5 (12-50) weeks;
\# Median (range) week of switching to open label = 13.4 (12-46) weeks, and median (range) week of dose escalation = 21.1 (17-49) weeks

From Figure 1 left Panel, the mean trough concentrations in subjects who received ADA 160/80/40 eow and dose escalated to 40mg ew appeared marginally lower prior to dose escalation compared with subjects who continued on 40mg eow. ADA concentrations were not measured at the time of dose escalation unless the subject dose escalated at Week 32. The value was 22% lower at Week 8 in subjects who later dose escalated. The median (±SD) time of dose escalation was 24 (±9.8) weeks. After dose escalation, ADA concentrations at Week 52 were approximately double in subjects who dose escalated to 40mg ew compared with those who received 40mg eow. Similar results were observed among subjects who were randomised to placebo and later received 40mg eow OL (Right Panel).

In the DB ADA 160/80/40 eow treatment group, 20 subjects had measurable baseline ADA concentrations (Week 0; range 0.056 to 18.8 μg/mL), as well as measurable infliximab concentrations. Infliximab is known to cross-react with ADA in the serum ADA ELISA assay, which probably gave rise to these measurable baseline ADA concentrations. Due to the differences in median elimination half-lives between ADA and infliximab (5 days versus 7.7 to 9.5 days, respectively), infliximab interference is expected to diminish by Week 8.

In the DB placebo treatment group, 24 subjects had ADA concentrations from Weeks 0 to 8 (range 0.036 to 6.01 μg/mL). All subjects had measurable baseline infliximab concentrations or were anti-TNF experienced, which suggests infliximab interfered with the ADA assay. Three additional subjects (anti-TNF naïve and randomised to placebo) also had measurable ADA concentrations from Weeks 0 to 8, for reasons unknown.

> **Comment:** The observed cross-reactivity in the serum assay, between ADA and infliximab (and potentially other similar monoclonal antibody agents), may be a major source of measurement bias in Study 827, and thereby limit the accuracy of the ADA PK results from that study.

4.3.1. Anti-TNF status

In the DB ADA 160/80/40 eow population (n=245), 59.6% subjects (n=146) were randomised as being anti-TNF naive. Once baseline infliximab and HACA levels were considered, this number dropped to 135 (with 110 subjects in the DB placebo group who were anti-TNF experienced). Among 242 subjects in the placebo treatment group, 108 were anti-TNF experienced.

Summaries were provided for the mean ADA concentrations over time (first 8 weeks) for subjects in the DB ADA 160/80/40 eow treatment group by previous anti-TNF treatment status. The results between the anti-TNF naive and anti-TNF experienced groups were similar at the end of the induction period (Week 4): mean (±SD) serum ADA concentration for previous anti-TNF exposure in the DB ADA 160/80/40 eow treatment group was 11.6 μg/mL ± 5.51 and anti-TNF naive subjects were slightly higher, 11.9 μg/mL ± 5.52.

However, at Week 8 there was a 9.6% separation, favouring higher mean serum ADA levels in the anti-TNF naive group. No comparative results at 52 weeks have been provided, which may reflect the small numbers of subjects who completed the DB period of the study.

> **Comments:** If prior exposure to anti-TNF treatment reduces efficacy in this subgroup, reduced mean serum ADA concentration would be expected too (if we assume concentration is highly correlated with effect). Furthermore, if there was reduced efficacy in the previously exposed to anti-TNF subjects, it may also be an indicator that those subjects had more severe or treatment-resistant disease compared with the anti-TNF naïve subjects. The 9.6% separation at Week 8 suggests further separation between these subgroups might be expected over the study duration. Further information is to be requested.
>
> Twenty-nine (29) subjects in the DB ADA 160/80/40 eow treatment group and 23 subjects in the DB placebo group had no infliximab concentration reported due to lack of

samples or inadequate sampling. This represents 21.2% total missing baseline data, a sizeable loss, albeit similarly distributed between groups.

4.3.2. HACA status

21.2% (n=52) of the DB ADA 160/80/40 population and 18.2% subjects (n=44) of the DB placebo group had measurable baseline HACA+ results. Subjects randomised to anti-TNF naive in both DB treatment arms, but had measurable baseline HACA+ results, were analysed as anti-TNF experienced.

From Table 2, ADA trough concentrations were lower in HACA+ subjects than in HACA- subjects for the DB ADA 160/80/40 treatment group in the DB maintenance phase. At Week 52, the mean (±SD) serum ADA concentration in the HACA- DB eow treatment arm was 8.65 µg/mL ± 6.53, whereas the mean (±SD) serum ADA concentration in the HACA+ DB eow treatment arm was 5.52 µg/mL ± 3.57. Hence, presence of HACA appears to reduce the mean serum ADA concentration by 26.2% by Week 52. In those who dose-escalated within the DB ADA 160/80/40 treatment group, at Week 52, those identified as HACA+ at baseline had 60.7% lower levels than HACA- subjects at baseline (6.60 versus 16.8, respectively). The effect of HACA status on mean serum ADA concentration for subjects who went from DB placebo to OL ADA eow was unclear. However, the previous effect of lower serum ADA concentrations with HACA+ status was more evident in DB placebo subjects who went onto OL ADA and then dose-escalated.

Table 2: Summary of Adalimumab Concentrations versus Time by Dose and Baseline HACA Status

		Mean ± SD (Min - Max), N_{nmiss}					
		Week					
		0	2	4	8	32	52
Double-blind 160/80/40 mg eow continued (N = 178)*	HACA- (N = 123)	0.191 ± 1.703 (0.000 - 18.8), 123	12.0 ± 3.77 (0.000 - 23.1), 118	12.5 ± 5.49 (0.000 - 25.6), 115	9.63 ± 4.70 (0.000 - 22.8), 108	8.79 ± 5.11 (0.000 - 26.9), 81	8.65 ± 6.53 (0.000 - 39.3), 76
	HACA+ (N = 37)	0.163 ± 0.990 (0.000 - 6.02), 37	11.2 ± 4.59 (0.000 - 18.5), 35	12.2 ± 5.94 (0.000 - 26.2), 30	8.06 ± 5.25 (0.000 - 21.8), 29	6.30 ± 4.18 (0.000 - 18.1), 18	5.52 ± 3.57 (0.000 - 12.9), 15
Double-blind 160/80/40 mg eow to Weekly (N = 67)*	HACA- (N = 44)	0.450 ± 2.47 (0.000 - 16.4), 44	11.4 ±4.32 (0.923 - 25.7), 43	10.3 ± 5.55 (0.823 - 22.6), 41	7.46 ±4.74 (0.000 - 18.5), 42	12.5 ± 8.91 (0.000 - 32.5), 30	16.8 ± 8.68 (0.047 - 38.0), 25
	HACA+ (N = 15)	0.000±0.000 (0.000 - 0.000), 15	10.6 ± 4.73 (1.50 - 17.5), 15	8.76 ± 5.31 (0.000 - 18.7), 15	5.49 ± 3.26 (0.000 - 10.5), 15	3.45 ± 4.16 (0.000 - 9.57), 10	6.60 ± 5.97 (0.000 - 16.4), 6
Double-blind placebo to Open-label 40 mg eow (N = 50)#	HACA- (N = 37)	0.018 ± 0.084 (0.000 - 0.476), 37	0.005 ± 0.029 (0.000 - 0.171), 35	0.002 ± 0.011 (0.000 - 0.066), 36	0.000±0.000 (0.000 - 0.000), 35	4.55 ± 5.68 (0.000 - 20.2), 28	6.21 ± 5.76 (0.000 - 18.2), 25
	HACA+ (N = 8)	0.751 ± 2.13 (0.000 - 6.01), 8	0.638 ± 1.80 (0.000 - 5.10), 8	0.451 ± 1.28 (0.000-3.61), 8	0.228 ± 0.643 (0.000 - 1.82), 8	3.83 ± 4.04 (0.000-8.99), 6	8.63 ± 0.815 (7.72 - 9.48), 4
Double-blind placebo to Open-label 40 mg eow to Weekly (N = 84)#	HACA- (N = 60)	0.097 ± 0.426 (0.000 - 2.92), 60	0.028 ± 0.170 (0.000-1.31), 60	0.009 ± 0.047 (0.000 - 0.320), 59	0.026 ± 0.185 (0.000-1.42), 59	11.6 ± 8.81 (0.000 - 27.3), 35	17.5 ± 8.79 (0.000 - 36.5), 29
	HACA+ (N = 16)	0.000 ± 0.000 (0.000 - 0.000), 16	0.007 ± 0.029 (0.000 - 0.117), 16	0.000 ± 0.000 (0.000 - 0.000), 14	0.000 ± 0.000 (0.000 - 0.000), 14	7.89 ± 8.47 (0.000 - 26.6), 11	12.0 ± 10.0 (0.000 - 32.1), 9
Double-blind placebo continued (N = 108)#	HACA- (N = 81)	0.045 ± 0.210 (0.000 - 1.60), 81	0.090 ± 0.641 (0.000 - 5.42), 73	0.031 ± 0.194 (0.000 - 1.52), 66	0.021 ± 0.152 (0.000 - 1.14), 56	0.000 ± 0.000 (0.000 - 0.000), 43	0.000 ± 0.000 (0.000 - 0.000), 38
	HACA+ (N = 20)	0.000 ± 0.000 (0.000 - 0.000), 20	0.251 ± 1.063 (0.000 - 4.51), 18	0.000 ± 0.000 (0.000 - 0.000), 13	0.000 ± 0.000 (0.000 - 0.000), 13	0.000 ± 0.000 (0.000 - 0.000), 8	0.000 ± 0.000 (0.000 - 0.000), 8

N_{nmiss} = Number of non-missing observations
* Total of 26 subjects did not have HACA results in double-blind 160/80/40 mg eow treatment group.
\# Total of 20 subjects did not have HACA results in double-blind placebo treatment group.

Comments: Twenty-six (26) subjects in the DB ADA 160/80/40 eow treatment group and 20 subjects in the DB placebo group had no HACA concentrations reported due to lack of samples or inadequate sampling. This represents 19.0% missing baseline data in total, a sizeable loss, albeit similarly distributed between the groups.

Given the small subject numbers with PK data at Week 52, as well as the significant amount of missing data, these results need to be interpreted with caution, but do strongly suggest the presence of HACA is associated with reduced ADA concentration..

4.3.3. Anti-TNF and HACA status combined

Summarises are provided for the combined effect of previous anti-TNF history and baseline HACA status in DB ADA 160/80/40 eow treatment group on mean serum ADA concentration. Albeit subject numbers with PK data at Week 52 were small and there was approximately 20%

missing data, similar patterns (and magnitude) of results were found as for baseline HACA status, with no deleterious effect on mean serum ADA trough concentrations from those subjects who received prior anti-TNF treatment. However, only the effect of anti-TNF status on PK of ADA within the first 8 weeks of treatment is reported in this submission (Section 4.3.1).

4.3.4. Immunogenicity of adalimumab

4.3.4.1. Immunogenicity overview

From the PI:

> Development of AAA during ADA treatment has been recognised in all Humira licensed indications. Approximately 5.5% adult RA patients developed low-titre AAA at least once during treatment, which were neutralising in vitro. Similar rates of AAA development were found in AS and psoriatic arthritis. RA patients treated with MTX had a lower rate of antibody development than patients on Humira monotherapy (1% versus 12%, respectively), although subjects with psoriatic arthritis given MTX had a higher incidence than in RA (7% versus 1%, respectively). With monotherapy, patients receiving fortnightly dosing may develop antibodies more frequently than those receiving weekly dosing. In patients receiving the recommended dosage of 40mg fortnightly as monotherapy, the ACR 20 response was lower among AAA+ patients than AAA- patients. The long-term immunogenicity of Humira is unknown. In polyarticular juvenile idiopathic arthritis 25.6% of patients treated with ADA became AAA+, however the incidence rate dropped to 5.9% in those subjects were who co-administered MTX. The immunogenicity rate was 8% for psoriasis patients given Humira monotherapy. In patients with CD, 2.6% (n=7/269) subjects became AAA+ in up to 56 weeks ADA treatment.

4.3.4.2. Study 827

Overall, 19 subjects (3.9%) were AAA+ during the entire study (3.7% [n=8] in anti-TNF experienced subjects and 4.1% [n=11] in anti-TNF naive subjects, respectively). Subject disposition is summarised in Table 3. Of note, seven cases (4.0%) were identified in the DB ADA 160/80/40 eow group. Higher rates of AAA+ were noted in subjects who dose-escalated in either the DB or OL study phases. This is not consistent with the information regarding dose interval and total doses and development of HACA in the PI, though it is based on small numbers of subjects.

Table 3: AAA Positive Subject Disposition and Information

Treatment	AAA+ (n)	Remitters at Week 8 (n)	Remitters at Week 52 (n)	Responder at Week 8 (n)	Responder at Week 52 (n)	Previous Infliximab Use (n)	HACA+ at Baseline (n)	Concomitant Use of Immuno-Suppressants[a] (n)
40 mg eow	7	2[b]	2[b]	5[c]	4	2[d]	1	0
40 mg eow to Weekly	6	0	0	2	0	3	3	0
Placebo Stayed	0	0	0	0	0	0	0	0
Placebo to 40 mg eow	2	1	0	1	0	0	0	0
Placebo to 40 mg eow to Weekly	4	0	0	0	0	3	2	1
Total	19[e]	3	2	8	4	8	6[f]	1[g]

AAA = anti-adalimumab antibody; HACA = human anti-chimeric antibody

a. Methotrexate, 6-MP, and/or azathioprine.
b. One subject was a remitter at Week 8 and Week 52.
c. Three subjects achieved clinical response at Week 8 and Week 52.
d. One subject was included as infliximab experienced since there was measurable baseline HACA result even though the subject was anti-TNF naive in the clinical data base.
e. One subject was excluded from the AAA analysis due to site non-compliance.
f. One subject had no HACA result.
g. One subject received concomitant methotrexate.

Of subjects who had measurable HACA at Week 0, six were AAA+ (6/96, 6.5%). One AAA positive subject (80616) received a concomitant immunomodulator (IMM), MTX (1/19, 5.3%).

Table 4 summarises the individual ADA concentrations for AAA positive subjects. The earliest time point at which a subject was identified as AAA positive was at Week 8. Most subjects (10/19, 52.6%) became AAA+ at Week 32. Six (6/19, 31.6%) subjects were AAA+ at early termination (ET). Three AAA positive subjects (15.8%) were in remission at Week 8 and two (10.5%) at Week 52. One subject (5.3%) was in remission at both Weeks 8 and 52.

According to the AAA Validation report, R&D 05/014, the ELISA for determination of AAA is a quasi-quantitative assay. This is due to the lack of similarity between the standard samples and the test samples, because the reference material may not accurately reflect the antibodies affinities, proportions and other conditions in the test sample. Due to the nature of the ELISA method both assays are only able to determine free AAA. ADA interferes in the assay by binding to AAA and prevents them from binding to capture and detection antibody. Therefore, samples with ADA levels above 2mg/L are not analysed for AAA

Table 4: Individual Adalimumab Concentrations (µg/mL) for AAA Positive Subjects

	Week							Week Became AAA+	Remitter at Week 8	Remitter at Week 52
Treatment Group	0	2	4	8	32	52	ET			
40 mg eow	0	9.27	0	0	0	0	NR	32	No	Yes
	0	7.81	3.00	0.035	0	0	NR	32	No	Yes
	0	6.21	5.85	2.45	0	0	NR	32	No	No
	0	13.6	5.05	0	0	0	NR	32	No	No
	0	7.67	7.20	1.86	0	0	NR	32	No	No
	0	17.5	25.5	15.5	NR	NR	0	29	Yes	No
	0	10.3	7.80	4.00	0	0.052	NR	32	No	No
	0	11.2	10.5	7.42	2.21	0	NR	52	Yes	Yes
40 mg eow then dose escalated to 40 mg weekly	0	10.9	1.18	0	NR	NR	0	28	No	No
	0	10.2	1.16	0	2.27	18.3	NR	8	No	No
	0	1.50	0	0	0	0	NR	8	No	No
	0	14.7	8.16	4.27	0	NR	1.45	32	No	No
	0	9.09	8.33	4.81	0	NR	0	32	No	No
	0	5.60	0.823	0.033	NR	NR	0	30	No	No
Placebo to 40 mg eow	0	0	0	0	0	NR	0	49	Yes	No
	0	0	0	0	NR	0	0	25	No	No
Placebo to 40 mg eow to Weekly	0	0	0	0	0	0	NR	32	No	No
	0.042	0	0	0	NR	NR	0	26	No	No
	0	0	0	0	0	0	NR	32	No	No
	0	0	NR	0	0	0	NR	32	No	No

ET = early termination; NR = No result; * subject excluded from the AAA analysis due to site non-compliance
Note: This Table has been amended from the original to remove patient identifier numbers.

Comments: There appears to be a significant lag time between onset of rapid reduction in serum ADA concentration and identification of AAA. This may reflect the limitations of the specific ADA ELISA assay. If a lag time truly exists, delays in diagnosis of AAA+ of at least 24 weeks after onset has major implications for efficacy and safety.

The number of AAA+ subjects in each treatment group are too small (n≤7) to conclude on the impact of immunogenicity on serum ADA concentrations and its efficacy, however the rapid reductions in ADA concentrations seen in this group of subjects suggests a rapid loss in efficacy might be expected in this group given sufficient follow-up. Also given the 2mg/L detection level, the numbers of subjects identified as AAA positive in this study are likely to be an underestimate.

It is unclear whether AAA status monitoring continued into the OL extension trial, Study 223. Clarification is to be sought.

4.3.5. Remitter status

In those subjects who achieved clinical remission (CR) in the DB ADA 160/80/40 treatment group, mean serum ADA concentrations were consistently higher than non-remitters at all time points, despite lower baseline levels (see Table 5).

Table 5: 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

Furthermore, the rate of CR and rate of clinical response (CRESP), as assessed by Mayo score, were higher in the anti-TNF naïve group than the anti-TNF experienced group. The percentage of subjects who achieved mucosal healing (MH) as assessed by endoscopy was also higher in the anti-TNF naïve group than the anti-TNF experienced group. CRESP and MH for anti-TNF naive subjects were statistically significantly superior to anti-TNF experienced subjects at all time points recorded, although no such trend was seen in CR between these groups.

The rate of CR, CRESP and MH appeared comparable in the anti-TNF experienced sub-groups, irrespective of HACA status. The Sponsor has concluded from the analyses that the difference in efficacy between the anti-TNF naive and anti-TNF experienced groups is not explained by baseline HACA status. However, no comparison was made between the anti-TNF experienced/HACA- subgroup and the anti-TNF naive/HACA- group or the anti-TNF experienced/HACA+ subgroup and the anti-TNF naive/HACA- group. The first comparison would measure the effect of prior anti-TNF exposure independently of baseline HACA status and provide a more confident result in any effect of baseline HACA status on rates of CR, CRESP and MH.

> **Comment**: Given the previous findings of reduced mean serum ADA concentrations in those subjects with baseline HACA+ status, reduced mean serum ADA concentrations in non-remitters and reduced efficacy (CRESP rates and MH rates) in anti-TNF experienced subjects (with possibly lower mean serum ADA concentrations in anti-TNF experienced subjects – subject of a clinical question) it is important to establish whether there is an negative effect of prior (i.e. failed) response to anti-TNF treatment, as this has dosing implications or may even negate ADA treatment in this subgroup all together.

4.4. Population pharmacokinetics

ADA apparent clearance (CL/F) and apparent volume of distribution (V/F) were estimated for subjects in Study 827 via a Pop-PK analysis. Data from every subject who received ADA and had at least one measurable ADA concentration were included in the Pop-PK analysis (n=353). Pop-PK analysis was performed on actual sampling times not protocol specified times. PK models were built with non-linear mixed effect modelling (NONMEM) software. The structure of the starting PK model was based on observations from a Pop-PK analysis performed with adult RA subjects. ADA PK, when only trough concentrations are available, is best described by a one compartmental model with first-order absorption from the depot compartment and first order elimination from the central compartment. An increase of bodyweight by 10kg is expected to increase CL/F by approximately 13%. The presence of AAA would lead to approximately double

of CL/F. Similar impact of bodyweight and AAA on ADA PK parameters was observed in subjects with RA, juvenile RA, psoriasis, AS, and CD. Recent literature reported plasma albumin is a significant covariate on the PK of infliximab in UC subjects. Plasma albumin was tested as a covariate in the ADA PK model for UC subjects. An increase in plasma albumin concentration by 1g/dL was expected to decrease ADA CL/F by approximately 41%, an effect comparable to infliximab.

Parameter estimates for the final Pop-PK model revealed an apparent clearance of 0.371L/day (15.2mL/h) and an apparent volume of distribution of 4.80L. The model predicted CL/F was 0.258L/day for a patient weighing 50kg and 0.504L/day for a 100kg patient, respectively.

4.4.1. Concomitantly administered immunosuppressants

The effects of concomitantly-administered immunosuppressants (MTX, AZA and 6-MP) on ADA PK were evaluated. Although none of these immunosuppressants were statistically significant covariates, ADA clearance was approximately 17% lower.

4.4.2. Alternative induction regimen

The treatment of subjects with UC consists of an induction dosage regimen of 160mg and 80mg ADA administered at Week 0 and Week 2, respectively. The 160mg dose requires four 40mg SC injections on a single day. This may give rise to non-adherence in some patients. Simulations were therefore performed using the final Pop-PK model to justify the administration of 160mg given on two consecutive days (80mg on Days 0 and 1). This approach is accepted for dosage induction in CD.

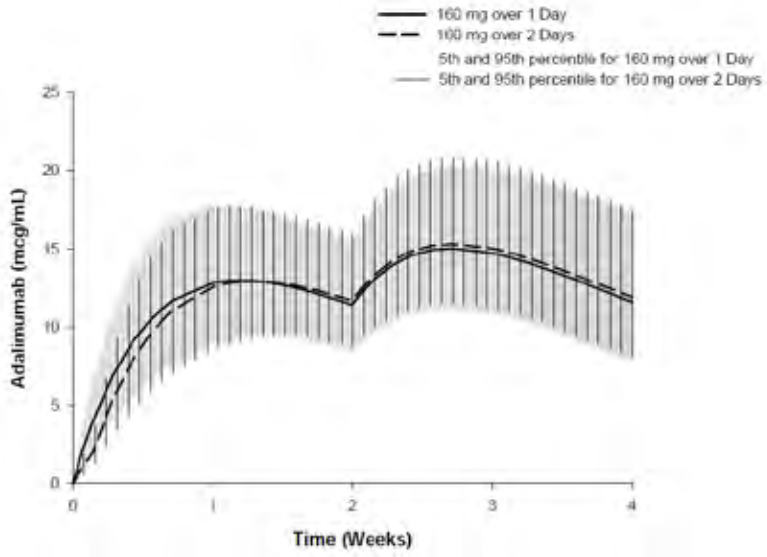
A total of 2500 subjects were simulated for each of the two dosage regimens. This assumed 100% compliance and was compared with the concentration values observed in Study 827. Bodyweight, AAA and albumin were used as covariate values in the simulations. The results (see Figure 2) indicate that by Week 1, the serum ADA concentrations expected following administration of the160mg/80mg induction regimen with the 160mg dose given over one or two days during the induction period almost completely overlay. On this basis splitting the induction dose to two 80mg doses administered over two consecutive days would not expect to adversely affect efficacy.

4.5. Summary of PK

4.5.1. Pharmacokinetics

Comparison of serum trough concentration instead of maximum serum concentration is standard practice with studies using monoclonal antibodies. Serum ADA 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 (when anti-TNF experienced subjects appeared to have a 9.6% mean reduction in serum ADA concentration compared with anti-TNF naive subjects).

Figure 2: Serum Mean Adalimumab Concentrations for 160mg Adalimumab given over 1 or 2 Days at Week 0, followed by 80mg Adalimumab over 1 Day at Week 2



In contrast, anti-TNF naive remitters consistently had higher mean serum ADA 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 CR and CRESP rates (as assessed by Mayo score) in the anti-TNF naïve group support this assertion. The percentage of subjects who achieved 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 ADA, particularly CD. Furthermore, the estimated covariate effects of bodyweight, AAA positive status and albumin concentration, suggest no need for dosage adjustment. Similarly, no dosage adjustment was needed with co-administration of ADA with the immunosuppressant agents, MTX, AZA and 6-MP.

The final Pop-PK model simulations support the proposed split-dose alternative induction regimen – 160mg given over two days and then 80mg at 14 days and 40mg at 28 days. The effect on the PK profile of ADA 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.

4.5.2. Immunogenicity

Baseline HACA+ status appeared to result in lower mean serum ADA 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 naive subjects with 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.

Study 827 design quality is detailed in Sections 7 & 8 of this CER. 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 ADA ELISA assay with previous infliximab treatment, as well as an apparent lag time between onset of development of AAA and a measurable level of AAA, 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.

AAA+ 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. 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 RA, with much larger study numbers than the other approved indications, and these found an average rate of 12% AAA+ in ADA monotherapy. Given an apparent lag time between rapid reduction in serum ADA 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.

4.6. Evaluator's overall conclusions on PK

4.6.1. Pharmacokinetics

Study 827 was generally well designed and conducted. Limitations included missing data and the use of the specific ADA ELISA assay. In particular, the assay could not detect AAA above 2mg/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 ADA trough concentrations from Study 827 had a good relationship to the administered ADA dose. The PK parameters presented for UC in this submission were consistent with other licensed ADA indications, particularly CD (induction and maintenance). While the mean serum trough ADA concentrations during the 48-week maintenance period were consistent with, and expected to be similar to, the levels achieved in subjects with CD, the serum trough ADA concentrations were derived from a combination of randomised DB and OL ADA treatment data. Technically, this was not a true maintenance phase. Therefore the levels achieved in this treatment phase should be interpreted with caution alongside the efficacy results (Section 7 of this CER).

Administration of the first dose of the induction regimen i.e. 160mg over one or two days had minimal impact on the PK of ADA during the induction period and is therefore 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 MTX, AZA or 6-MP immunosuppressant therapy.

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

4.6.2. 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 ADA is unclear from the study results presented in this submission. The Sponsor will be asked to clarify these issues under specific clinical questions.

5. Pharmacodynamics

No data.

6. Dosage selection for the pivotal studies

From the Clinical Overview:

Doses for the Phase III clinical studies (Studies 826 & 827) were selected based on a combination of expert clinical advice, clinical data from the ADA development program in CD, and extensive PK data accumulated in the ADA 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 ADA induction dosing arm of 80/40mg. Earlier that year, both 160/80/40mg and 80/40mg induction regimens had been approved in the EU as induction treatment for CD. The ADA induction dosing regimen of 80/40 was therefore included so both of these approved induction regimens would be evaluated for the induction of remission of UC.

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

In clinical studies conducted in subjects with CD, induction regimens comprising 160mg ADA at Week 0 and 80mg ADA at Week 2 (160/80/40 regimen) or 80mg ADA at Week 0 and 40mg ADA 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 ADA induction regimens experienced CR-70 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 ADA induction regimen compared with subjects on placebo experienced CR-100 clinical response at Week 4 (48.7% versus 23.6%, respectively). Subjects in the 80/40 ADA 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 40mg ADA eow dosing maintenance regimen (following the 160/80mg ADA 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 ADA 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; $P = 0.004$).

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

7. Clinical efficacy

7.1. Pivotal efficacy studies

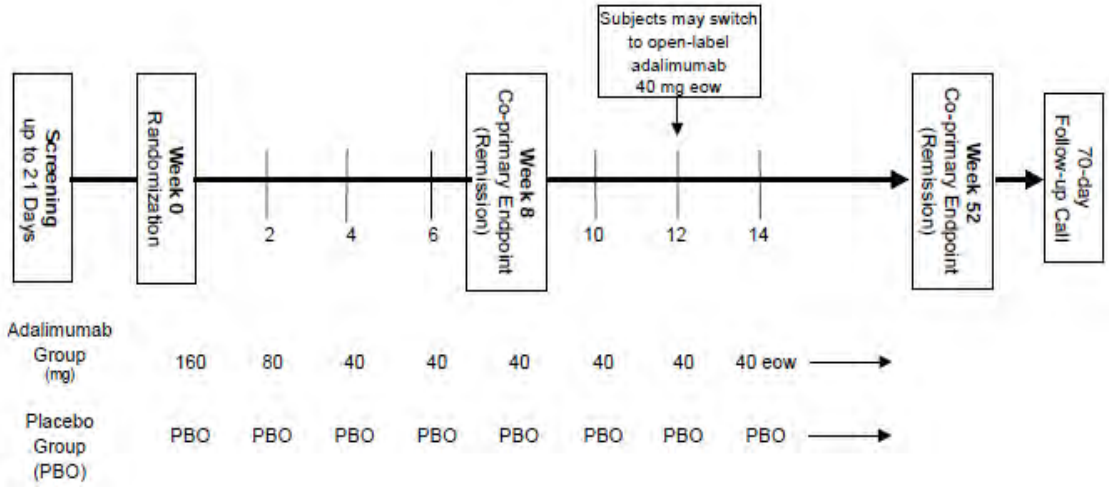
7.1.1. Study 827

7.1.1.1. Study design, objectives, locations and dates

The study design is a 52-week Phase III multinational, multicentre, randomised, DB, placebo-controlled trial conducted between 20 November 2006 (first subject, first visit) and 2 March 2010 (last subject, last visit) in 103 centres in the US, Canada, Austria, Belgium, Denmark, France, Germany, Israel, Norway, Portugal, Spain, Switzerland, the Czech Republic, Hungary, Poland, Australia and New Zealand. The number of subjects per site ranged from 1 to 22. The study protocol and amendments were reviewed by an IEC or IRB. The study was sponsored wholly by Abbott.

The study consisted of a screening period within 21 days prior to randomisation (baseline), an induction period of eight weeks, a 44-week maintenance period and a 70-day follow-up period (Figure 3). The design incorporated a period for rescue medication (OL ADA) that included dose-escalation if needed. On study completion patients could enrol in the OL extension trial, Study 223.

Figure 3: M06-827 Study Design



Study visits took place at screening, baseline (Week 0), and Weeks 2, 4, 8, 12, 16, 20, 26, 32, 38, 44 and 52/Early Termination (ET). A colonoscopy was performed during the screening period if the subject had not had a colonoscopy within six months of screening otherwise a flexible sigmoidoscopy was undertaken at screening and other specified visits. During the screening endoscopy, biopsies from the most severely affected areas were taken and evaluated by a qualified local pathologist to confirm the diagnosis of UC. To assign an endoscopy subscore (0 to 3 points) for the Mayo score calculation, regardless of the endoscopy type performed, only the last 30 cm on scope retraction was used for scoring.

The primary objective of this study was to assess the efficacy and safety of ADA for the induction and maintenance of clinical remission (CR) in subjects with moderately to severely active UC. The secondary objective of this study was to assess the PK of ADA following SC administration (see Section 4).

> **Comment**: Induction was examined in the initial DB, placebo-controlled phase of this study. At the beginning of the maintenance phase, subjects with an inadequate response were offered OL ADA which, if non-response continued, was dose escalated. Subjects with persistent inadequate response could discontinue the study. Hence, it would be

anticipated that subjects remaining on treatment at end-of-study were those who had an adequate response to ADA.

7.1.1.2. Inclusion and exclusion criteria

The main criteria for inclusion included:

- Male or female ≥18 years of age.
- Diagnosis of UC for > 90 days prior to baseline.
- Diagnosis of active UC confirmed by colonoscopy with biopsy or flexible sigmoidoscopy with biopsy during the screening period, with exclusion of infection.
- 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 ≥20mg/day or equivalent) for at least 14 days prior to baseline or stable oral corticosteroid dose (prednisone <20mg/day) for at least 40 days prior to baseline and/or
  - At least a consecutive 90-day course of AZA or 6-MP prior to baseline, with a dose of azathioprine ≥1.5mg/kg/day or 6-MP ≥1mg/kg/day (rounded to the nearest available tablet formulation), or a dose that is the highest tolerated by the subject (e.g. 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, defined as follows:
  - Loss of response – In a subject whom the investigator judged to have responded to the anti-TNF agent in the past, loss of response was defined as meeting either of the following criteria after the last dose (a subject with prior infliximab exposure must have responded to a dose of ≥5 mg/kg and demonstrated loss of response ≥14 days after receiving at least two subsequent and sequential doses of ≥5mg/kg at an interval not exceeding 56 days):
    - § Experienced an overall lack of improvement;
    - § Experienced a worsening of the following, but not inclusive, UC-related signs/symptoms: stool frequency, abdominal pain, rectal bleeding, fever, and/or weight loss. Intolerance to anti-TNF agent.
  - A subject was considered intolerant when, in the opinion of the Investigator, therapy was discontinued as a result of a significant acute or delayed reaction to the medication. A reaction was considered significant if at least 1 of the clinical characteristics listed below was captured in the medical history and documented in progress notes or other source documents:
    - § Acute reaction: An adverse reaction, whether immunologically or non-immunologically based, which occurs during or within 24 hours of administration of an anti-TNF agent that is manifested by ≥1 of the sign/symptoms and is judged to be related to the medication: fever >100°F, chills or rigors, itching, rash, flushing, urticaria or angioedema, breathing difficulties (dyspnoea, chest pain or tightness, shortness of breath, wheezing, stridor), and/or clinical hypotension (pallor, diaphoresis, faintness, syncope), or orthostatic decrease in blood pressure.
    - § Delayed reaction: An adverse reaction occurring more than 24 hours and <14 days after anti-TNF agent administration manifested by ≥1 of the following

signs/symptoms and judged to be related to the medication: myalgias, arthralgias, fever >100°F, malaise, and/or rash.

The main criteria for exclusion included:

- History of subtotal colectomy with ileorectostomy or colectomy with ileoanal pouch, Koch pouch, or ileostomy for UC, or planned bowel surgery.
- Received previous treatment with adalimumab or previous participation in an adalimumab clinical study.
- Received cyclosporine, tacrolimus, or mycophenolate mofetil within 30 days of baseline.
- Received intravenous (IV) corticosteroids within 14 days of screening or during the screening period.
- Received therapeutic enema or suppository, other than required for endoscopy, within 14 days of the screening endoscopy and during the remainder of the screening period.
- Current diagnosis of fulminant colitis and/or toxic megacolon.
- Disease limited to the rectum (ulcerative proctitis).
- Current diagnosis of indeterminate colitis.
- Current diagnosis and/or history of CD.
- Currently receiving total parenteral nutrition.
- Used aminosalicylates for <90 days before baseline or not on a stable dose for at least 28 days before baseline or discontinued use within 28 days of baseline.
- Positive Clostridium difficile stool assay.
- Previously used infliximab or any anti-TNF agent within 56 days of baseline.
- Previously used infliximab or any anti-TNF agent without clinical response at any time ("primary non-responder") unless subject experienced a treatment-limiting reaction.
- Infections requiring treatment with IV antibiotics, antivirals, or antifungals within 30 days of baseline or oral antibiotics, antivirals, or antifungals within 14 days of baseline.
- History of malignancy other than a successfully treated non-metastatic cutaneous squamous cell or basal cell carcinoma and/or localized carcinoma in situ of the cervix. If the screening colonoscopy/flexible sigmoidoscopy showed evidence of dysplasia or a malignancy, subject was not to be enrolled in the study.

7.1.1.2.1. Study treatments

The study consisted of an 8-week blinded induction treatment phase followed by a 44-week (blinded) maintenance treatment phase (total study duration 52 weeks). During the induction phase, subjects were randomised to receive either ADA 160/80/40 or placebo by SC injection. Each ADA subject received 160mg at Week 0 and 80mg at Week 2, and 40mg eow thereafter, starting at Week 4. Subjects assigned to placebo treatment received matching placebo i.e. four injections at Week 0, two injections at Week 2, and one injection eow thereafter starting at Week 4. The last dose of study drug was given either at Week 50 or 51 depending on whether the subject was on an ew or eow dosing schedule.

At, or after Week 10, subjects who met the criteria for inadequate response could switch to OL ADA 40mg 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 inadequate response at two consecutive visits at least 14 days apart while on OL ADA 40mg eow were permitted to dose escalate to ADA 40mg ew. Subjects with persistent inadequate response while on ADA 40mg ew could discontinue from the study at the Investigator's discretion.

- **Prior and concomitant therapy**

Permissible medications included: Enrolled subjects continued taking aminosalicylates, AZA or 6-MP, but doses remained unchanged throughout the study. No dose adjustments of UC-related concomitant treatments were allowed, except for corticosteroid (CS) taper between Weeks 8 and 52 and a dose decrease of other UC-related concomitant treatments in the event of treatment-related toxicities (e.g. leukopenia or elevated liver enzymes) considered moderate to severe in the opinion of the Investigator. Given maintenance of CR in UC is desirable without CS, subjects who responded ≥Week 8 were permitted to taper CS.

Prohibited medications included: Live vaccines could not be given concurrently while on study drug or for 70 days after the last dose of study drug. Cyclosporine, tacrolimus, mycophenolate mofetil, and investigational agents were prohibited within 30 days or five half-lives prior to baseline and during the study. Subjects who took these medications during the study were discontinued. The use of Kineret® (anakinra), Tysabri® (natalizumab), Orencia® (abatacept), or any biologic therapy was prohibited during the study. Intravenous CS use was prohibited within 14 days prior to screening, during the screening period, and during the study. Subjects who took these medications during the study were discontinued. Rectal therapy with any therapeutic enemas or suppositories, with the exception of those required for endoscopy, was prohibited within 14 days prior to screening endoscopy, during the remainder of the screening period, and during the study.

7.1.1.2.2. Efficacy variables and outcomes

The definitions of Mayo score, partial Mayo score, response and remission are summarised in Table 6. Mild UC is Mayo score is 0-5, moderate 6-9 and severe 10-12.

Table 6: Definition of Efficacy Variables used in the Pivotal Adalimumab Studies

Term	Definition
Mayo Score	Composite score of UC disease activity based on the subscores of stool frequency (0 to 3), rectal bleeding (0-3), physician's global assessment (0 to 3) and endoscopy (0 to 3). This score ranges from 0 to 12 points with higher scores representing more severe disease.
Partial Mayo Score	Composite score of UC disease activity based on the subscores of stool frequency, rectal bleeding, and physician's global assessment and DOES NOT include the endoscopy subscore. This score ranges from 0 to 9 points.
Response	A decrease in Mayo Score of ≥ 3 points and ≥ 30% from Baseline PLUS a decrease in the rectal bleeding subscore [RBS] ≥ 1 or an absolute RBS of 0 or 1.
Inadequate Responder	• Subject with a Baseline Partial Mayo Score of 4 to 7 who presents with a Partial Mayo Score greater than or equal to their Baseline score on two consecutive visits at least 14 days apart. • Subject with a Baseline Partial Mayo Score of 8 or 9 who presents with a Partial Mayo Score ≥ 7 on two consecutive visits at least 14 days apart.
Remission	Mayo Score ≤ 2 with no subscore > 1.

- **Ranked co-primary efficacy endpoints**

1. The proportion of subjects who achieved remission at Week 8 and;

2. The proportion of subjects who achieved remission at Week 52.

· **Ranked secondary efficacy endpoints**

The first eight ranked secondary endpoints were:

1. Proportion of subjects with remission (sustained) at both Weeks 8 and 52.
2. Proportion of subjects who achieved clinical response per Mayo score at Week 8.
3. Proportion of subjects who achieved clinical response per Mayo score at Week 52.
4. Proportion of subjects who achieved clinical response per Mayo score (sustained) at both Weeks 8 and 52.
5. Proportion of subjects who achieved mucosal healing at Week 8.
6. Proportion of subjects who achieved mucosal healing at Week 52.
7. Proportion of subjects who achieved mucosal healing (sustained) at both Weeks 8 and 52.
8. Proportion of subjects who discontinued corticosteroid use before Week 52 and achieved remission at Week 52.

Comment: The CHMP emphasised the need for ADA to achieve both primary endpoints, as well as the first ranked secondary endpoint of sustained remission from Weeks 8 to 52 for the application to be successful. In view of this requirement, the primary and secondary endpoints are satisfactory. These endpoints are considered to be reliable measures of clinical benefit in patients with UC.

7.1.1.2.3. Randomisation and blinding methods

Randomisation: An Interactive Voice Response System (IVRS) centrally managed the clinical study drug randomisation, drug-dispensing kits, inventory and unblinding. Subjects were randomised 1:1 at baseline to receive ADA or placebo by SC injection according to a randomisation scheme generated by Abbott GmbH & Co KG, Ludwigshafen, Germany. Randomisation was stratified according to prior anti-TNF exposure into 'anti-TNF experienced' and 'anti-TNF naive' subjects.

Comment: The central randomisation process appears satisfactory. However, given the randomisation code was not generated independently, this is a potential source of selection bias. The stratification was appropriate in view of the proposed indication. It would also have been helpful to have information on efficacy stratified by prior HACA status, given the reduced trough concentrations in subjects with prior HACAs.

Blinding: Abbott, the Investigator, site study personnel, and subject were blinded to each subject's treatment. Whenever possible, the same physician determined Mayo and PM scores for an individual subject. ADA and placebo injections appeared identical, to maintain the treatment blind. The same endoscopist (whenever possible, the Investigator or sub-Investigator) performed all endoscopies for an individual subject throughout the study.

Comment: The blinding processes were satisfactory.

7.1.1.2.4. Analysis populations

Four sets of study data were analysed (Table 7):

· ITT Analysis Set: Subjects with confirmed UC at baseline who were randomised and received at least one injection of DB study drug;

· Modified ITT Analysis Set: Subjects from the ITT analysis set who received at least one injection of ADA 40mg eow or placebo (for exploratory analyses only);

- Per Protocol (PP) Analysis Set: Subjects in the ITT analysis set after excluding subjects with major protocol deviations (for sensitivity analysis);
- Safety Analysis Set: Subjects who received at least one dose of study drug (irrespective of compliance status).

Table 7: Study M06-827 Analysis Sets

	Number (%) of Subjects		
Analysis Set	Placebo N = 260	Adalimumab N = 258	Total N = 518
Safety	260	257[a]	517
Intent-to-Treat	246	248	494
Modified Intent-to-Treat	246	247	493
Per Protocol	212	212	424

a. One subject was randomized to adalimumab but never treated.

Note: A total of 24 subjects were excluded from the ITT and mITT analysis set due to non-compliance with GCP and protocol requirements at the investigative sites (Sites 22635, 36809, and 27010).

7.1.1.2.5. Sample size

Assuming 5% of subjects in the placebo group achieved CR at Week 52 or Week 8, a sample size of 250 subjects in each treatment group was deemed adequate to detect a difference of at least seven (7) percentage points from the ADA group using Chi-square test with 80% power at a 0.05 two-sided significance level. Hence, 500 subjects in total were selected for randomisation.

7.1.1.2.6. Statistical methods

The designated biostatistician at Abbott GmbH & Co KG, Ludwigshafen, Germany, was responsible for data analysis.

The primary efficacy analysis was performed on the ITT analysis set and consisted of two ranked primary efficacy endpoints: (1) the proportion of subjects achieving CR at Week 8 and (2) the proportion of subjects achieving CR at Week 52. Hypothesis testing for the ranked endpoints was carried out in a hierarchical order using a two-sided Cochran-Mantel-Haenszel (CMH) test, adjusted for prior exposure to infliximab or other anti-TNF agents. The Week 8 CR rate was tested first. If the null hypothesis of no difference between ADA and placebo in CR rate at Week 8 was rejected at $\alpha = 0.05$, then the CR rate at Week 52 was tested at $\alpha = 0.05$.

To claim maintenance of CR, it was necessary to reject not only both hypotheses on the two ranked co-primary endpoints, but also to reject the hypothesis on the first ranked secondary endpoint (proportion of subjects in remission at Weeks 8 and 52). This first ranked secondary endpoint was incorporated in the confirmatory testing procedure conducted in hierarchical order from the first to the second ranked co-primary efficacy endpoint, and then to the ranked secondary endpoints, and stopped whenever a hypothesis could not be rejected at a significance level of 0.05. If a ranked endpoint did not meet the criteria for statistical significance, the analyses of the rest of the ranked secondary endpoints would be considered exploratory. This ensured the multiple significance level was controlled at 0.05.

Non-responder imputation (NRI) rate was used in the primary analysis. Subjects who discontinued the study for any reason, and subjects with a missing Mayo score, were counted as non-remitters. Subjects who switched to OL drug were counted as non-remitters from the time of switching onward. The last observation carried forward (LOCF) method was used for sensitivity analyses. For subjects who switched to OL drug, the non-missing value at the visit when the subject switched to the OL drug was carried forward in the LOCF analysis.

Time in CRESP per PM score was analysed using Kaplan-Meier curves and a proportional hazards model included treatment factors and prior exposure to infliximab or other anti-TNF

agents. The start of the CRESP was the date the first CRESP per PM score was achieved while a subject received DB study drug. End of CRESP per PM score was defined as the earliest instance of 1) the loss of CRESP on at least two consecutive evaluations (the date at the end of CRESP was the earlier of the two consecutive evaluations), 2) the date of a subject's premature discontinuation, or 3) the date the subject switched to OL administration. Subjects who completed the study on DB study drug without having experienced a loss of CRESP were censored on the date of study completion.

Secondary efficacy analyses were performed on the ITT set. The testing of ranked secondary endpoints was initiated only in case of statistically significant differences between the treatment groups for both ranked co-primary endpoints.

> **Comment**: The statistical methods used are conventional and appropriate. The use of NRI for the primary efficacy analyses instead of LOCF provides a more conservative estimate of treatment effect. The statistical analysis plan is acceptable to this evaluator. Lack of an independent biostatistician has the potential to introduce bias into the results.

7.1.1.2.7. Participant flow

Prior to Week 8, 11.9% subjects in the ITT analysis set discontinued treatment (9.3% in the ADA group and 14.6% in the placebo group, respectively). At Week 52, 37.9% (n=94) subjects in the ADA group discontinued prematurely and 46.7% (n=115) in the placebo group. The greatest proportion of subjects who discontinued at Weeks 8 and 52 withdrew from lack of efficacy. Reasons for discontinuation were comparable between groups (see Table 8), although the placebo group recorded a higher AE rate at Week 52 than the ADA group (10.2% and 4.8%, respectively).

Of 435 subjects who completed Week 8, 251 (57.7%) entered the OL study with an initial ADA 40mg eow dosing regimen (see Figure 4). Only 82 subjects (33.6%) of the DB ADA group completed the DB phase compared to 56 subjects (22.4%) in the DB placebo group. The overall DB completion rate was 27.9%.

Of those who entered the OL phase (135 initially randomised to placebo and 116 initially randomised to ADA), 58.6% (n=147) completed the study. During the OL phase, 39.4% subjects (n=99) remained on ADA 40mg eow dosing while 60.6% subjects (n=152) dose-escalated to 40mg ADA ew (84 initially randomised to placebo and 68 initially randomised to ADA). 62.6% subjects (n=62/99) completed OL ADA 40mg eow dosing and 55.9% (n=85/152) completed OL ADA ew dosing.

Table 8: Disposition of Subjects from Study M06-827

Subject Status – All randomized	Number (%) of Subjects		
	Placebo	Adalimumab	Total
Randomized	260	258	518
Treated	260	257	517
Subject Status – Final (ITT Analysis Set)	**Number (%) of Subjects**		
	Placebo N = 246	**Adalimumab N = 248**	**Total N = 494**
Discontinued study	115 (46.7)	94 (37.9)	209 (42.3)
Reasons for discontinuation[a]			
Adverse event	25 (10.2)	12 (4.8)	37 (7.5)
Withdrew consent	4 (1.6)	8 (3.2)	12 (2.4)
Lost to follow-up	0	1 (0.4)	1 (0.2)
Lack of efficacy	70 (28.5)	63 (25.4)	133 (26.9)
Protocol violation	5 (2.0)	1 (0.4)	6 (1.2)
Other[b]	11 (4.5)	9 (3.6)	20 (4.0)
Subject Status – Week 8 (ITT Analysis Set)			
Discontinued study prior to Week 8	36 (14.6)	23 (9.3)	59 (11.9)
Reasons for discontinuation[a]			
Adverse event	10 (4.1)	5 (2.0)	15 (3.0)
Withdrew consent	2 (0.8)	1 (0.4)	3 (0.6)
Lost to follow-up	0	0	0
Lack of efficacy	15 (6.1)	13 (5.2)	28 (5.7)
Protocol violation	3 (1.2)	1 (0.4)	4 (0.8)
Other[b]	6 (2.4)	3 (1.2)	9 (1.8)

a. Primary reason.

b. Reasons for discontinuation recorded as "other" included: diagnosis of CD, loss of response, primary nonresponder, UC symptoms not improving, investigator decision, subject noncompliance, positive TB skin test, subject wanted to start family, or total colectomy surgery within the 70-day follow-up period.

Comments: Only 27% of the DB population completed the 52-week study. Furthermore, a large proportion of subjects who received ADA DB and OL treatment (including those who dose-escalated) withdrew from the study secondary to lack of efficacy. These findings suggest ADA is not effective in most subjects with moderately severe to severe UC.

It is unclear from the submitted data what number of subjects entered the screening period of Study 827, as well as the proportion of subjects who failed to complete the screening period, and for what reasons. Clarification will be sought from the Sponsor.

- **Major protocol violations/deviations**

Protocol deviations in the ITT Analysis set are summarised in Table 9. Inclusion Criterion No. 3, the requirement subjects be diagnosed with active UC confirmed by colonoscopy with biopsy or flexible sigmoidoscopy with biopsy, was the most frequently violated inclusion/exclusion criteria (6.7%), and occurred in similar proportions of subjects in both treatment groups.

Three Subjects [**Information redacted**] were erroneously enrolled in the study after having biopsies showing evidence of dysplasia at screening. Subject [**Information redacted**] discontinued after receiving 28 days of DB ADA treatment when the deviation was identified. Subjects [**Information redacted**] and [**Information redacted**] were not identified as having had screening biopsies showing evidence of dysplasia until after study completion. Subject **[Redacted information]** switched to OL ADA administration. No subject experienced a malignancy-related TEAE during the study.

No major differences were found between the PP and the primary efficacy ITT analyses.

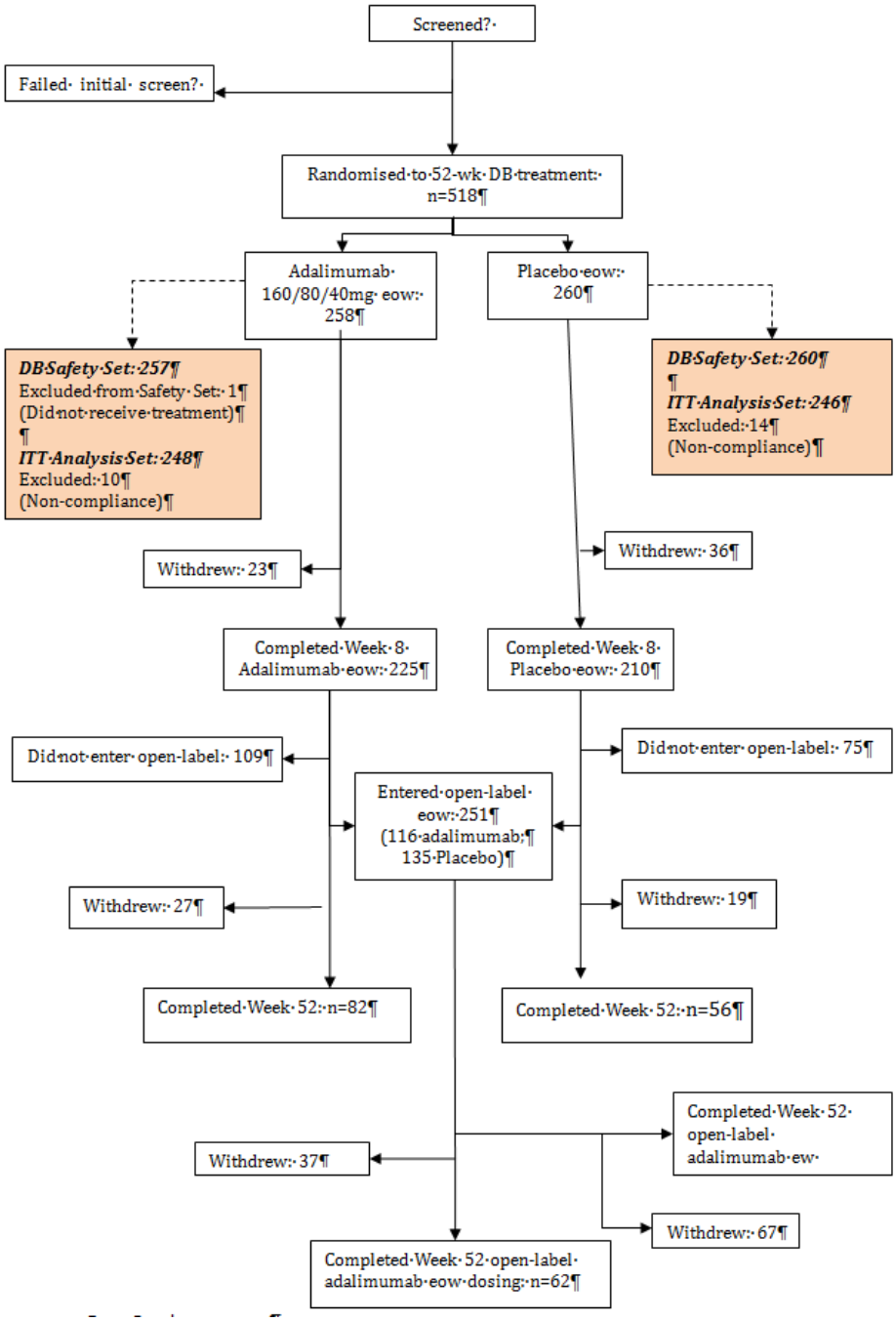
Table 9: Study M06-827 Protocol Deviations (ITT Analysis Set)

	Number (%) of Subjects		
Deviation Category	**Placebo N = 246**	**Adalimumab N = 248**	**Total N = 494**
Inclusion/Exclusion Criteria Violation	32 (13.0)	40 (16.1)	72 (14.6)
Developed Withdrawal Criteria/Was Not Withdrawn	0	0	0
Received Wrong Treatment or Incorrect Dose	26 (10.6)	31 (12.5)	57 (11.5)
Received Excluded Concomitant Treatment	55 (22.4)	45 (18.1)	100 (20.2)

Comments: Table 9 does not include 24 subjects who violated GCP. The PP population of 424 subjects means 14.2% of the ITT population had major protocol violations or deviations (18.1% if the 24 excluded subjects are included). However, sensitivity analyses suggest minor differences in efficacy results between the PP and ITT populations, supporting the internal validity of the study design. It is unclear from the submission what excluded medications were administered during DB treatment in the ADA and placebo groups.

After completion of the initial study report, the Sponsor identified five instances in which subjects received expired study drug. These subjects were not excluded from analyses on the basis of in-house stability testing data. However, while reduced efficacy cannot be discounted for these subjects, overall efficacy results are unlikely to be affected.

Figure 4: Study M06-827 Participant flow



- **Treatment compliance**

Subjects or their designee injected study medication at home between scheduled clinic visits and documented each administration in a log book. Table 10 summarises the mean and median compliance rates across treatment groups. Both groups achieved approximately 100% median and mean compliance, although overdosing occurred in each group to a similar extent. The latter suggests subject-attributed dosing errors occurred while home dosing or incorrect data entry into the subject's log book.

Table 10: Study M06-827 Treatment Compliance (ITT Analysis Set)

Percentage Compliance	Placebo N = 246	Adalimumab N = 247	Total N = 493[a]
Mean ± SD	99.47 ± 2.880	99.65 ± 2.124	99.56 ± 2.528
Median	100.00	100.00	100.00
Min – Max	76.7 – 113.5	89.4 – 108.9	76.7 – 113.5

a. One randomized subject did not receive any medication (Subject 79908) and is not included in this table.

Note: Number of possible injections between last drug and first drug injection was calculated taking into consideration periods with eow and ew dosing. Study discontinuation date = last injection date.

Cross reference: Table 14.1_3.1.2

7.1.1.2.8. Baseline data

The baseline demographic characteristics between the ADA and placebo treatment groups were comparable and representative of a population with UC in terms of age, gender and race distribution i.e. primarily white adult males.

The baseline disease/medical history characteristics (including medications used for UC and non-UC indications) between ADA and placebo treatment groups were comparable. 100% 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 (out of 12) and the mean baseline PM score was 6.5 (out of 9), both indicative of moderate to severe disease activity. The mean rectal bleeding subscore (RBS) of 1.7 (out of 3.0) indicates mild-moderate disease activity, whereas the mean stool frequency subscore (2.6 out of 3.0) reported by subjects indicated more severe disease activity, yet the physician's global assessment (PGA) score of 2.2 (out of 3.0) suggests a more moderate disease activity overall. Subscores were similar between groups with no statistical differences found.

In terms of UC-related medicines used in the five years before study randomisation these were comparable between treatments with approximately 88% subjects using CS and 40% anti-TNF medication (principally infliximab). In the 90 days preceding randomisation approximately two-thirds of subjects received CS and aminosalicylates. A greater proportion of subjects in the ADA received AZA than placebo (33.5% and 27.6%, respectively). These same trends were found at baseline (approximately 60% each group were receiving CS and aminosalicylates; the proportion of subjects in the ADA group receiving AZA was greater than in the placebo group: 30.6% and 26.0%, respectively).

The proportion of subjects who had prior infliximab/anti-TNF exposure was similar across treatment groups. Most subjects were anti-TNF naive (59.7%).

ADA treated subjects had statistically significantly higher SF-36 mental component summary score and role-emotional functional and mental health component scores compared with placebo treated subjects.

The ITT, PP and safety populations had similar baseline demographics.

> **Comment**: Overall, placebo and ADA treatment groups were generally well balanced with regard to key baseline variables. The majority of subjects in each treatment group were male and Caucasian, with no significant differences noted (other than SF-36 and component scores). Participants had moderate to severe UC (Mayo score ≥6 and an endoscopy subscore≥2) and most received previous CS or AZA prior to study entry. Approximately 40% participants had prior exposure to infliximab or other anti-TNF treatment, and had either loss of response or intolerance to such treatment.

7.1.1.2.9. Results for the primary efficacy outcome

7.1.1.2.9.1. Primary end-points

Remission at Week 8 (induction period)

A statistically significantly greater proportion of ADA subjects demonstrated CR at Week 8 compared with placebo subjects, assessed by Mayo score (16.5% versus 9.3%, respectively, p=0.019; Table 11). NNT = 14 i.e. 16.5-9.3 = 7.2%; 1/0.072 = 13.9.

Remission at Week 52 (maintenance period)

A statistically significantly greater proportion of ADA subjects demonstrated CR at Week 52 compared with placebo subjects, assessed by Mayo score (17.3% versus 8.5%, respectively, p=0.004; Table 12). NNT = 11 i.e. 17.3-8.5 = 8.8%; 1/0.088 = 11.4.

Table 11: 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=246)	(N=248)	
YES	23 (9.3)	41 (16.5)	0.019
NO	223 (90.7)	207 (83.5)	
DIFFERENCE IN PROPORTION[B]		7.2	
ADJUSTED DIFFERENCE IN PROPORTION[B]		7.1	
95% CONFIDENCE INTERVAL[C]		(1.2, 12.9)	
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]		(-9.3, 7.8)	
PRIOR ANTI-TNF NAIVE[E]	(N=145)	(N=150)	
YES	16 (11.0)	32 (21.3)	0.017
NO	129 (89.0)	118 (78.7)	
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 12: 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=246)	(N=248)	
YES	21 (8.5)	43 (17.3)	0.004
NO	225 (91.5)	205 (82.7)	
DIFFERENCE IN PROPORTION[B]		8.8	
ADJUSTED DIFFERENCE IN PROPORTION[B]		8.6	
95% CONFIDENCE INTERVAL[C]		(2.8, 14.5)	
PRIOR ANTI-TNF[E]	(N=101)	(N= 98)	
YES	3 (3.0)	10 (10.2)	0.039
NO	98 (97.0)	88 (89.8)	
DIFFERENCE IN PROPORTION[B]		7.2	
95% CONFIDENCE INTERVAL[D]		(0.4, 14.1)	
PRIOR ANTI-TNF NAIVE[E]	(N=145)	(N=150)	
YES	18 (12.4)	33 (22.0)	0.029
NO	127 (87.6)	117 (78.0)	
DIFFERENCE IN PROPORTION[B]		9.6	
95% CONFIDENCE INTERVAL[D]		(1.1, 18.1)	

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).

Comments: The efficacy of ADA in UC appears to be less than in CD because about half the patients required double the CD dose during maintenance treatment yet the number with a complete response to treatment was much less.

Although a direct comparison with infliximab in UC cannot be made due to differences in study design, it is evident from the Remicade PI that CR rates at Week 8 were markedly higher for infliximab-treated subjects versus placebo: 29.8 to 36.4% for infliximab versus 10.2% for adalimumab, respectively i.e. approximately double the effect found in Study 827. At Week 54 in Study ACT1 (combined infliximab doses) CR was achieved in 34.6% infliximab-treated subjects versus 16.5% placebo subjects (NNT 5), again showing a much greater clinical effect versus ADA at Week 52 (NNT 11).

7.1.1.2.9.2. Sub-group analyses of the primary end-points

Among anti-TNF naive subjects at study entry, a statistically significantly higher proportion of those treated with ADA 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: Table 11) and 52 (22.0% versus 12.4%, respectively, p=0.029; Table 12). Although statistical significance was not achieved in the first ranked secondary end-point, most other ranked secondary end-points statistically significantly favoured ADA treatment over placebo for anti-TNF naive subjects.

Among anti-TNF experienced subjects at study entry, ADA did not achieve statistical separation against placebo at the first primary end-point i.e. CR per Mayo score at Week 8 (9.2% versus 6.9%, respectively, p=0.559, Table 11). While statistically significantly greater proportions of ADA-treated subjects compared with placebo-treated subjects obtained CR per Mayo score at Week 52 (second primary end-point) as well as the ranked secondary end-points, clinical response per Mayo score at Week 52 and sustained clinical response per Mayo score at both Weeks 8 and 52, these results have little relevance to the overall study findings in view of the failure to achieve the primary endpoint.

Comments: The results of the subgroup analyses support the primary analysis of the primary endpoints, favouring ADA treatment over placebo only for anti-TNF naive subjects at study entry. Efficacy was not established in subjects with prior anti-TNF exposure.

Comparison between anti-TNF experienced subjects in CD Study II (see PI) i.e. subjects who had lost response or were intolerant to infliximab, and Study 827 revealed a similar trend in CR rate (albeit an overall reduction in magnitude secondary to anti-TNF exposure): 21% for ADA subjects versus 7% for placebo subjects, in CD and 9.2% for ADA subjects versus 6.9% for placebo subjects, in UC, respectively. Again, CR rates achieved in CD for the ADA 160/80/40 induction regimen approximately doubled that found in UC (irrespective of prior anti-TNF exposure).

7.1.1.2.9.3. Secondary end-points (ranked)

Fifteen ranked secondary variables were tested in a hierarchical order. Testing was only allowed if the ranked co-primary endpoints were significant. Statistically significant results ($p \leq 0.05$) had to be achieved for a comparison in the higher rank to initiate the next comparison in the lower rank. The first eight ranked secondary endpoints met the criteria for statistical significance. Indeed, other than failure to achieve statistical significance at ranked endpoint 9 (PGA≤1 at Week 8), ranked endpoints 10 to 15, inclusive, achieved statistical separation compared with placebo.

The first ranked secondary endpoint, sustained CR per Mayo score at both Weeks 8 and 52, provides a robust estimate of ADA ability to maintain efficacy over 44 weeks from the induction period. In the ADA 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) ADA subjects and 43.5% (n=10/23) placebo subjects). In terms of those subjects who completed DB treatment, 25.6% (n=21/82) ADA subjects had sustained CR and 17.9% (n=10/56) placebo subjects had sustained CR. When anti-TNF status is considered, 90% (n=9/10) of placebo subjects who had sustained CR (at Week 52) were anti-TNF naive compared with 76.2% (n=16/21) ADA subjects.

> **Comments**: Most ranked secondary endpoint results support the primary endpoint analyses. In regards to 'maintenance of clinical remission', a completion rate of 8.5% in the DB ADA group, with only a 4.4 greater difference in proportions compared with placebo, does not lend support for ADA as maintenance treatment in UC. Furthermore, efficacy was not established in those subjects with prior anti-TNF treatment [Section 7.1.1.2.9.2].
>
> For comparison with infliximab (see Remicade PI), sustained remission in UC was achieved at Week 54 in 20.2% combined infliximab-treated subjects versus 6.6% of placebo treated subjects. The remission rates versus placebo at Week 30 in UC and CD for Remicade were comparable (29.8-36.4% versus 13.1% and 39-45% versus 21%, respectively), whereas ADA in Study 827 appeared to achieve half the effect in UC compared with its effect in CD at Weeks 8 and 52. Although no conclusions can be made from these cross-study comparisons, this finding suggests infliximab may have a clinical advantage over ADA in some subjects and/or the design and conduct of Study 827 may have lead to an underestimate of the true effect of ADA in the study population (although the power of Study 827 appeared reasonable). It is possible Study 827 included more subjects with previous anti-TNF exposure and hence higher antibody levels. Subgroup analyses of efficacy will be very important to clarify this concern.

7.1.1.2.9.4. Secondary end-points (non-ranked)

With regard to non-ranked secondary measures, statistically significant differences were observed in favour of the ADA dosing regimen compared with placebo administration for the endpoints of CR and CRESP as assessed by Mayo score, PM score (except remission per PM score at Week 38 and response per PM score at Week 32 and 44), RBS ≤1 (except Week 44), SFS ≤1, PGA subscore ≤1 (except Weeks 8 and 44), MH (endoscopy score ≤1), CRP levels (significant only for Weeks 4 and 8), and proportion of IBDQ responders.

No subject had a colectomy during the 52-week study period. However, twenty-two subjects (12 randomised to placebo and 10 to ADA) underwent colectomy during the 70-day follow-up phase. Of the colectomy subjects 15 (68.2%) had prior anti-TNF exposure, similarly distributed across the ADA and placebo groups.

> **Comment**: The colectomy results suggest worse outcomes for subjects who had prior exposure to anti-TNF treatment but this is unclear from the submission as the subject number is small.

7.1.1.2.9.5. Other efficacy results

At Week 12, 54.9% (n=135/246) and 46.8% (n=116/248) subjects in the DB placebo and DB ADA groups, respectively, had inadequate CRESP and switched to OL ADA i.e. 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 ADA groups, respectively, dose escalated from 40mg eow to 40mg ew i.e. approximately one quarter of ADA-treated subjects required dose-escalation.

In subjects who dose-escalated to OL ADA 40mg ew, not surprisingly a greater proportion of subjects previously randomised to the placebo group appeared to achieve CR at Week 52 compared with the ADA 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 ADA subjects had missing data. Hence, meaningful conclusions could not be made with this data, especially in view of the

limitations on control in an OL trial and the different dosing regimens employed (once-a-week versus once-a-fortnight treatment).

> **Comment**: It is unclear from this submission whether dose-escalation provides an additional benefit in terms of CR. From the PI for CD [Table 15], ADA given once-a-week did not show statistically higher remission rates than the ADA group who received fortnightly dosing. In the absence of a direct comparison in Study 827, it can be reasonably assumed dose-escalation in UC is unlikely to result in more subjects having CR.

7.1.1.2.10. Week 8 responder analyses

Given the low proportion of subjects who achieved CR at Weeks 8 and 52, and sustained CR between Weeks 8 and 52, the EMA and FDA requested the Sponsor to undertake an early responder analysis (R&D/12/180). The proposed indication to discontinue ADA treatment in patients who fail to respond before 8 weeks is based on this early responder report. The US and European product labels have approved this restriction based on results from the early responder report.

These post hoc (exploratory) analyses evaluated the influence of early response (between Weeks 2 and 8) to ADA on efficacy outcomes, to identify whether early response was predictive of efficacy/remission and support the limitation of use of ADA to only those responding early. The trial was not originally designed to assess effects in initially responding patients, and a re-randomisation step along with treatment withdrawal was also not part of the design. Intuitively, for parity, it may be expected that the proper comparison is between ADA and placebo responders; however, this comparison is not appropriate due to the low placebo response. The representation of the initial clinical decision to not treat is designated by the total placebo group.

Analyses were undertaken on CRESP and CR rates at Week 52 in ADA-treated subjects who achieved CRESP per PM score at Week 2 (ADA Week 2 PM responders), Week 4 (ADA Week 4 PM responders) and Week 8 (ADA Week 8 PM responders). Since full Mayo (FM) score results were available at Week 8 in Study 827, an assessment was also made based on Week 8 FM score (ADA Week 8 FM responders).

- Results

CRESP per PM score was observed as early as Week 2. There was a positive trend towards CRESP per PM score and duration of exposure in both treatment arms, favouring ADA over placebo (treatment difference exceeded 10% at all time points; see Table 13).

Table 13: Subjects who achieved Clinical Response per PM Score at Weeks 2, 4 and 8 (Study 827 ITT NRI)

	Number (%) of Subjects			
Study Visit	Placebo N = 246	Adalimumab N = 248	Δ[a]	*P* value[b]
Week 2	49 (19.9)	97 (39.1)	19.2	< 0.001
Week 4	78 (31.7)	113 (45.6)	13.9	0.002
Week 8	86 (35.0)	123 (49.6)	14.6	0.001

a. Percent difference between active treatment and placebo.

b. *P* value to compare adalimumab with placebo was based on CMH test.

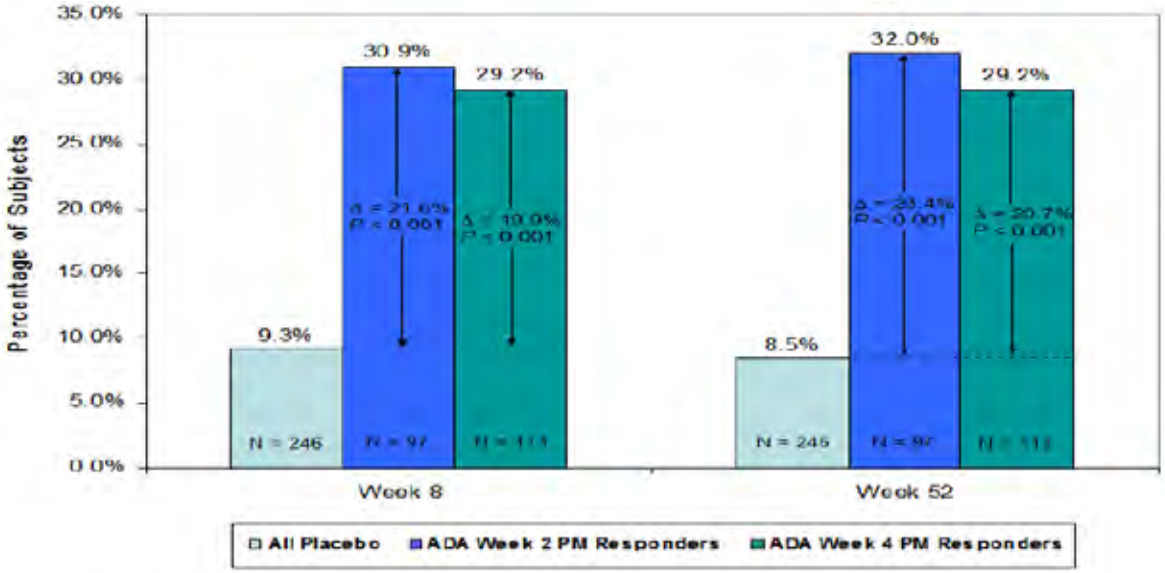
Notes: Response based on the PM score was defined as a decrease from Baseline in PM score ≥ 2 points AND a decrease from Baseline in PM score ≥ 30%. In addition, subjects must have had a decrease from Baseline in RBS ≥ 1 OR a RBS of 0 or 1.

According to the NRI method, all missing response values were considered to be nonresponses.

Cross reference: Study M06-827 CSR (R&D/10/236) Table 14.2__22.1

ADA-treated Week 2 and Week 4 PM responders achieved remission per FM score at Weeks 8 and 52 at rates that exceeded those observed in the all placebo group by approximately 20% or more ($p<0.001$ for both time points; Figure 5). Similarly, statistically significant differences in clinical response per FM score at Week 8 (by approximately 43% or more) and Week 52 (by approximately 28% or more; $p<0.001$ for both time points) in favour of the ADA treated population were observed in ADA-treated Week 2 and Week 4 PM responders, compared to the all placebo group (Figure 6).

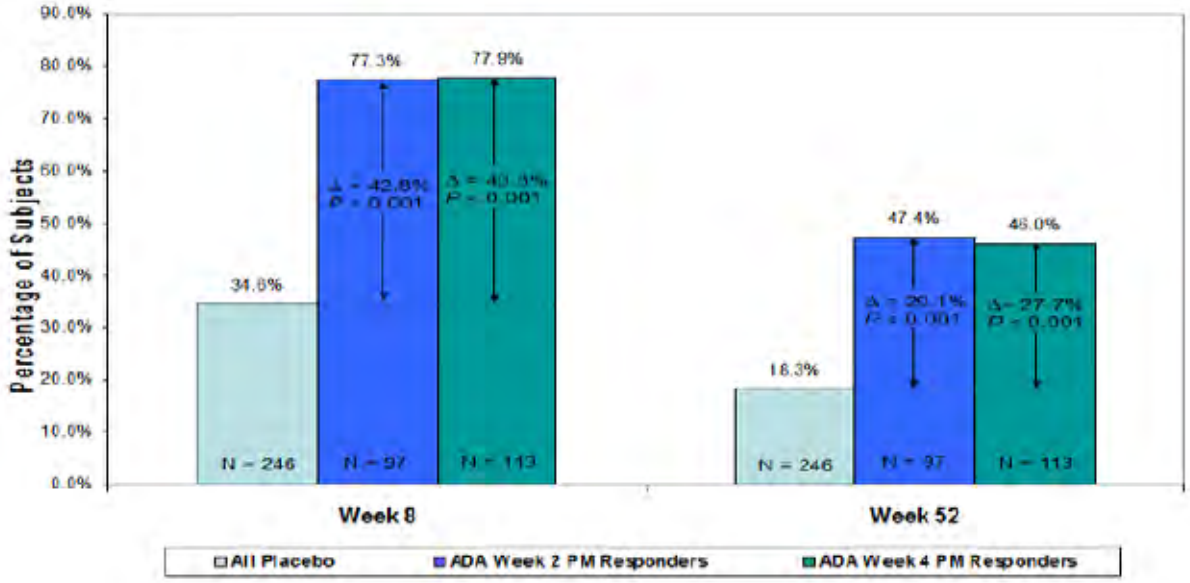
Figure 5: Clinical Remission per FM Score at Weeks 8 & 52 among Subjects Randomised to Adalimumab who achieved CRESP per PM Score at Weeks 2 & 4 Versus all Subjects randomised to Placebo (ITT NRI)



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

Cross reference: Table 1__1, Table 1__2, Table 1__62, Table 1__63

Figure 6: Clinical Response per FM Score at Weeks 8 & 52 among Subjects Randomised to Adalimumab who achieved CRESP per PM Score at Weeks 2 & 4 Versus all Subjects randomised to Placebo (ITT NRI)



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

Cross reference: Table 1__3, Table 1__4, Table 1__64, Table 1__65

At Week 8 and at Week 52, the absolute percent differences between the ADA and all placebo groups were similar for anti-TNF-experienced and anti-TNF-naïve subjects (Table 14). At Week 8 and at Week 52, the differences between treatment groups were statistically significantly in favour of ADA therapy with the exception of clinical remission per FM at Week 8 in Week 2 responders per PM for anti-TNF experienced subjects.

Table 14: Subjects by TNF Stratum achieving Clinical Remission and Clinical Response per FM Score at Weeks 8 & 52 (NRI) among Subjects Randomised to Adalimumab who achieved Clinical Response per PM Score (NRI) at Weeks 2 & 4 Versus all Subjects Randomised to Placebo (ITT Set)

Endpoint TNF Stratum Study Visit	Placebo n/N (%)	ADA Week 2 PM Responders[a] n/N (%)	 Δ^b	 *P* value[c]	ADA Week 4PM Responders[a] n/N (%)	 Δ^b	 *P* value[c]
Clinical Remission Per FM Score							
Anti-TNF-naive							
Week 8	16/145 (11.0)	24/67 (35.8)	24.8	< 0.001	25/83 (30.1)	19.1	< 0.001
Week 52	18/145 (12.4)	24/67 (35.8)	23.4	< 0.001	24/83 (28.9)	16.5	0.002
Anti-TNF-experienced							
Week 8	7/101 (6.9)	6/30 (20.0)	13.1	0.074	8/30 (26.7)	19.7	0.006
Week 52	3/101 (3.0)	7/30 (23.3)	20.4	0.001	9/30 (30.0)	27.0	< 0.001
Clinical Response Per FM Score							
Anti-TNF-naive							
Week 8	56/145 (38.6)	56/67 (83.6)	45.0	< 0.001	67/83 (80.7)	42.1	< 0.001
Week 52	35/145 (24.1)	36/67 (53.7)	29.6	< 0.001	38/83 (45.8)	21.6	< 0.001
Anti-TNF-experienced							
Week 8	29/101 (28.7)	19/30 (63.3)	34.6	< 0.001	21/30 (70.0)	41.3	< 0.001
Week 52	10/101 (9.9)	10/30 (33.3)	23.4	0.004	14/30 (46.7)	36.8	< 0.001

a. Subjects treated with adalimumab who achieved clinical response per PM score at Week 2 or Week 4 (defined as a ≥ 30% reduction in PM score compared with Baseline [minimum decrease of 2 points] and a ≥ 1-point decrease from Baseline in RBS or a RBS of 0 or 1).

b. Percent difference between active treatment and placebo.

c. *P* value comparing active treatment to placebo based on chi-square test (or Fisher's exact test if ≥ 20% of the cells had an expected cell count < 5).

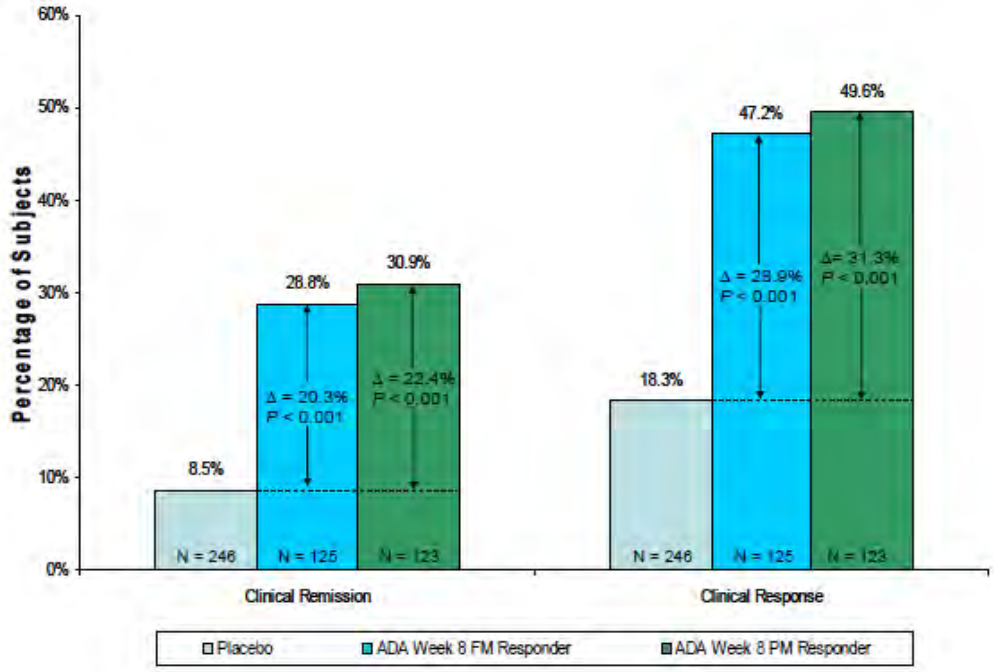
Notes: Remission was defined as Mayo score ≤ 2 with no subscore > 1.
Response was defined as a decrease from Baseline in Mayo score ≥ 3 points AND a decrease from Baseline in Mayo score ≥ 30%. In addition, subjects must have had a decrease from Baseline in RBS ≥ 1 OR a RBS of 0 or 1.
According to the 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.

Cross reference: Tables 1__1 through 1__4, Tables 1__62 through 1__65

A statistically significantly greater proportion of ADA Week 8 FM and PM responders achieved CR (>20% difference) or CRESP (>30% difference) per FM score at Week 52 compared with all randomised placebo subjects (Figure 7).

The proportions of subjects who had ≥50% reductions from baseline in FM score at Week 52 were numerically and statistically significantly greater in the ADA-treated Week 8 FM and PM responders (i.e. nearly half for each group) compared with placebo. The difference compared with placebo was statistically significant (p<0.001) and the effect size was similar (i.e. 24% to 31%) in anti-TNF-experienced and anti-TNF naïve subjects.

Figure 7: Clinical Remission and Response per FM 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.

Cross reference: Tables 1 77 through 1 80

A responder analysis evaluated MH. Among ADA Week 8 FM and PM responders, a statistically significant and >25% higher proportion of subjects achieved MH at Week 52 compared with placebo (p<0.001). A similar magnitude of treatment difference was obtained in subjects with and without prior anti-TNF exposure.

ADA Week 8 FM and PM responders experienced two-fold greater reductions in endoscopy subscore from baseline (LOCF) at Week 8 compared with placebo (approximately –54% versus approximately –27%, respectively; p<0.001), a difference sustained through endoscopy evaluations at Weeks 32 and 52. Moreover, the absolute changes in endoscopy subscore at Week 52 in the ADA Week 8 FM and PM responders groups (placebo: –0.7; ADA Week 8 FM and PM Responders: –1.3) were almost twice as great as those observed in the placebo group. Using a more conservative sensitivity analysis (worst-rank imputation method), more than one-third of ADA Week 8 FM and PM responders who entered the study with a baseline endoscopy subscore of 3, completed the study on DB therapy and achieved MH at Week 52 (34.6% of ADA Week 8 FM responders and 38.0% of ADA Week 8 PM responders), compared with <10% of placebo subjects.

· Discussion

These results suggest there is a consistent favourable effect over the total ADA treatment group (at each time point) through to Week 52 of ADA treatment for Weeks 2, 4, and 8 PM responders and Week 8 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 ADA, the magnitude of the differences measured, compared with placebo, consistently exceeded 10% and was consistently higher on every parameter measured against the total ADA 160/80/40 group results.

Many of the analyses failed to demonstrate differences between early responders who had prior anti-TNF exposure and those who did not. This conflicts with a consistent finding in the primary and secondary analyses that efficacy was not clearly demonstrated in subjects with prior anti-TNF exposure. The numbers of early responders who had prior anti-TNF exposure are small and therefore these post hoc analyses, undertaken on a subset of the ADA-treated subjects only (not placebo responders), are of limited predictive value.

> **Comments**: While these exploratory analyses lend support to treating subjects who respond early to ADA treatment, Study 827 was not designed to undertake such analyses. Furthermore, placebo subjects were not analysed specifically due to the small numbers that achieved remission. Indeed, the numbers of DB ADA treated subjects that achieved remission, and especially sustained remission throughout the maintenance phase suggest the early responder analyses be interpreted and applied with caution.
>
> While the results of the early responder analyses lend support to the restriction of indication in UC to early responders to ADA treatment, it would be more helpful to the prescribing clinician if they could predict which subjects would respond best to ADA treatment. Further information is requested on baseline characteristics of the early responder group to try and identify predictors of early/good response to ADA treatment.

7.1.2. Study 826

7.1.2.1. Study design, objectives, locations and dates

The study design is a multicentre, multinational, 52-week Phase III randomised, DB, placebo-controlled trial conducted between 13 November 2006 (first subject, first visit) and 5 March 2010 (last subject, last visit) in 80 centres. On study completion patients could enrol in the OL extension trial, Study 223.

The primary study objective was to assess the efficacy and safety of two dosing regimens of ADA for the induction of CR in subjects with moderately to severely active UC. The secondary objective was to provide supportive information on the maintenance of CR during the OL phase of the study.

In August 2007, the study design was amended to incorporate an additional ADA induction dosing arm of 80/40mg (at the request of the Swedish Medicines Agency). Earlier that year, both 160/80/40mg and 80/40mg induction regimens were approved in the EU as induction treatment for CD. The ADA induction dosing regimen of 80/40mg was therefore included so both approved induction regimens would be evaluated for induction of remission of UC. Figure 8 provides the Post-Amendment 3 schema.

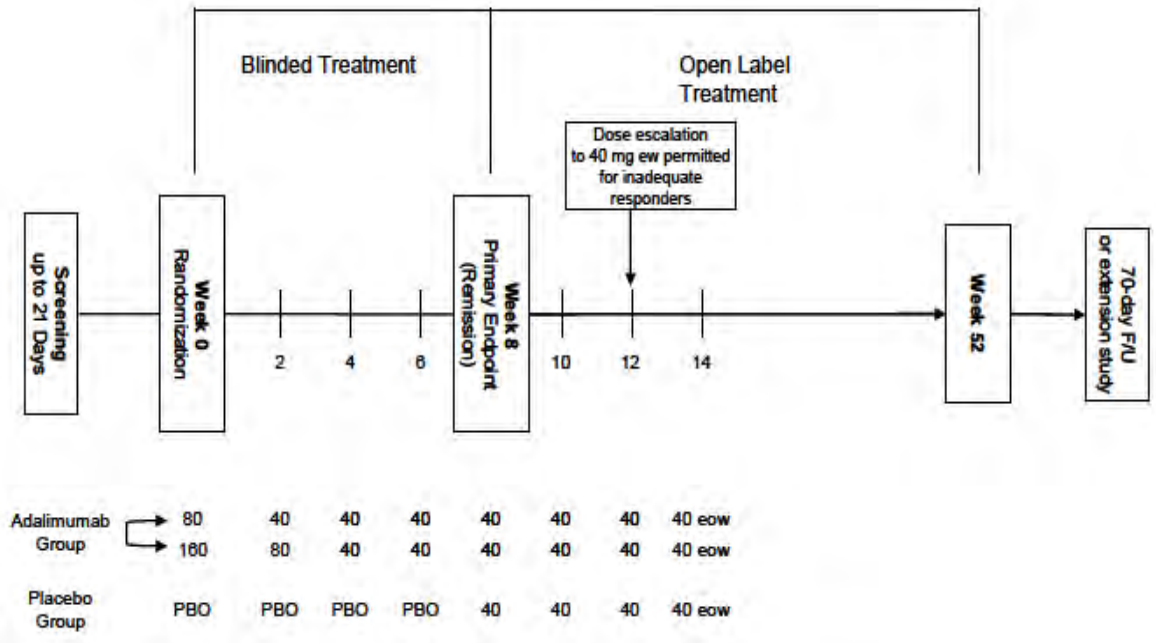
7.1.2.2. Inclusion and exclusion criteria

Adult subjects with moderate to severe 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.

> **Comment**: Study 826 had essentially the same inclusion and exclusion criteria as Study 827 except Study 827 included subjects with prior exposure to anti-TNF treatment

(approximately 40% of study population) whereas Study 826 recruited only anti-TNF naive subjects.

Figure 8: Study Design after Amendment 3



Study visits: screening, baseline (Week 0) and Weeks 2, 4, 6, 8, 10, 12, 16, 22, 28, 36, 44 and 52/ET.

7.1.2.3. Study treatments

In Study 826, subjects were randomised to two treatment groups (DB ADA 160/80/40 versus placebo) prior to Protocol Amendment 3 and to three treatment groups (DB ADA 160/80/40 versus ADA 80/40 versus placebo) under Protocol Amendment 3 or later. Between Weeks 8 to 12, subjects randomised to placebo received DB ADA 160/80/40 eow (for subjects included before Amendment 3 of the protocol) or OL ADA 40mg eow (for subjects included in or after Amendment 3). From Week 12 onwards, all subjects received OL ADA 40mg eow up to Week 52. At Week 12 (Week 14 for subjects randomised prior to Protocol Amendment 3) or thereafter, subjects with inadequate response (see defined criteria under Section 7.1.1.2.1) were allowed to dose escalate to 40mg ew. Hence, subjects received DB treatment from baseline until Week 8 and OL therapy from Week 8 until the end of the study.

7.1.2.3.1. Prior and concomitant medication

Permissible medicines: See Section 7.1.1.2.4.

Prohibited medicines: Any use of infliximab or any other anti-TNF agent, or abatacept, or any biological therapy was prohibited prior to and during the study.

7.1.2.4. Efficacy variables and outcomes

The primary induction endpoint was the proportion of subjects with CR at Week 8 (analysis conducted following completion of the last subject's Week 8 study visit).

The first four ranked secondary efficacy endpoints assessed at Week 8 (in order of testing) were:

1. Proportion of subjects with CRESP per Mayo score at Week 8 (ADA 160/80/40 versus placebo);
2. Proportion of subjects with MH at Week 8 (ADA 160/80/40 versus placebo);

3. Proportion of subjects with RBS indicative of mild disease (≤1) at Week 8 (ADA 160/80/40 versus placebo);
4. Proportion of subjects with PGA subscore indicative of mild disease (≤1) at Week 8 (ADA 160/80/40 versus placebo).

7.1.2.5. Randomisation and blinding methods

Randomisation: Central randomisation and study drug management occurred via the IVRS as detailed in Study 827, Section 7.1.1.2.3. Subjects enrolled after Amendment 3 were randomised 1:1:1 to receive one of two SC injection regimens of ADA or placebo during the 8-week DB induction period.

Blinding: Throughout the study, the Investigator, site study personnel and subject were blind to the subject's treatment allocation. Abbott remained blind until the database of the 8-week DB study phase was locked and the interim analysis was conducted. ADA and placebo injections appeared identical to maintain treatment blind.

7.1.2.6. Analysis populations

- The Intent-To-Treat - A3 (ITT-A3) Population: Subjects with confirmed UC at baseline who were randomised according to the revised study design described in Amendment 3 (and Amendment 4) and received at least one injection of ADA 160/80/40, ADA 80/40 or placebo (primary analyses of induction endpoints)^;
- The Intent-To-Treat - A2 (ITT-A2)* Population: Subjects with confirmed UC at baseline who were randomised into the study, under any version and received at least one injection of ADA 160/80/40, ADA 80/40 or placebo;
- The Safety Population: Subjects who received at least one injection of study drug;
- The Per Protocol (PP) Population: Subjects from ITT-A3 population without any major protocol deviations.

^ According to the Sponsor the ITT-A3 set allowed for a comparison of a homogeneous population.

*The ITT-A2 analysis set defined in the protocol (after Amendment 3) was renamed to the ITT-E (Intent-To-Treat – Extended) analysis set in the SAP and was used for analyses of maintenance during the OL phase, through Week 52 of the study.

Table 15: Number of Subjects by Analysis Set

	Number of Subjects			
Analysis Set	Placebo	Adalimumab 80/40	Adalimumab 160/80/40	Total
ITT-A3	130	130	130	390
ITT-E	222	130	223	575
Per Protocol	120	122	124	366
Safety	223	130	223	576

Cross reference: Table 14.1__1

Key differences in study design before and after Amendment 3 are shown in Table 16.

> **Comment**: Results are useful in showing an effect in an anti-TNF naïve population. The 40mg eow given in the maintenance phase was used by only about half of patients in the pivotal study (the rest used a double dose i.e. 40mg weekly). This supports the need for the 160mg initial dose during induction.

7.1.2.7. Sample size

Assuming 15% of subjects in the placebo group achieved CR at Week 8, a sample size of 125 in each treatment group in the ITT-A3 population would be adequate to detect a 15% difference using a Chi-square test with 80% power at a 0.05 two-sided significance level. Hence, a total of 375 subjects were planned to be randomised following Amendment 3 of the study.

The study actually enrolled 576 subjects, which included 186 subjects under the original protocol and Amendments 1 and 2, and 390 subjects under protocol Amendments 3 and 4.

Table 16: Key Differences in Study Design before and after Amendment 3

Prior to Amendment 3	After Amendment 3
Two treatment arms: Placebo Adalimumab 160/80/40	Three treatment arms: Placebo Adalimumab 80/40 Adalimumab 160/80/40
Double-blind period lasting for 12 weeks.	Double-blind period lasting for 8 weeks.
Stable (± 5 mg) corticosteroid dose (prednisone of ≥ 20 mg/day or equivalent) for at least 14 days prior to Baseline or maintenance corticosteroid dose (prednisone of ≥ 10 mg/day and < 20 mg/day or equivalent) for at least 40 days prior to Baseline.	Subjects had to be stable on prednisone ≥ 20 mg/day or equivalent for at least 14 days prior to Baseline; for doses of prednisone < 20 mg/day or equivalent, subjects had to be stable for at least 40 days prior to Baseline.
Prior and concurrent infliximab or anti-TNF excluded.	All prior and concurrent biologics excluded (including infliximab and anti-TNFs).
Immunosuppressants other than azathioprine or 6-MP (e.g., cyclosporine, methotrexate, or tacrolimus) prohibited within 60 days prior to Baseline and during the study.	Cyclosporine, tacrolimus, mycophenolate mofetil, and investigational agents prohibited 30 days or 5 half-lives prior to Baseline and during the study. Intravenous corticosteroid use prohibited within 14 days prior to Screening, during the Screening Period, and during the study.

7.1.2.8. Statistical methods

All statistical tests were two-tailed at α=0.05 significance. 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. Descriptive statistics were presented for the OL period through Week 52.

The primary and ranked secondary efficacy analyses were conducted in the ITT-A3 population. The objective of the primary efficacy analysis was to demonstrate ADA was statistically significantly superior to placebo in efficacy at Week 8, using the Chi-square test (two-sided) at an alpha level of 0.05. Analyses were carried out in hierarchical order to handle the multiplicity issues induced by two comparisons to placebo (and preserve the overall alpha level of 0.05):

1. Comparison of remission rates of ADA 160/80/40 and placebo at Week 8 (a $p \leq 0.05$ was necessary to initiate the next comparison).
2. Comparison of remission rates of ADA 80/40 and placebo at Week 8.

On 12 March 2009, in response to FDA comments on protocol Amendment 3, the hierarchical method of testing the 12 ranked secondary endpoints was changed in Amendment 4. Statistical comparisons for ranked secondary endpoints were carried out in hierarchical order in the ITT-

A3 analysis set. Statistically significant results ($p \leq 0.05$) must be achieved for a comparison in the higher rank, in order to initiate the next comparison in the lower rank. The difference in proportion of subjects who achieved response between ADA and placebo were assessed using the Chi-square or Fisher's exact test, as appropriate. Descriptive statistics were presented for the variables analysed during the OL phase.

7.1.2.9. Participant flow

A total of 185 subjects were enrolled before Amendment 3 and 390 subjects after Amendment 3. Figure 9 shows the disposition of subjects enrolled prior to Amendment 3. These subjects formed part of the ITT-E Analysis Set. Figure 9 shows the disposition of subjects enrolled after Amendment 3, the primary efficacy analysis set, ITT-A3.

From the CSR, most study discontinuations occurred from AEs, lack of efficacy or withdrawn consent. Table 17 summarises the rates of these withdrawals for subjects taking ADA 160/80/40 pre- and post-Amendment 3. Those subjects who received DB ADA 160/80/40 eow prior to Amendment 3 consistently had around twice the rate of study withdrawals from AEs, lack of efficacy and withdrawn consent at Weeks 8 and 52, compared with the same group after Amendment 3 was implemented.

Table 17: Comparative Rates of Withdrawals in Study M06-826 for Subjects who Received Adalimumab 160/80/40mg Pre- and Post-Amendment 3

Reason for Withdrawal	Pre-Amendment 3 Adalimumab 160/80/40, N=93 % of Subjects (n)		Post-Amendment 3 Adalimumab 160/80/40, N=130 % of Subjects (n)	
	Week 8	Week 52	Week 8	Week 52
Adverse event	8.6 (8)	20.4 (19)	3.7 (4)	10.8 (14)
Lack of efficacy	5.4 (5)	22.6 (21)	1.5 (2)	13.1 (17)
Withdrew consent	5.4 (5)	11.8 (11)	3.8 (5)	3.8 (5)
Protocol violation	2.2 (2)	3.2 (3)	1.5 (2)	2.3 (3)

The overall discontinuation rate was 31.1% for placebo, 33.8% for ADA 80/40 and 35.9% for ADA 160/80/40.

From Figures 9 and 10, the withdrawal rates between the ADA regimens after Amendment 3 were comparable to placebo at Weeks 8 and 52. The subjects on DB ADA 160/80/40 eow prior to Amendment 3 had much greater numbers of discontinued subjects compared with the same group after Amendment 3 at Week 8 (16.1% versus 6.9%, respectively) and at Week 52 (48.4% versus 26.9%, respectively).

> **Comment**: The Sponsor will be asked to reconcile these differences in withdrawal rates between Amendments.

7.1.2.10. Major protocol violations/deviations

Table 18 summarises the major protocol deviations in the ITT-A3 analysis set. The distribution of violations was comparable among treatment groups. The ITT-E set revealed comparable distributions across treatment groups of similar magnitude as in the ITT-A3 set except proportionately more inclusion/exclusion criteria deviations occurred in the ITT-E placebo group compared with the ITT-A3 set. This difference is explained by more placebo deviations in

those subjects randomised prior to Amendment 3 than when Amendment 3 was implemented (17.4%, n=16/92 versus 6.2%, n=8/130, respectively).

Figure 9: Participant Flow for Pre-Amendment 3 Subjects

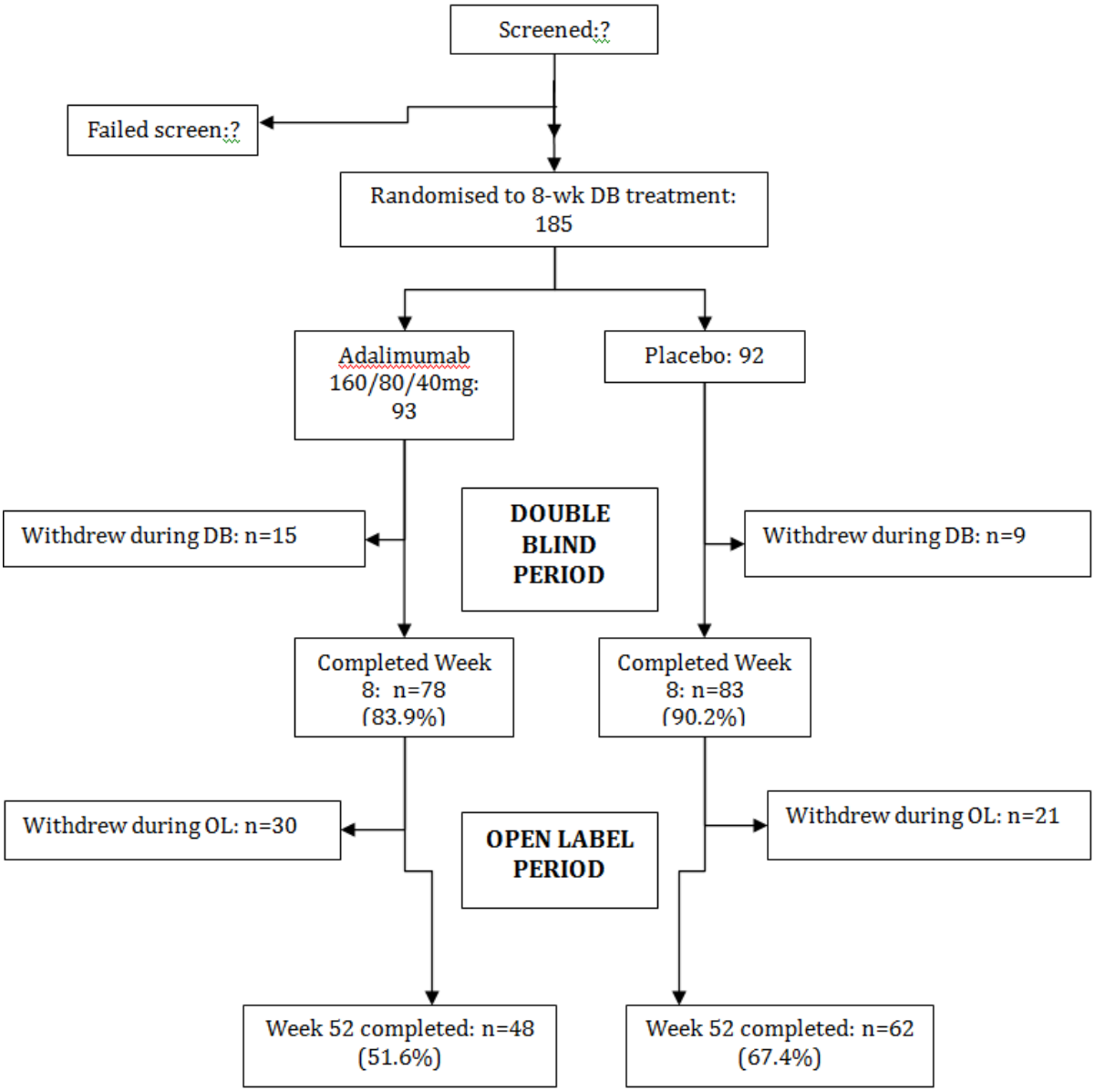
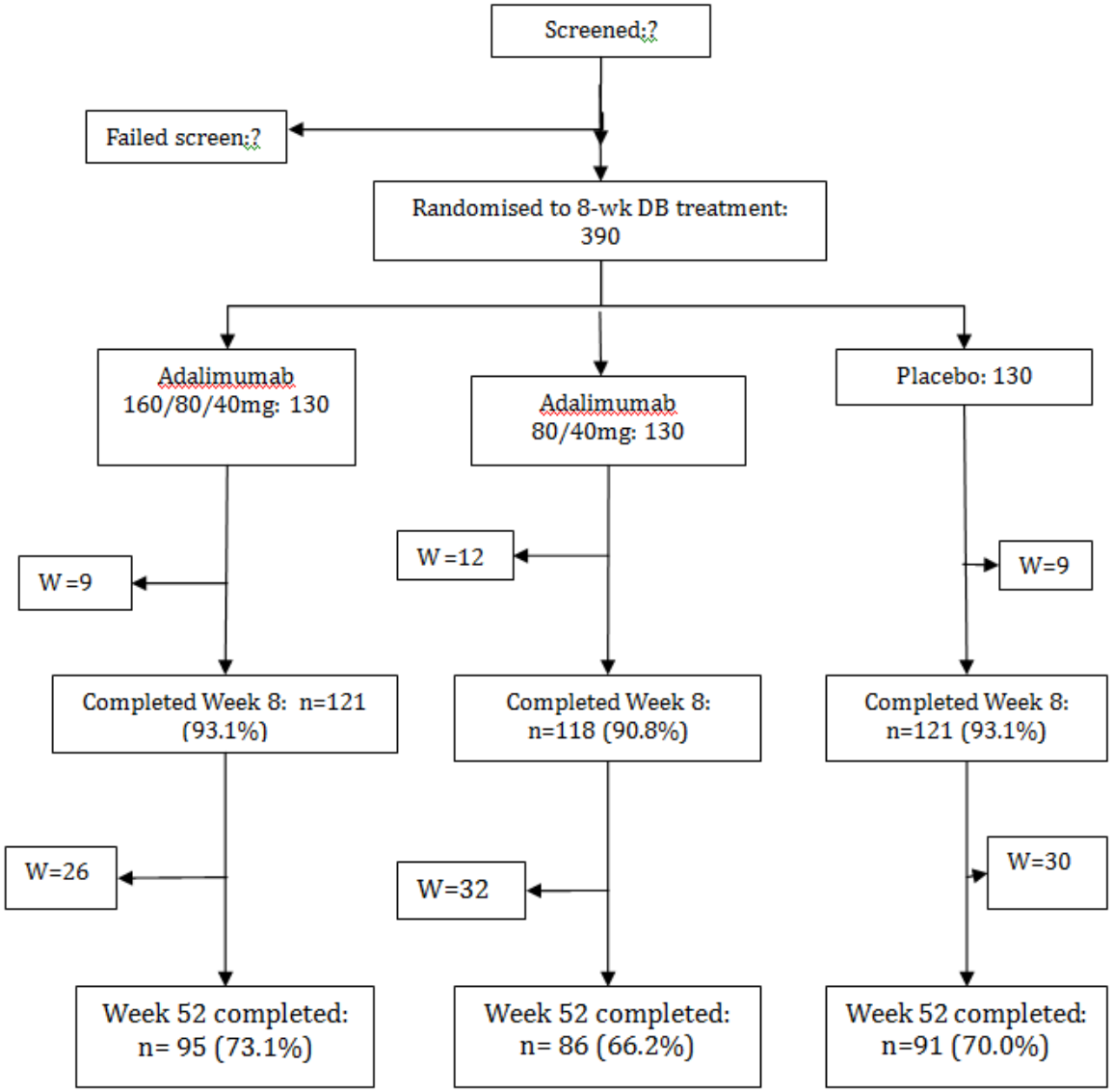


Table 18: Protocol Deviations during DB Period to Week 8 (ITT-A3 Set)

Deviation Category	Number (%) of Subjects			
	Placebo N = 130	Adalimumab 80/40 N = 130	Adalimumab 160/80/40 N = 130	Total N = 390
Inclusion/exclusion criteria deviations	8 (6.2)	9 (6.9)	8 (6.2)	25 (6.4)
Developed withdrawal criteria but was not withdrawn	0	0	1 (0.8)	1 (0.3)
Received wrong treatment or incorrect dose	10 (7.7)	10 (7.7)	11 (8.5)	31 (7.9)
Received excluded concomitant treatment	11 (8.5)	13 (10.0)	8 (6.2)	32 (8.2)

Note: Subjects could have had more than 1 deviation but are counted once in each respective category.
Cross reference: Table 14.1__2.4

Figure 10: Participant Flow for Post-Amendment 3 Subjects (ITT-A3 Analysis Set)



W=withdrawn

Comment: Protocol deviations do not explain the difference in withdrawal rates between subjects who completed 8 weeks of DB ADA 160/80/40 eow treatment prior to Amendment 3 compared with those who complied with Amendment 3.

7.1.2.10.1.1. Treatment compliance

Compliance was defined as the number of study drug injections received divided by the number of study drug injections planned during the subject's study participation for the first 8 weeks (i.e. DB phase).

Comment: From Table 19, median compliance was 100%. However, the way the mean information is presented is not helpful. The Sponsor explains the >100% mean compliance rates across treatment groups was due primarily to an extra injection at Week 8 (not the end-of-study). However, this only partially explains the results, for the range of values indicates very low compliance in all groups (most probably those subjects who withdrew during this period) and up to 100% overdose in the ADA 160/80/40 group, which is a concern.

Table 19: Treatment Compliance – DB Period through to Week 8 (ITT-A3 Set)

% Compliance[a]	Placebo N = 130	Adalimumab 80/40 N = 130	Adalimumab 160/80/40 N = 130
Mean ± SD	104.7 ± 15.18	102.7 ± 12.38	104.5 ± 16.38
Median	100.0	100.0	100.0
Min – Max	33 – 125	33 – 133	25 – 200

a. Due to windowing rules for the compliance analysis, some subjects could have been calculated to have > 100% compliance.

Cross reference: Table 14.1__3.3.1

7.1.2.11. Baseline data

The majority of study subjects in the ITT-A3 set (and ITT-E set) were male, white and <65 years old. Placebo subjects in the ITT-A3 set had a lesser mean duration of UC at baseline and a greater proportion of subjects with pancolitis than the ADA treatment groups (see Table 20).

Table 20: Baseline Disease History (ITT-A3 Set)

Demographic Characteristic	Placebo N = 130	Adalimumab 80/40 N = 130	Adalimumab 160/80/40 N = 130
Duration of UC (mean ± SD, years)	7.48 ± 7.159	8.57 ± 7.511	8.11 ± 7.247
Site of UC (n [%])			
Pancolitis	73 (56.2)	70 (53.8)	60 (46.2)
Descending colon	42 (32.3)	48 (36.9)	61 (46.9)
Other	15 (11.5)	12 (9.2)	9 (6.9)
UC confirmed by biopsy (n [%])			
Yes	130 (100)	129 (99.2)	130 (100)
No	0	1 (0.8)	0
Evidence of dysplasia/malignancy (n [%])			
Yes	0	0	0
No	130 (100)	129 (100)	130 (100)
Missing	0	1	0

SD = standard deviation

Note: Subjects randomized to the placebo group received adalimumab 40 mg eow or adalimumab 160/80/40 eow starting from Week 8. Percentages calculated on non-missing values. Evidence of infection from biopsy was collected only for subjects enrolled prior to amendment 3 therefore this information is not included in this table.

Cross reference: Table 14.1__6.1.1, Table 14.1__6.2.1, Table 14.1__6.3.1

The ITT-A3 treatment groups had comparable baseline disease activity (see Table 21) with most subjects demonstrating moderate to severe disease (Mayo score ≥6 and an endoscopy subscore of ≥2) in Mayo score and subscore ratings.

A statistically significant difference (p=0.009) was observed across treatment groups in baseline PGA subscore in the ITT-E set. A greater proportion of subjects randomised to ADA had mild or severe disease compared with subjects randomised to placebo (7.9% versus 3.6% and 34.6% versus 26.1%, respectively), whereas a greater proportion of subjects randomised to placebo had moderate disease compared with subjects randomised to ADA (70.3% versus 57.2%, respectively).

Comments: Generally, the treatment groups were similar in terms of demographics, medical history, mean baseline disease activity scores (albeit placebo had less duration of disease and ADA 160/80/40 had more descending colon disease than the other groups in the ITT-A3 set), ECG, TB skin test for positivity, CXR and prior/concomitant medications.

No baseline data for the pre-Amendment 3 population in terms of demographics, disease history and disease activity has been provided in this submission. This information is to be requested.

Table 21: Baseline Disease Activity (ITT-A3 Set)

	Mean ± SD		
Efficacy Measure	**Placebo N = 130**	**Adalimumab 80/40 N = 130**	**Adalimumab 160/80/40 N = 130**
Mayo score	8.7 ± 1.56	9.0 ± 1.62	8.8 ± 1.61
Partial Mayo score	6.2 ± 1.41	6.5 ± 1.43	6.4 ± 1.51
Endoscopy subscore (mucosal healing)	2.5 ± 0.52	2.5 ± 0.50	2.4 ± 0.50
Rectal bleeding subscore	1.6 ± 0.79	1.7 ± 0.78	1.7 ± 0.88
Physician's Global Assessment subscore	2.2 ± 0.50	2.3 ± 0.62	2.2 ± 0.57
Stool frequency subscore	2.4 ± 0.74	2.5 ± 0.72	2.5 ± 0.78
IBDQ score[a]	125.2 ± 31.94	125.6 ± 35.25	131.9 ± 35.07
SF-36 physical component score[b]	40.30 ± 7.947	40.85 ± 7.850	41.99 ± 8.793
SF-36 mental component score[b]	36.68 ± 11.006	37.22 ± 11.791	36.84 ± 12.767

SD = standard deviation

a. Assessed in 127 placebo subjects, 125 adalimumab 80/40 subjects, and 120 adalimumab 160/80/40 subjects.

b. Assessed in 125 placebo subjects, 126 adalimumab 80/40 subjects, and 128 adalimumab 160/80/40 subjects.

Cross reference: Table 14.1__5.3.1, Table 14.1__5.4.1, Table 14.1__5.6.1

7.1.2.12. Results for the primary efficacy outcome

The results for the CR rates per Mayo score at Week 8 are presented in Table 22. The ADA 160/80/40 regimen demonstrated statistically significantly higher remission rates against placebo in the primary (ITT-A3 NRI) analysis (18.5% versus 9.2%, p=0.031), with similar findings in the sensitivity analyses.

ADA 80/40 regimen consistently failed to demonstrate statistical superiority against placebo.

Table 22: Number of Subjects with Clinical Remission per Mayo Score at Week 8 in the Primary Efficacy and Sensitivity Analyses

	Placebo		Adalimumab 80/40			Adalimumab 160/80/40		
Analysis	N	n (%)	N	n (%)	*P* value[a]	N	n (%)	*P* value[a]
Primary Efficacy Analysis								
ITT-A3 Set – NRI	130	12 (9.2)	130	13 (10.0)	0.833	130	24 (18.5)	0.031
Sensitivity Analyses								
ITT-A3 Set – LOCF[b]	123	12 (9.8)	120	13 (10.8)	0.782	124	24 (19.4)	0.033
Per Protocol Set – NRI	120	10 (8.3)	122	12 (9.8)	0.684	124	23 (18.5)	0.020
ITT-E Set – NRI	222	16 (7.2)	130	13 (10.0)	0.358	223	35 (15.7)	0.005

LOCF = last observation carried forward; NRI = non-responder imputation

a. *P* values for adalimumab versus placebo in ITT-A3 set (NRI and LOCF analyses) and placebo set from chi-square test (or Fisher's exact test if ≥ 20% of cells had expected cell count < 5). For subjects in the ITT-E set, the *P* value to compare adalimumab 160/80/40 versus placebo is from CMH test with subjects in/not in the ITT-A3 set as the stratification factor; and the *P* value to compare adalimumab 80/40 versus placebo is from chi-square test (or Fisher's exact test if ≥ 20% of cells had expected cell count < 5).

b. Per the LOCF analysis, the last non-missing post-Baseline values were carried forward..

Cross reference: Table 14.2__1, Tables 14.2__2.1 through 14.2__2.3

Comments: The CR rates for placebo and ADA 160/80/40 at the end of DB treatment (Week 8) are consistent with the rates found at the same time point in Study 827. Study 826 does not support the ADA 80/40 regimen during the induction phase.

The DB ADA 160/80/40 and DB placebo remission rates for the induction period for anti-TNF naive subjects in Study 827 are comparable to the results of Study 826 (21.3% versus 18.5% and 11.0% versus 9.2%, respectively). Again, the rate of CR for the ADA 160/80/40 regimen achieved in UC is approximately half that achieved at four weeks in CD.

No efficacy results for pre-Amendment 3 have been provided in this submission.

7.1.2.13. Results for other efficacy outcomes

Induction: While the third and fourth ranked secondary endpoints demonstrated statistical separation of ADA 160/80/40 against placebo (and other ranked secondary endpoints for ADA 160/80/40 were numerically greater than placebo), the first ranked secondary endpoint (clinical response per Mayo score at Week 8 in the ADA 160/80/40 treatment group versus placebo) did not meet the criteria for statistical significance. ADA 80/40mg did not demonstrate statistical separation against placebo for any ranked secondary endpoint.

Maintenance: In both ADA treatment groups, the proportion of subjects with CR per Mayo score increased from Weeks 8 to 52 (Table 23). In the placebo treatment group, the proportion of subjects with CR per Mayo score increased after subjects switched from placebo to ADA at Week 8. This improvement was similar between subjects who switched from placebo to ADA 40mg eow directly and those who switched to the ADA 160/80/40 induction regimen. A numerically higher percentage of subjects who switched to ADA 40mg eow directly were in remission at both Weeks 8 and 52 compared with those who switched to ADA 160/80/40. However, a higher proportion of placebo patients who directly went to 40mg eow had already been in CR at Week 8 compared to placebo patients who went on to ADA 160/80/40 therapy.

Table 23: 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

Fewer subjects in the ADA 160/80/40 treatment group required dose escalation (from 40mg eow to 40mg weekly) as compared to the ADA 80/40 or placebo groups (22.9% versus 30.0% and 31.1%, respectively). Within the placebo group, a lower proportion of subjects who received ADA 160/80/40 at the start of the OL period dose escalated as compared to those who switched directly to ADA 40mg eow (21.7% versus 37.7%, respectively). When analysed using the NRI method, the CR rate per Mayo score at Week 52 among all subjects combined was 24.2% (139/575 subjects).

Thirteen subjects (2.3%) had a colectomy after the last study dose (3.6%, n=8, randomised to placebo and 1.4%, n=5, randomised to ADA). More subjects who received the higher ADA induction regimen required a colectomy, but numbers are too small to draw meaningful conclusions.

Comments: Efficacy was not established in the first ranked secondary endpoint for the induction period for ADA 160/80/40 treatment.

During OL ADA treatment all treatment groups tended to have higher CR rates at Week 52 compared with Week 8. Not surprisingly, the greatest rates were found in previously placebo-treated subjects and subjects in the ADA 80/40 regimen. However, the sustained remission rates were still <10% in all groups and therefore of questionable clinical significance.

7.2. Non-pivotal efficacy study

7.2.1. Study M10-223

The interim study results for efficacy (cut off date 31 December 2009) are presented here as descriptive statistics. In view of the OL design (and hence lack of controlled conditions), the efficacy results are considered as supportive data only.

7.2.1.1. Study design, objectives, locations and dates

Study 223 was a multicentre, OL (extension) study that evaluated the long-term safety, tolerability and maintenance of response of ADA administration in subjects with UC who participated in and successfully completed either Study 826 or Study 827.

The first subject visit in this study was 27 November 2007. Sites included Australia, Austria, Belgium, Canada, Czech Republic, France, Germany, Hungary, Italy, The Netherlands, New Zealand, Poland, Puerto Rico, Slovakia, Spain, Sweden, Switzerland and the US.

7.2.1.2. Inclusion and exclusion criteria

Subjects included those who successfully completed Study 826 or Study 827. Subjects who did not respond to ADA ew dosing in the preceding study were not eligible for inclusion.

> **Comment**: Subjects who entered Study 223 from the three sites who violated GCP were subsequently removed from the efficacy data analyses following SAP Amendment 1, 23 February 2010, but formed part of the safety data set.

7.2.1.3. Study treatments

Day 1 (baseline) visit for subjects entering Study 223 was Week 52 of Studies 826 or 827. Subjects who entered from a blinded cohort were assigned OL ADA 40mg eow initially and could dose-escalate after Week 12 if they had an inadequate response to treatment and/or a disease flare-up. Subjects who entered from an OL cohort continued their previous eow or ew dosing regimen. Inadequate responders on 40mg eow ADA and those who continued an inadequate response could dose-escalate to 40mg ew at the Week 2 visit or thereafter.

Forty (40) subjects (8.0%) had received just placebo treatment before entering Study 223. Most subjects (382 subjects; 76.7%) were receiving eow dosing (230/290 from Study 826 and 152/208 from Study 827).

Subjects who received tapering CS from a previous study were permitted to continue the taper immediately upon enrolment into Study 223. From Week 12, UC-related concomitant medications (including IMMs) were permitted to be reduced or discontinued in subjects who showed clinical response.

7.2.1.4. Efficacy variables and outcomes

Efficacy was evaluated by PM scores at each study visit (absolute scores and change from baseline), Mayo scores at Week 48 (absolute scores and change from baseline), Mayo subscores (Endoscopy, RBS, SFS, PGA) at Week 48 or each study visit (absolute scores and change from baseline) and colectomy rates. Quality of life (QoL) was evaluated using IBDQ, SF-36, the Work Productivity and Activity Impairment Questionnaire at each visit or visits specified in the protocol, and health care resources utilisation (physician visit, emergency room visits, hospital admissions/days in hospital).

7.2.1.5. Randomisation and blinding methods

This was an OL extension study.

7.2.1.6. Analysis populations

The following data sets were analysed:

- ITT-1 (n=494): Subjects who received at least one dose of study drug;
- ITT-2 (n-448): ITT-1 subjects with a between-studies gap* of ≤17 days. This represents a sensitivity analysis of ITT-1;
- Safety set (n=498): Subjects who received at least one dose of study drug (including non-GCP compliant subjects).

*These gaps occurred from delays in IRB/IEC approval, logistical issues and inter-site subject transfers.

7.2.1.7. Sample size

Sample size assessment was not applicable.

More than 600 subjects from Studies 826 and 827 were potentially eligible for enrolment. Four hundred ninety-eight (498) subjects were enrolled at the data cut-off date: 290 (58.2%) from Study 826 and 208 (41.8%) from Study 827.

> **Comment**: Of the 382 subjects who completed Study 826, 334 (87.4%) enrolled in Study 223. Of the 296 subjects who completed Study 827, 258 (87.2%) enrolled in Study 223 as of 16 December 2011. Only interim data were available for evaluation

7.2.1.8. Statistical methods

Descriptive statistical analyses were performed for demographic, efficacy and safety parameters.

7.2.1.9. Participant flow

On 31 December 2009, 18.9% (n=94) of subjects had completed Week 60 and 13.5% (n=67) had withdrawn from the study (see Table 24). AEs (4.6%) and lack of efficacy (4.8%) accounted for most study withdrawals.

Table 24: Study M10-223 Disposition of Subjects at Week 60 (Safety Analysis Set)

	Adalimumab 40 mg eow or ew N = 498
Ongoing at Week 60	337 (67.7)
Completed Week 60	94 (18.9)
Discontinued before Week 60	67 (13.5)
Primary reason for discontinuation	
Adverse event	17 (3.4)
Withdrew consent	14 (2.8)
Lost to follow-up	1 (0.2)
Protocol violation	1 (0.2)
Lack of efficacy	23 (4.6)
Other[a]	11 (2.2)
All reasons for discontinuation[b]	
Adverse event	23 (4.6)
Withdrew consent	14 (2.8)
Lost to follow-up	1 (0.2)
Protocol violation	1 (0.2)
Lack of efficacy	24 (4.8)
Other[b]	12 (2.4)

eow = every other week; ew = every week

a. Death; exacerbation of UC; investigator withdrew subject at his discretion/noncompliance; per Sponsor's instructions; pregnancy; prohibited concomitant medications; protocol violation; Sponsor terminated study at site; suboptimal response.

b. Subjects who discontinued study drug were counted under each reason given for discontinuation; therefore, the sum of the counts given for the reasons may be greater than the overall number of discontinuations.

Note: Subjects discontinued before a respective week were subjects who discontinued the study and also did not have any dose of study drug on or after that time point as per the dosing information on the CRF.

7.2.1.10. Major protocol violations/deviations

On 31 December 2009, 29 major protocol deviations were documented (Table 25).

Table 25: Study 223 Summary of Protocol Deviations (Safety Analysis Set)

Deviation	Adalimumab 40 mg eow/ew N = 498
Inclusion criteria violated	0
Exclusion criteria violated	1 (0.2)
Developed withdrawal criteria/was not withdrawn	3 (0.6)
Received wrong treatment or incorrect dose	19 (3.8)
Received excluded concomitant treatment	6 (1.2)

eow = every other week; ew = every week

Cross reference: Table 14.1__2.3.3

7.2.1.11. Baseline data

From the CSR, most subjects were white males. The subject population was similarly distributed between those under/above 40 years of age.

The mean (±SD) and median PM scores were low at baseline (2.5 ± 1.99; n=493 and 2.0, respectively). The same trend was found with Mayo scores: mean (±SD) and median Mayo score was 3.5 ± 2.68; n=492 and 3.0, respectively. These values indicate low i.e. mild disease activity at baseline and this is further supported by the PM subscores, particularly the mean endoscopy score of 1.0 that indicates MH.

> **Comment**: No major differences in baseline characteristics were noted at extension study entry (or initial study entry).

7.2.1.12. Results for efficacy outcome

The mean and median PM scores remained stable throughout the first 60 weeks of OL ADA treatment (see Table 26). This trend was also found with mean and median full Mayo scores (and subscores e.g. mean endoscopy subscore maintained at 1.0 through Week 48).

Table 26: Partial Mayo Scores over Time, LOCF (ITT-1 Analysis Set)

	Adalimumab 40 mg eow/ew N = 498		
Time Point	n	Mean ± SD	Median
Week 0 (Baseline)	493	2.5 ± 1.99	2.0
Week 2	466	2.3 ± 2.06	2.0
Week 4	460	2.4 ± 2.06	2.0
Week 8	441	2.3 ± 2.04	2.0
Week 12	416	2.3 ± 2.09	2.0
Week 24	348	2.3 ± 2.0	2.0
Week 36	281	2.3 ± 2.15	2.0
Week 48	183	2.3 ± 2.26	2.0
Week 60	130	2.5 ± 2.50	2.0

eow = every other week; ew = every week; ITT = intent-to-treat; LOCF = last observation carried forward

Notes: At Weeks 2 through 60, only subjects with both Baseline and Visit Values are shown.

The observation period stopped on 31 December 2009. No data were carried forward beyond this point. Data after Week 60 are not shown, because less than 10% of subjects had reached a visit later than Week 60 as of the cut-off date.

Cross reference: Table 14.2__1.1.1.1 and Table 14.2__1.1.1.2

A total of 43 subjects (8.4%) required dose-escalation from 40mg eow to 40mg ew. The median PM score decreased (i.e. improved) by 50% (from last eow = 6.0 to last ew value = 3.0) among ITT-1 subjects who switched from eow to ew dosing. Five (5; n=1.0%) subjects required a colectomy during the interim phase of the study.

The Sponsor claims the QoL results support the efficacy findings. However, absenteeism, presenteeism, total work productivity and total activity impairment was recorded to be slightly higher (i.e. worse) from baseline to Week 60.

7.2.2. Analyses performed across trials (pooled analyses)

7.2.2.1. Hospitalisation

The objectives of the integrated analysis were to assess the effect of ADA maintenance therapy on the risk of all-cause hospitalisation, UC-related hospitalisation, UC- or drug-related hospitalisation in the pooled Study 826 and Study 827 trials. Reduction in hospitalisation rate may reflect a tangible benefit to patients, physicians and society. All-cause hospitalisation can be viewed as a composite indicator for benefit-risk profile of therapy since it includes hospitalisation due to AEs of therapy and every hospitalisation is considered a SAE in clinical trials.

For subjects who switched from placebo to OL ADA, hospitalisations that occurred during the first 70 days of OL ADA were attributed to placebo, to capture the potential for delayed hospitalisation/colectomy resulting from the failure of DB placebo treatment.

The overall follow-up time in the all patient population was longer for ADA-treated subjects than placebo-treated subjects (e.g. UC-related hospitalisation time was 389 PYs for ADA and 216 PYs for placebo). The incidence rates per 100 PYs of all-cause hospitalisation in the ADA and placebo groups were 18% and 26%, respectively (p=0.030).

For UC-related hospitalisation, the rates were 12% in the ADA group and 22% in the placebo group (p=0.002). For the Week 8 ADA responder population based on full Mayo score, the incidence rates for UC-related hospitalisation were also significantly lower in the ADA group than in the placebo group (5% versus 22%, respectively; p<0.0001), indicating a significant benefit of treatment with ADA. Similar results were obtained with PM scores for Week 8 ADA responders.

In a Table from R&D/12/280 on all patient population, significantly fewer patients in the ADA group were hospitalised for UC- or drug-related events versus placebo (14% and 24%, respectively; p=0.005). For Week 8 ADA responders based on full Mayo score, the incidence rate was also lower in the ADA group than in the placebo group (6% versus 24%; p< 0.0001). Similar results were obtained with PM scores for Week 8 ADA responders.

> **Comment**: These analyses suggest ADA consistently reduces the rate of hospitalisations compared with placebo (particularly in early ADA responders), which is clinically meaningful even allowing for study limitations.

7.2.2.2. Dose escalation

A total of 38.2% subjects (n=354/978) in the all adalimumab set (AAS; representing Studies 826, 827 and 223) required dose escalation from ADA 40mg eow to 40mg ew. LOCF analysis demonstrated 16.0% subjects were in CR per full Mayo score after 100 weeks of weekly ADA dosing and 33.1% in CRESP. The effects on CR and CRESP appeared to have been maintained from Week 52 (15.7% and 34.2%, respectively), which suggest once weekly dosing may be an effective treatment option for subjects who did not achieve sufficient response on the eow regimen.

> **Comment**: This data supports the proposed PI dosage statement, although subject characteristics that may help predict those subjects most likely to benefit treatment were not identified in this submission.

7.2.3. Evaluator's conclusions on clinical efficacy for UC

For ADA treatment in moderately to severely active UC, the clinical development program included one pivotal induction study (M06-826) that compared two induction regimens [ADA

160/80/40 and ADA 80/40] against placebo, one pivotal induction and maintenance study (M06-827) that compared ADA 160/80/40 against placebo and one ongoing open-label supportive extension study (M10-223). At the request of the EMA and FDA, early responder analyses (during the 8-week DB phase) were undertaken in Study 827 to identify subjects most likely to benefit from ADA 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, CHMP/EWP/18463/2006.

Induction

In Study 827, a statistically significantly greater proportion of ADA 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 ADA 160/80/40 subjects demonstrated CR at Week 8 compared with placebo subjects in the primary (ITT-A3 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 ADA 160/80/40 against placebo (and most other ranked secondary endpoints for ADA 160/80/40 were numerically greater than placebo), the first ranked secondary endpoint (clinical response per Mayo score at Week 8 in the ADA 160/80/40 treatment group versus placebo) did not meet the criteria for statistical significance.

The ADA 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 ADA 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 ADA ability to maintain efficacy over 44 weeks from the induction period. In the ADA 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) ADA subjects and 43.5% (n=10/23) placebo subjects). In terms of those subjects who completed DB treatment, 25.6% (n=21/82) ADA 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 ADA treatment group (at each time point) through to Week 52 of ADA treatment for Weeks 2, 4, and 8 PM responders and Week 8 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 ADA, the magnitude of the differences measured, compared with placebo, consistently exceeded 10% and was consistently higher on every parameter measured against the total ADA 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 QoL endpoints, such as IBDQ and SF-36 scores, provided supportive evidence of ada 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 ADA but is of limited usefulness in the assessment of maintenance of treatment. Disease activity (based on Mayo and PM scores) remained stable for 60 weeks in a subset of the ADA 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 naive subjects, a statistically significantly higher proportion of those treated with ADA 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 naive and 4% for experienced), most other ranked secondary end-points statistically significantly favoured ADA treatment over placebo for anti-TNF naive subjects.

Among anti-TNF experienced subjects, ADA did not achieve statistical separation against placebo at the first primary end-point i.e. CR per Mayo score at Week 8 (9.2% versus 6.9%, respectively, p=0.559). Although statistical significance was achieved at the second primary endpoint and several secondary endpoints the results have limited usefulness.

The early responder analyses failed to demonstrate statistically meaningful 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 ADA 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, the analyses presented in this submission suggest subjects who respond early to ADA 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 to be non-GCP compliant). The original design of Study 826 was changed at the request of the Swedish Medicines Agency after 185 subjects had entered the study proper, with the introduction of another treatment arm, which is far from ideal, especially as the new treatment arm is not 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 ADA induction dosage regimen), effectively 'diluting the results' for the proposed dosage regimen in UC. Study 826 appeared to lack the power to detect meaningful differences between active/placebo treatments.

The most notable issues with the efficacy studies were the considerable number of protocol deviations and violations, as well as the large number of subjects who withdrew from lack of efficacy/worsening UC. On a positive note, these were generally well balanced across the treatment groups, thereby not favouring one group over another.

The ADA 160/80/40 induction regimen demonstrated statistical superiority over placebo treatment in the primary endpoints i.e. ADA 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 ADA treatment were consistently observed across the ranked secondary endpoints, although statistical significance

was not wholly achieved. Of note, the magnitude of effect in UC was approximately half that observed with this ADA induction regimen in CD and similarly for infliximab in the treatment of the proposed indication (UC).

The ADA 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 very modest (a 4.4% positive difference compared with placebo; p=0.047). This effect is supported by statistically superior results of ADA over placebo in the first eight ranked secondary endpoints. Steroid-free remission is an important clinical endpoint in practice and while positive differences of ADA over placebo occurred numerically, these findings are descriptive.

The early responder analyses required by the EMA and FDA lend support for the benefit of those subjects who responded early to ADA treatment to gain a longer-term benefit. However, the analyses were exploratory and lacked a randomised comparison, and did not form part of the original statistical plan. Furthermore, the early responder analyses did not identify subjects who were most likely to respond to early treatment.

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

Overall, this evaluator concludes 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 ADA 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 doubtful clinical significance. Early responder analyses, hospitalisation rates and QoL parameters also tend to favour ADA treatment. However, on balance, the efficacy results in this submission are not compelling or convincing, particularly in terms of maintenance treatment (beyond 8 weeks).

8. Clinical safety

8.1. Studies providing evaluable safety data

The safety of ADA in UC was determined using data from three clinical studies: two completed multicentre, multinational, DB, 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 CS, IMM, 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 ISS report for Study 223 was 31 December 2009, but this was extended to 16 December 2011 to form the 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 DB, efficacy and safety study in Japanese subjects with moderately to severely active UC (Study M10-447). No study protocol/CSR was provided in this submission and so only comments on SAEs and deaths will be noted in this CER as it was beyond the scope of this submission to evaluate Study M10-447.

Safety of ADA throughout the studies was monitored and assessed by AEs, physical examination, laboratory data and vital signs. The ISS and ISSU 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 ADA administration in UC patients. Generally the TEAE rates in the ISS and ISSU were comparable across treatment groups with no new safety signal identified.

8.2. 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 ADA (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 ADA 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 ADA in Studies 826, 827 and 223, through to 16 December 2011. The AAS includes 610 subjects randomised to ADA in Studies 826 or 827 and 400 subjects randomised to placebo in Studies 826 or 827 who switched to OL ADA 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 (ADA 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 27). More subjects randomised to DB placebo switched to OL ADA treatment during the maintenance period because of an inadequate response, hence the lower median exposure observed in placebo subjects.

Table 27: 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 ADA as of 16 December 2011 (i.e. the AAS), for a cumulative exposure of 1891.7 patient years (PYs). Of these subjects, 622 (61.6%) had >12 months of ADA exposure; 530 (52.5%) had >18 months of ADA exposure, 459 (45.4%) had >24 months of ADA exposure, 291 (28.8%) had >36 months of ADA exposure and 75 (7.4%) had >48 months of ADA exposure.

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

8.3. Adverse events

8.3.1. All adverse events (irrespective of relationship to study treatment)

Events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 12.1. Generally, placebo subjects demonstrated higher incident rates than ADA subjects (events per 100 patient years [E/100 PY) for any AEs, SAEs and AEs that lead to study discontinuation, any infectious AE and any UC worsening/flare (see Table 28).

From Table 28, four deaths occurred in the AAS whereas no subjects died with placebo (see Section 8.3.3). Haematological AEs had a slightly higher rate in ADA compared with placebo (1.22 E/100 PY versus 0.66 E/100 PY, respectively), but this was not statistically significant.

Table 28: Overview of Treatment-Emergent Adverse Events (Placebo Set versus All Adalimumab Set)

Subjects with:	Placebo N=483 PYs= 151.88	All adalimumab N=1010 PYs= 1891.73	
	E (E/100PY)	n (%)	E (E/100PY)
Any AE	1321 (869.75)	864 (85.5)	7264 (393.99)
Any AE at least possibly drug related	284 (186.99)	460 (45.5)	1598 (84.47)
Any severe AE	75 (51.36)	276 (27.3)	453 (23.95)
Any serious AE	69 (45.43)	241 (23.9)	347 (18.34)

Subjects with:	Placebo N=483 PYs= 151.88	All adalimumab N=1010 PYs= 1891.73	
	E (E/100PY)	n (%)	E (E/100PY)
Any serious AE at least possibly drug related	10 (6.58)	52 (5.1)	63 (3.33)
Any AE leading to study drug discontinuation	62 (40.82)	204 (20.2)	231 (12.21)
Any AE at least possibly drug related leading to discontinuation	25 (16.46)	57 (5.6)	64 (3.38)
Any AEs leading to death	0	2 (0.2)	2 (0.11)
Any allergic reaction	2 (1.32)	16 (1.6)	18 (0.95)
Any injection site reaction	25 (16.46)	108 (10.7)	241 (12.74)
Any opportunistic infection (excluding TB)	3 (1.98)	25 (2.5)	29 (1.53)
Any congestive heart failure	0	3 (0.3)	3 (0.16)
Any demyelinating disease	0	2 (0.2)	2 (0.11)
Any lupus-like syndrome	0	2 (0.2)	2 (0.11)
Any malignancy	2 (1.32)	19 (1.9)	20 (1.06)
Any lymphoma	0	3 (0.3)	3 (0.16)
Any NMSC	1 (0.66)	5 (0.5)	6 (0.32)
Any malignancy excluding lymphoma and NMSC	1 (0.66)	11 (1.1)	11 (0.58)
Any infectious AE	218 (143.53)	533 (52.8)	1512 (79.93)
Any serious infection	10 (6.58)	56 (5.5)	64 (3.38)
Any haematological event	1 (0.66)	21 (2.1)	23 (1.22)
Any hepatic event	12 (7.90)	54 (5.3)	84 (4.44)
Any vasculitis event	0	0	0
Any diverticulitis event	0	3 (0.3)	7 (0.37)

Subjects with:	Placebo N=483 PYs= 151.88	All adalimumab N=1010 PYs= 1891.73	
	E (E/100PY)	n (%)	E (E/100PY)
Any intestinal perforation event	1 (0.66)	6 (0.6)	6 (0.32)
Any interstitial lung disease	0	0	0
Any Stevens-Johnson syndrome	0	0	0
Any pancreatitis event	1 (0.66)	1 (<0.1)	1 (0.05)
Any UC worsening/flare	106 (69.79)	363 (35.9)	531 (28.07)

8.3.1.1. Induction set

The overall findings in Table 28 were generally consistent with those found in the IS. Subjects who experienced TEAEs ranged from 54% to 58% across treatment groups. A statistically significantly smaller proportion of subjects in the ADA 160/80/40 group compared with the placebo group reported UC worsening/flare (7.3% versus 12.2%; p=0.012). The ADA 80/40 group had a similar proportion to the higher induction regimen (7.7%), but this was not statistically significant. Injection site reactions were reported by a statistically significantly greater proportion of subjects in the ADA 160/80/40 treatment group compared with the placebo group (6.3% versus 3.1%; p=0.022) with a dose-response trend observed. This finding is not evident from Table 28.

There were borderline statistically significantly greater proportions of subjects in the ADA 160/80/40 treatment group compared with the placebo group for haematological events (1.3% versus 0.2%, respectively; p=0.069) or hepatic events (2.1% versus 0.6%, respectively; p=0.055). The latter finding was not evident from Table 28. The ADA 80/40 treatment group reported higher incidence of any infectious AE than placebo or the ADA 160/80/40 group (20.0% versus 18.4% and 17.7%, respectively). This finding is at odds with Table 28, which indicates less infectious AEs associated with ADA treatment.

8.3.1.2. Maintenance set

The MS results differ considerably compared with Table 28. The ADA 160/80/40 group demonstrated higher incident rates compared with placebo of overall AEs (68.2% and 73.1%, respectively) i.e. the longer duration of treatment in the MS compared with the IS lead to greater proportions of subjects experiencing TEAEs in both treatment groups.

Furthermore, the ADA 160/80/40 group demonstrated higher incident rates compared with placebo of any AE at least possibly drug related (30.8% versus 21.5%; p=0.026; not found in the IS) and injection site reactions (6.8% versus 1.3%; p=0.004; consistent with the IS results). Although not statistically significant, the ADA group had numerically higher proportions of severe and SAEs compared with the placebo group, as well as any infectious AE (7.5% proportional difference over placebo of borderline significance; p=0.095). No difference in rate of UC worsening/flare between ADA and placebo was demonstrated.

> **Comments**: The MS is derived from Study 827, but is not synonymous with the DB safety set from 827 because the latter includes subjects who also completed the induction period

(first 8 weeks of DB treatment incorporated into the IS results). A comparison of the findings of the MS and the DB safety set were not surprisingly similar. In particular, the association between injection site reactions in the ADA group versus placebo in the DB safety set was even greater ($p<0.001$) and there was a statistically significant difference between ADA subjects and placebo in terms of 'any haematological AEs' (1.9% versus 0.0%, respectively). The DB safety set reported slightly higher incidence rates of ADA compared with placebo than the MS for any malignancies and allergic AEs, but the numbers were too small to draw meaningful conclusions.

Although injection site reactions were found to be statistically significantly different between ADA 160/80/40 and placebo in both the IS and the MS (towards ADA treatment), none of these events were considered serious although four lead to study treatment discontinuation.

The MS (and DB safety set in Study 827) included subjects on OL (rescue) ADA treatment and so the results need to be considered in context of the limitations on study control that an OL design provides, especially with subjects who also dose-escalated.

8.3.1.3. All Adalimumab Set

In the AAS, 85.5% of subjects reported TEAEs, with a higher percentage among subjects who dose escalated to the ew regimen compared with those who remained on the eow regimen (89.4% and 82.8%, respectively). Not surprisingly, more ew-dosed subjects reported worsening UC/flare compared with eow-dosed subjects (46.3% versus 28.7%, respectively), probably because of their inadequate response to OL eow dosing. Ew-dosed subjects tended to have proportionately more possibly drug-related AEs, severe AEs and infectious AEs compared with eow-dosed subjects, perhaps reflecting a dose-response trend in toxicity. However, subject numbers are too small to draw meaningful conclusions.

8.3.2. Treatment-related adverse events (adverse drug reactions)

Most TEAEs were mild or moderate in severity. In the IS, placebo subjects experienced more severe AEs than ADA subjects (8.5% versus 6.9% in ADA 80/40 and 7.3% in ADA 160/80/40, respectively). This trend was reversed in the MS (7.2% for placebo subjects and 10.3% for ADA 160/80/40 subjects, respectively) although the AAS found no appreciable proportional difference between those subjects who remained on an eow dosing regimen and those who dose-escalated.

The most frequently reported TEAE across the analysis sets was UC [preferred term colitis ulcerative when discussed as an AE of special interest] worsening/flare (range across treatment groups, 7.3% to 12.2% in the IS; 16.2% to 16.6% in the MS and 28.7% to 46.3% in the AAS). Other TEAEs reported ≥5% in any treatment group in the IS were nasopharyngitis (5.2% with any ADA versus 4.8% with placebo, respectively) and headache (4.8% and 8.7%). In the MS: abdominal pain (7.7% with ADA and 5.4% with placebo, respectively); arthralgia (7.3% and 4.0%) and nausea (3.8% and 5.4%).

From the DB safety analysis set in Study 826 (Weeks 0 to 8), no reported AE for ADA had greater than 5% rate difference compared with placebo. However, in the safety analysis set in Study 827, ≥5% was recorded for nasopharyngitis (17.5% ADA 160/80/40 versus 10.4% with placebo, respectively) and headache (8.6% versus 14.2%). The latter were not identified at ≥5% in the MS, suggesting they occurred primarily in the IS.

TEAEs ≥2% in any treatment group in the IS: injection site pain in the ADA 160/80/40 group (2.3%); rash in the ADA 80/40 group (3.1%); headache and injection site pain in the placebo group (4.1% and 2.3%, respectively). In the MS, the ADA 160/80/40 group reported: injection site erythema (3.0%); colitis ulcerative (2.6%); injection site reaction (2.6%); arthralgia (2.1%) and rash (2.1%).

From the DB safety analysis set in Study 826, ADA 80/40 had greater than 2% rate difference compared with placebo for: abdominal tenderness (3.1% in ADA 80/40 versus 0.9% in placebo, respectively); toothache (2.3% versus 0.9%; p=0.049); nasopharyngitis (4.6% versus 1.8%, respectively); arthralgia (3.8% versus 0.4%, respectively; p=0.027) and rash (3.8% versus 0.4%; p=0.027). No difference between ADA 160/80/40 and placebo at the 2% level. In the safety analysis set in Study 827, ADA 160/80/40 had greater than 2% rate difference compared with placebo for oropharyngeal pain (5.8% versus 2.7%, respectively).

The results in the OL safety set for Study 826 were consistent with the DB analyses with more injection site reactions recorded for those with prior exposure with ADA.

The overall safety results for Study 827 were consistent with those ADRs identified during DB administration). Those subjects randomised to ADA 160/80/40 treatment showed a statistically significantly lower rate compared to the randomised placebo group for colitis ulcerative (28.8% versus 37.7%, respectively; p=0.032) and a statistically significant higher rate of nasopharyngitis (21.8% versus 13.8%; p=0.021).

> **Comment**: Generally the results in the individual CSRs for Studies 826 and 827 (DB and OL) are consistent with the results presented in the IS and MS analyses. No new or unexpected ADR was reported. The high rates of UC worsening/flare across treatment groups may reflect lack of ADA efficacy. The TEAE overview (Table 28) may mislead the reader into believing placebo is much safer than active treatment in most domains. For example, in the individual study reports, the IS and MS analyses consistently identified a statistically significantly greater proportion of injection site reactions of ADA treatment versus placebo yet the opposite effect is reported in Table 28, which may mislead the reader into believing ADA is safer than it actually may be.

8.3.3. Deaths and other serious adverse events

8.3.3.1. Deaths

Four deaths were reported in the UC clinical program through the 16 December 2011 cut-off applied to Study 223: two treatment-emergent deaths and two non-treatment emergent deaths.

8.3.3.1.1. Treatment-emergent deaths

Subject **[Redacted information]**, a 34-year-old male,, included in the original ISS (AAS), had received ADA 160/80/40 in Study 827 and OL ADA in Study 223 (escalated dose to 40mg ew). He died from cardio-respiratory arrest due to life-threatening infection, bilateral adrenal haemorrhage and shock. The event was assessed as possibly drug-related by the Investigator.

Subject **[Redacted information]**, a 47-year-old white female who was receiving OL ADA 40mg eow in Study 223, experienced an event of right ventricular failure and died on Day 1132. The Investigator considered her right ventricular failure more likely related to cardiac arrhythmia than ADA.

8.3.3.1.2. Non-treatment-emergent deaths

Subject **[Redacted information]**, a 71-year-old white female, was reported as deceased during a follow-up contact. The subject was previously reported as a lymphoma, which was reported as resolved. No additional information was provided as an autopsy was not performed. Study drug was previously permanently discontinued approximately two years earlier for the event B‑cell lymphoma. The Investigator considered the event of death to be possibly related to study drug. The Sponsor considered the event of death to be probably not related to study drug, as the subject had stopped study drug approximately two years before death, but more likely related to age (>70 years) and other risk factors of hypertension, previous smoking and lymphoma.

Subject **[Redacted information]**, a 46-year-old obese white female, with a relevant history of UC since 1989 and obesity, experienced an event of pulmonary embolism (Post-treatment Day 72) with an outcome of death. No further information was available as no autopsy was

performed. The Investigator considered the event of pulmonary embolism to be probably not related to study drug, but more likely related to suspected deep vein thrombosis. The Sponsor considered the event of pulmonary embolism to be probably not related to study drug but more likely related to obesity and the underlying disease, as the subject had tolerated study drug well for more than two years.

8.3.3.1.3. Deaths in Japanese study M10-447

Two additional deaths were reported in the ISSU from the ADA 160/80/40 treatment group during the ongoing Japanese trial, Study M10-447:

Subject **[Redacted information]**, a 65-year-old Asian male, died due to TB, symptoms which first occurred 44 days after his last dose of study drug. Baseline CXR was normal and PPD test was negative (erythema >10 mm, but no induration). The event was severe and the Investigator considered it probably not related. Steroid use was an alternative aetiology (he received prednisone 20mg/day).

Subject **[Redacted information]**, a 54-year-old Asian male, died 62 days post-treatment. This subject also had an SAE of pancreatic carcinoma reported on Day 29, 14 days after his last injection of study drug that led to premature discontinuation from the study. He had a medical history of pancreatic enlargement and ascites, and was a moderate drinker. The Investigator considered both SAEs of pancreatic carcinoma and death not related.

> **Comment**: No association between death and ADA treatment was clearly identified in the ISSU but autopsy reports were not available in four of the cases not considered related to study drug, so causality cannot be ruled out. It is worth noting that anti-TNF agents including ADA have been associated with increases in infection and malignancy. Some of the fatal cases discussed above are consistent with ADA contributing to the cause of death. Heart failure has also been associated with another anti-TNF agent (as per the ADA PI).

8.3.3.2. Non-fatal serious adverse events

In the IS, a higher percentage of subjects experienced SAEs in the placebo group (8.3%) than in either of the ADA treatment groups (3.8% and 5.2% in the 80/40 and 160/80/40 groups, respectively). Colitis ulcerative was the most frequently reported SAE in all three treatment groups (5.6%, 2.3%, and 2.7% of subjects in the placebo, ADA 80/40 and ADA 160/80/40 treatment groups, respectively).

In the MS, a higher percentage of subjects experienced SAEs in the adalimumab 160/80/40 group (6.4%) than in the placebo group (4.9%). Colitis ulcerative was the most frequently reported SAE (2.6% of subjects in the ADA 160/80/40 group and 1.8% in the placebo group).

In the AAS, SAEs were reported by 23.9% of subjects. A similar percentage of subjects who dose escalated to ADA 40 mg ew experienced SAEs compared with subjects who remained on ADA 40 mg eow (23.5% versus 24.1%). Colitis ulcerative was the SAE reported by the highest percentage of subjects (10.6% with ew dosing and 8.9% with eow dosing). Besides colitis ulcerative, the remaining SAEs in the AAS occurred with <1% incidence.

8.3.3.2.1. SAEs in Japanese study M10-447

In Study M10-447, SAEs during the DB period were reported for 12.5% of subjects in the placebo group, 16.1% in the 80/40 mg ADA treatment group and 11.1% in the 160/80 ADA treatment group, with no statistically significant difference observed between treatment groups. Frequently reported SAEs (≥2 subjects in either the placebo treatment group or the combined ADA treatment groups) were UC, bronchitis, and pneumonia. Almost all SAEs were considered by the Investigator as not related or probably not related to study drug. Most subjects reported events that were mild to moderate in severity. Severe TEAEs were reported for five subjects in the placebo group (UC [three subjects], ventricular tachycardia [one], and enteritis infectious [one]) and for five subjects in the ADA treatment group combined (one in the 80/40 group

[osteonecrosis] and four in the 160/80 group [UC, gastrointestinal dysplasia, death, TB, pancreatic carcinoma]).

> **Comment:** In Study 827, four subjects in the placebo group developed pyoderma gangrenosum while no ADA subjects demonstrated this SAE. Colitis ulcerative was the most common SAE, evenly distributed across the randomised groups in the Safety Analysis Set. In the DB safety analysis set in Study 826, colitis ulcerative accounted for most SAEs, with a higher proportion in the placebo group and least proportion in the 160/80/40 ADA group. In the OL safety analysis group, again colitis ulcerative accounted for the majority of reported SAEs. Colitis ulcerative is indicative of lack of efficacy and hence higher rates would be expected in placebo subjects. No new or unexpected SAE was identified in the ISSU or in the ongoing Japanese trial, Study M10-447.

8.3.4. Discontinuation due to adverse events

In the IS, TEAEs leading to premature study drug discontinuation were reported as: 6.6% for placebo subjects, 6.2% for ADA 80/40 subjects and 5.0% for ADA 160/80/40 subjects. A similar trend was found in the MS: 6.3% for placebo subjects and 5.1% for ADA 160/80/40 subjects. Most subjects withdrew prematurely secondary to lack of efficacy or worsening UC/flare. The higher placebo drop-out rate was due to OL escape for inadequate response and lack of efficacy. In the AAS, the percentage of subjects who had AEs that lead to study drug withdrawal was 20.2% overall with a similar distribution among those who dose-escalated and those who did not (20.6% versus 19.9%, respectively). Colitis ulcerative was the most commonly reported AE that lead to discontinuation (8.3%).

The proportion of subjects who prematurely discontinued from OL Study 223 due to lack of efficacy or worsening of UC were higher in subjects receiving ADA treatment ew compared to those receiving eow treatment (10.5% versus 4.2%, respectively).

8.3.4.1. Discontinuation in Japanese study M10-447

A total of 17 subjects (9.6%) receiving ADA discontinued from the study due to TEAEs during the DB period. The most frequent of these events were UC worsening (n=7; 4.0%) and pyrexia (n=2; 1.1%). All other events leading to discontinuation occurred in only one subject.

> **Comment**: The higher withdrawal rate in OL ew ADA compared with eow ADA may in part be attributed to more treatment resistance in the ew group. The discontinuation rate in the ongoing Japanese study appears consistent with the rates identified in this submission.

8.3.5. Intrinsic factors

Intrinsic factors were investigated through an evaluation of AE event rates in specific subgroups. Within each subgroup, a Fisher's exact test was used to compare the proportion of ADA and placebo subjects experiencing AEs, and a Breslow Day test was used to compare the homogeneity of the odds ratio between subgroups.

8.3.5.1. Sex

Females tended to have more TEAEs than males across the treatment sets (IS, MS, AAS), each gender demonstrating a trend of increased TEAEs with duration of exposure to ADA 160/80/40 (59.3% versus 52.4% in the IS, 76.3% versus 71.5% in the MS and 87.9% versus 84.1% in the AAS). There were no notable differences between males and females in regard to the types of AEs reported in all groups except in the IS, where females had a statistically significantly greater proportion of injection site reactions than males (9.8% versus 3.8%; p=0.023).

8.3.5.2. Age

Across the age subgroups: <40 years, 40 to 64 years and ≥ 65 years, there were no statistically significant differences in the odds ratio of TEAEs for ADA 160/80/40 versus placebo in the IS,

MS or AAS. As expected, overall incidence of TEAEs increased with duration of exposure to study drug. Although there appeared to be a trend for increased rates of TEAEs with increasing age in the IS and AAS analyses, this effect was not consistent with the observed rates in the MS.

8.3.5.3. Race

There were no notable differences between white and non-white subjects in regard to the types of AEs reported in the IS, MS and AAS. As expected, the overall TEAE incident rate increased with increasing study drug exposure across all racial subgroups.

8.3.5.4. Bodyweight

For subjects in the IS, hepatic events were experienced by a smaller proportion of subjects weighing <70kg compared with those weighing ≥70kg (1.1% versus 2.7%). Among ADA-treated subjects in the MS, infections were reported by a greater proportion of subjects weighing <70kg compared with those weighing ≥70kg (45.9% versus 33.6%), and hepatic events were experienced by a smaller proportion of subjects weighing <70kg compared with those weighing ≥70kg (1.2% versus 2.7%). Statistically significant heterogeneity was found between bodyweight subgroups (<70kg versus ≥70kg at baseline) in the odds ratio of drug-related TEAEs for ADA 160/80/40 versus placebo (42.4% versus 24.2%, respectively; p=0.034). In AAS subjects weighing <70kg and 70kg at baseline, the percentage of subjects reporting hepatic events was higher in the ≥70kg subgroup (6.5%) compared with the <70kg subgroup (3.2%) There were no other notable differences among the weight subgroups in regard to the types of AEs reported.

8.3.5.5. BMI

There were no statistically significant differences among BMI subgroups (BMI <24.9kg/m^2 and ≥24.9kg/m^2) of TEAEs for ADA 160/80/40 versus placebo in the IS. In the MS, statistically significant differences among the BMI subgroups were observed for ADA over placebo for drug-related AEs, infections and hepatic AEs. In the AAS, greater percentages of subjects with BMI ≥24.9kg/m^2 experienced serious infections and hepatic events (7.3% and 7.9%, respectively) than subjects with BMI <24.9kg/m^2 (3.6% and 2.8%, respectively). There were no other notable differences among the BMI subgroups in regard to the types of AEs reported.

8.3.5.6. CRP

There were no statistically significant differences among CRP subgroups (CRP <1.0mg/dL and CRP ≥1.0mg/dL) of TEAEs for ADA 160/80/40 versus placebo in the IS. In the MS, a statistically significant difference was noted among CRP subgroups in the odds ratio of UC worsening/flare for ADA 160/80/40 versus placebo (21.4% versus 9.8%, respectively; p=0.047). In the AAS, greater percentages of subjects with CRP ≥1.0mg/dL experienced AEs leading to discontinuation (25.7%) than did subjects with CRP <1.0mg/dL (18.3%).

8.3.5.7. Geographic region

Analyses were undertaken between North America and the rest of the world (ROW). A statistically significant difference in severe AEs for ADA 160/80/40 treatment was observed in the IS (13.2% in North America versus 2.6% in the ROW, respectively; p=0.001). This suggests cultural factors may impact on the assessment of severity perhaps, especially for Japan. There was no statistically significant difference in serious events among regional subgroups (p=0.231). Across treatment groups, the most commonly reported severe AE was colitis ulcerative. There were no statistically significant differences among regional subgroups in the odds ratio of TEAEs for ADA 160/80/40 versus placebo in the MS. The percentages of subjects reporting AEs in most categories was generally greater for subjects from North America than those from ROW, including severe AEs (34.4% and 21.5%, respectively) and AEs leading to discontinuation (22.6% and 18.2%, respectively). One exception to this trend was serious infections, which were higher among subjects in ROW (7.4%) than in North America (3.3%).

8.3.5.8. Baseline Mayo score

For subjects in the IS (but not MS or AAS) with baseline Mayo scores of <10 and 10 to 12, a statistically significant difference was noted in the odds ratio of injection site reactions for ADA 160/80/40 versus placebo for the higher baseline Mayo subgroup (8.7% ADA versus 1.1% placebo; p=0.009).

> **Comment**: Females tended to have more TEAEs than males, particularly injection site reactions during the induction period. Injection site reactions tended to occur in subjects with Mayo scores 10 to 12 i.e. more severe disease. Not surprisingly UC worsening/flare was associated with elevated CRP levels (a marker for inflammation). Differences in racial background and age did not appear to affect the rates of TEAEs. While statistically significant differences were observed in some analysis sets under bodyweight, BMI and geographic region, their clinical relevance is unclear.

8.3.6. Extrinsic factors

8.3.6.1. Prior use of anti-TNF agents

A key difference between Studies 826 and 827 was the protocol entry criteria regarding prior anti-TNF use. In Study 826, subjects were required to be naïve to anti-TNF agents, and in Study 827, subjects must have been naïve to anti-TNF agents or discontinued use >56 days before baseline, due to a loss of response or intolerance to the agent. Approximately 40% of the study population, around 200 subjects in total, had prior anti-TNF exposure in Study 827.

In IS Subjects with prior anti-TNF use had higher TEAE incidence rates compared with subjects without prior anti-TNF use for placebo (76.0% and 53.6%, respectively) and for ADA 160/80/40 (69.4% and 52.1%, respectively). Among ADA-treated subjects, a greater proportion of subjects with prior anti-TNF use experienced proportionately more AEs (69.4% versus 51.1%, respectively), AEs at least possibly related to study drug (37.8% versus 19.1%), severe AEs (8.2% versus 7.1%), SAEs (7.1% versus 4.7%), injection site reactions (10.2% versus 5.2%,; p=0.044), any opportunistic infection (3.1% versus 0%), any infectious AE (26.5% versus 14.7%), any serious infection (3.1% versus 0%) and UC worsening/flare (13.3% versus 5.8%). More hepatic events were noted in the anti-TNF naive group compared with the experienced group (2.0% versus 0% and 2.6% versus 1.2%, respectively). The only deaths (n=2) were reported in the naive group.

In MS subjects with prior anti-TNF use, the overall incidence of TEAEs compared with subjects without prior anti-TNF use were similar for placebo (67.9% and 68.3%, respectively) and for ADA 160/80/40 (68.2% and 75.8%, respectively). These higher rates reflect the longer duration of exposure to study drug. There were fewer differences between the anti-TNF experienced and naive groups in the MS. Notable differences included any AE at least possibly drug-related (34.1% in prior exposed subjects and 19.1% in exposure naive subjects, respectively; p<0.05) and worsening UC/flare (18.8% versus 14.8%), both consistent with the IS. However, reverse effects were observed in any AE (68.2% in prior exposed subjects and 75.8% in exposure naive subjects, respectively), severe AE (8.2% versus 11.4%), serious AEs (5.9% versus 6.7%) and injection site reactions (4.7% versus 8.1%; p<0.05). The only death was in the naive group.

For subjects in the AAS with prior anti-TNF use and without prior anti-TNF use, the overall incident rate of TEAEs was 91.8% and 84.3%, respectively. A greater proportion of subjects with prior anti-TNF use, compared to those without prior anti-TNF use, experienced infections (59.1% versus 51.5%), opportunistic infections (5.3% versus 1.9%), and serious infections (7.0% versus 5.2%). In addition, a greater proportion of subjects with prior anti-TNF use, compared to those without prior anti-TNF use, experienced AEs assessed as possibly drug-related (57.9% versus 43.0%), SAEs (28.7% versus 22.9%), and UC worsening/flare (47.4% versus 33.6%). The naive group had a slightly higher rate of any malignancy than the experienced group, although there were numerically many more subjects in the naive group (2.0% [n=17] versus 1.2% [n=2], respectively).

Subjects who had prior anti-TNF exposure and dose-escalated to 40mg ew compared with anti-TNF naive subjects who dose-escalated had higher rates of drug-related AEs (60.0% versus 47.4%, respectively), SAEs (28.9% versus 22.0%), opportunistic infection (5.6% versus 2.1%), infections (64.4% versus 56.3%), serious infections (8.9% versus 4.6%) and UC worsening/flare (52.2% versus 44.6%) but had less severe AEs (23.3% versus 30.9%) and deaths (0.6% [n=2] versus 0%). For subjects who remained on an eow dosing regimen, subjects who had prior anti-TNF exposure had higher rates compared with anti-TNF naive subjects for any AEs (92.6% versus 81.3%, respectively), drug-related AEs (55.6% versus 40.2%), severe AEs (33.3% versus 24.8%), SAEs (28.4% versus 23.4%), opportunistic infection (4.9% versus 1.8%), infections (53.1% versus 48.4%) and UC worsening/flare (42.0% versus 26.6%). Anti-TNF naive subjects had higher rates than experienced subjects for hepatic events (6.1% versus 3.7%, respectively). The only deaths reported were in anti-TNF naive subjects, two in each of the ew and eow dosing regimens. While the malignancy rates were comparable in the prior and naive groups for the ew dosing regimen, the naive subjects on the eow regimen had a higher rate than the corresponding prior exposed group (2.7% versus 1.2%, respectively). Of note, 82.4% (n=14/17) of all malignancies in the anti-TNF naive group were observed on the eow dosing regimen.

In terms of trends in increased AE rates related to duration of ADA exposure, subjects with prior anti-TNF exposure demonstrated a trend for infections (26.5% in the IS, 36.5% in the MS and 59.1% in the AAS) and for UC worsening/flare (13.3%, 18.8% and 47.4%, respectively). Subjects who received ADA in the anti-TNF naive group demonstrated more trends of increasing AE rates with duration of study drug exposure: any AE, drug-related AEs, severe AEs, SAEs, and injection site reactions, malignancies, infections, serious infections and UC worsening/flare.

> **Comments**: Generally, subjects with prior anti-TNF exposure demonstrated higher rates of AEs of particular interest compared with anti-TNF naive subjects. The higher rates of worsening UC/flare are indicative of relatively reduced efficacy in the previously exposed anti-TNF group. Fewer positive trends in duration of exposure to ADA and AE incidence rates in the prior anti-TNF may in part be explained by the fewer subjects who entered Study 827 with prior exposure (approximately 40% of the study population). ADA 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.
>
> AAA status is unknown in either group, but may have contributed to these rates.

8.3.6.2. Concomitant use of corticosteroids and immunosuppressants

8.3.6.2.1. Corticosteroids

Among IS subjects using concomitant CS at baseline, a statistically significantly greater percentage of subjects in the placebo group had AEs leading to study drug discontinuation compared with the ADA group (7.5% versus 1.9%, p=0.028). Among subjects not using concomitant CS at baseline, a statistically significantly greater percentage of subjects in the ADA group had injection site reactions (7.7% versus 3.3%, p=0.016) and a statistically significantly greater percentage of subjects in the placebo group had UC worsening/flare (12.8% versus 7.7%, p=0.040). Generally ADA subjects with baseline CS demonstrated proportionately less AEs in most categories than ADA subjects who did not receive baseline CS, except for infections (20.1% versus 15.6%, respectively); serious infections (1.3% versus 0.3%) and opportunistic infections (excluding TB; 2.6% versus 0.3%).

Among MS subjects using concomitant CS at baseline, a statistically significantly greater percentage of subjects in the ADA group compared with the placebo group had TEAEs (77.8% versus 64.6%, p=0.021), TEAEs assessed by the Investigator as possibly or probably drug related (32.6% versus 19.7%, p=0.019), and injection site reactions (7.6% versus 1.6%,

p=0.023). Unlike the IS, generally ADA subjects with baseline CS demonstrated proportionately more AEs in most categories than ADA subjects who did not receive baseline CS.

From the ISSU, subjects who received concomitant CS at baseline tended to have lower TEAE incidence rates in most AE categories than those not receiving CS at baseline except for UC worsening/flare (36.8% subjects receiving CS compared with 34.8% not receiving CS), but this difference is not clinically meaningful.

8.3.6.2.2. Immunosuppressants

Among IS subjects using concomitant IMMs at baseline, a statistically significantly greater percentage of subjects in the placebo group had SAEs and UC worsening/flare compared with the ADA group (SAEs: 10.2% versus 2.7%, p=0.004; UC worsening: 13.6% versus 5.3%; p=0.011), and a statistically significantly greater percentage of subjects in the ADA group had haematological AEs compared with the placebo group (3.2% versus 0%, p=0.030). Generally, ADA subjects with baseline IMMs demonstrated proportionately less AEs in most categories than ADA subjects who did not receive baseline IMMs, except for: drug-related (26.2% versus 20.8%, respectively); injection site reactions (7.5% versus 5.5%); haematological events (3.2% versus 0%) and hepatic events (3.2% versus 1.4%).

Among MS subjects using concomitant IMMs at baseline, a statistically significantly greater percentage of subjects in the ADA group had injection site reactions compared with the placebo group (8.4% versus 1.3%, p=0.041). Like the IS, generally, ADA subjects with baseline IMMs demonstrated proportionately less AEs in most categories than ADA subjects who did not receive baseline IMMs, except for drug discontinuations (6.3% versus 4.3%, respectively); injection site reactions (8.4% versus 5.8%) and hepatic events (4.2% versus 0.7%).

Greater percentages of subjects who were receiving concomitant IMMs at baseline (AAS) compared to those who were not receiving IMMs reported the following TEAEs: SAEs (25.8% versus 22.5%); injection site reactions (13.5% versus 8.2%, respectively); serious infections (6.9% versus 4.7%) haematological events (5.1% versus 0.2%, respectively) and hepatic events (6.9% versus 4.4%, respectively).

> **Comment**: Generally, subjects on ADA treatment that had baseline IMMs and/or CS tended to exhibit lower incidence rates of TEAEs, except for injection site reactions. The higher rates of hepatic AEs observed with IMMs were expected.

8.4. Laboratory tests

8.4.1. Liver function

In Study 827, eleven (11) subjects had elevated liver function test values that reached the criteria for potentially clinically significant liver function tests during the DB phase (six in the placebo group and five in the ADA group). Elevated values of liver function tests were reported as AEs in four subjects: hepatic enzyme increased; hepatitis; AST increased and drug toxicity (attributed to AZA intolerance).

Among subjects who switched to OL administration, three subjects receiving ADA during OL administration had potentially clinically significant liver function tests; two of the three subjects had been randomised to the placebo group prior to starting OL administration. None of the liver function test results were reported as AEs.

In Study 826, during the DB period through Week 8, four subjects had potentially clinically significant liver function tests but none of these were reported as AEs.

In the AAS ISSU, potentially clinically significant values for total bilirubin, AST, ALT, and alkaline phosphatase were observed in 8.2%, 6.6%, 4.9%, and 1.0%, respectively, of subjects taking concomitant IMMs at baseline, compared with 4.4%, 3.4%, 1.6%, and 0.2%, respectively, of

subjects who were not taking concomitant IMMs at baseline. No subject met the criteria for Hy's Law.

8.4.2. Kidney function

In the DB period of Study 826, creatinine levels increased in a dose-dependent manner (0.5µmol/L in placebo, 1.3 in ADA 80/40 and 2.1 in ADA 160/80/40). However, the changes were too low to be clinically meaningful.

8.4.3. Other clinical chemistry

Thirty-one subjects in the placebo group and 30 subjects in the ADA group had clinical chemistry values CTC grade ≥3; of those, 49% of subjects (30/61) had abnormal inorganic phosphate levels of CTC grade ≥3. Seven subjects had clinical chemistry values of CTC grade ≥3 that were reported as AEs during DB administration (four placebo-treated subjects and ADA-treated subjects).

Among subjects who switched to OL administration, 16 subjects had clinical chemistry values of CTC grade ≥3; of those, 63% of subjects (10/16) had abnormal inorganic phosphate levels of CTC grade ≥3. The only clinical chemistry values of CTC grade ≥3 that were reported as AEs during OL administration occurred in two subjects: Subject **[Redacted information]** had a known history of hypoalbuminaemia reported AEs of hypoalbuminaemia, hyponatremia, renal failure acute, and malnutrition; Subject **[Redacted information]**, with a known history of diabetes mellitus, reported repeated AEs of diabetes mellitus.

8.4.4. Haematology

In Study 827, thirty-one subjects in the DB placebo group and 24 in the DB ADA group had haematology values CTC grade≥ 3. Twenty-two subjects (seven DB placebo; eight DB ADA; seven OL ADA) experienced AEs of anaemia or decreased haemoglobin.

During the DB period, ADA treatment appeared to increase the haemoglobin levels, as well as lymphocytes and monocytes, and decrease the levels of platelets, WBC and neutrophils. These trends were maintained over the entire duration of the study, also with increased levels of RBC and haematocrit that suggest active ADA treatment mitigates the pathologic haematology changes associated with UC. However, the overall magnitude of these mean changes was not clinically meaningful.

One subject (OL ADA) experienced an AE of WBC count decreased, and one subject (OL ADA) had an AE of neutropenia. Among subjects who switched to OL administration, 20 subjects had haematology values CTC grade ≥3; of those, the majority of subjects (13/22) had haemoglobin CTC grade ≥3.

In the 8-week DB period in Study 826, changes observed in the ADA treatment groups compared with placebo suggest active treatment mitigates the pathologic haematology changes associated with UC. These include improvement in anaemia and thrombocytopenia as evidenced by an increase in haemoglobin, haematocrit, and red blood count, and a decrease in platelet count. Furthermore, most changes were observed in a dose-dependent manner. However, the overall magnitude of these mean changes was not clinically meaningful.

8.4.5. C - reactive protein

From the CSR for Study 827, mean baseline CRP levels decreased with duration of ADA exposure (12.428mg/L at Week 8, 11.351mg/L at Week 32 and 10.481mg/L at Week 52), which is consistent with reduced inflammation/an effect of ADA.

> **Comments**: In the DB period of Study 826, the changes observed in the ADA treatment groups compared with placebo suggest active treatment mitigates the pathologic clinical chemistry changes associated with UC. These include decrease in CRP and alkaline phosphatase as well as increase of albumin and total protein concentration. These

parameters occurred in a dose-dependent manner with similar trends also for aspartate transaminase and total cholesterol (both increased levels with increasing dose). The results in the DB period of Study 827 support the findings (reduced platelets, reduced CRP, reduced alkaline phosphatase, raised haemoglobin, albumin and total protein) and these were maintained throughout the entire study. The AAS results are also consistent.

8.4.6. Purified protein derivative (PPD, tuberculin skin test)

Approximately 4% of subjects across analysis sets were enrolled in TB prophylaxis therapy. At entry into Study 826 and Study 827, six subjects in the IS had a positive PPD skin test but did not receive TB prophylaxis, including two subjects with a marginally positive PPD test (induration=5 mm). Seven subjects who did not have positive PPD test findings received TB prophylaxis. Two of these seven were considered to be at higher risk, and another two were suspected to have had previous TB exposure.

8.4.7. Urinalysis

Although some statistically significant differences were seen between the ADA treatment groups and the placebo group, overall, no mean change from baseline value to Week 8 in Studies 826 and 827 were considered clinically meaningful.

8.4.8. Electrocardiograph

ECG findings were normal in the majority of subjects. Six subjects had clinically significant abnormal ECGs, including conduction abnormalities; none had cardiac-related TEAEs.

8.4.9. Vital signs

During DB administration in Study 827, statistically significant treatment differences in changes from baseline vital signs were found for systolic blood pressure (greater increase in the placebo group compared to the ADA group at Week 44), weight (greater increase in the ADA group compared to the placebo group at all visits except Weeks 8, 26, 38, 44 and 52), and temperature (greater decrease in the ADA group compared to the placebo group at Weeks 4 and 12). None of the mean changes from baseline value for vital sign parameters were considered clinically meaningful.

8.4.10. Chest x-ray

Most subjects in all analysis sets had normal baseline CXRs.

Comment: Evaluation of the laboratory data did not reveal any new safety concerns. There were no overall meaningful changes from baseline in terms of haematological, clinical chemistry or urinalysis. The changes that did occur were expected from the known pharmacology of TNF-alpha antagonists, CS or IMM.

8.4.11. AEs of special interest

Twenty-two (22) AE categories of special interest were identified based on the known safety profile of ADA, potential safety issues associated with TNF inhibitors in general, or due to higher rates of some events in the UC population. These categories were infections, serious infections, opportunistic infections (excluding TB), malignancies, lymphomas, NMSC, malignancies (excluding lymphomas and NMSC), malignancies (including lymphomas, excluding NMSC), injection site reactions, CHF, demyelinating diseases, hepatic events, allergic reactions, lupus-like syndrome, haematological events, vasculitis, diverticulitis, intestinal perforations, interstitial lung disease, Stevens-Johnson syndrome, pancreatitis, and UC worsening/flare.

8.4.11.1. Infections

The proportion of subjects who experienced infections was comparable (17.1% to 20.0%) across treatment groups in the IS. Overall, the most frequently reported types of infections were nasopharyngitis (4.8%, 4.6%, and 5.4% of subjects in the placebo, ADA 80/40, and ADA

160/80/40 groups, respectively) and upper respiratory tract infections (2.5%, 4.6%, and 1.0% of subjects in the placebo, ADA 80/40, and ADA 160/80/40 groups, respectively).

In the MS, a greater percentage of subjects in the ADA 160/80/40 treatment group experienced one or more infections compared with subjects in the placebo group 38.0% versus 30.5%. Overall, the most frequently reported types of infections were nasopharyngitis (11.1% versus 4.9% in ADA 160/80/40 and placebo treatment groups, respectively); pharyngitis (2.6% versus 0.4%, respectively); oral herpes (2.6% versus 0.9%, respectively) and gastroenteritis (2.6% versus 0.9%, respectively). The percentages of subjects who experienced infections were higher in the MS than in the IS, consistent with longer treatment.

In the AAS, any infectious AE was reported in 52.8% subjects overall with more reported in the dose-escalated group (49.1% with ADA eow and 58.0% with ADA ew). Nasopharyngitis accounted for most AEs (18.4%). Other frequently reported AEs included upper respiratory tract infection (8.9%), sinusitis (7.5%), bronchitis (5.3%), influenza (4.7%), urinary tract infection (4.3%) and gastroenteritis (4.0%). This overall percentage is higher than that of the other analysis sets, which is consistent with the longer duration of exposure in the AAS. Furthermore, anti-TNF experienced subjects had higher rates of TEAEs compared with naive subjects in dose-escalators and those who remained on the eow regimen.

The majority of infectious TEAEs were not serious and were considered probably not or not related to study drug, as assessed by the Investigator. These TEAEs were common infections that were generally easily medically managed.

8.4.11.2. Serious infections

Serious infections reported by subjects in the IS are summarised in the ISS. Pneumonia, experienced by two subjects (0.4%) in the placebo group, was the only serious infection reported by more than one subject per treatment group. The lowest rate of serious infections was identified in the ADA 160/80/40 group (0.6% of subjects, compared with 1.4% and 1.5% in the placebo and ADA 80/40 groups, respectively).

In the MS, one subject in the placebo treatment group (0.4%) had serious infections of liver abscess and pneumonia necrotising. In the ADA treatment group, one subject (0.4%) had a serious infection of appendicitis.

In the AAS, serious infections occurred in 5.5% subjects. The most frequently reported serious infections were appendicitis, pneumonia, anal abscess, and lobar pneumonia. There was one SAE report of pulmonary TB, Subject **[Redacted information]**, a 25-year-old white male from Poland who received ADA 160/80/40 during Study 827. The Investigator considered the event to be severe and probably related to study drug. The event resolved 89 days after last dose (duration 118 days).

Most subjects who had a serious infection had events that were possibly or probably related to study drug by the Investigator and had events that were moderate to severe in intensity. Approximately 20% of subjects with serious infections prematurely discontinued from the study as a result of their event. Incidence of serious infections may be related to duration of treatment.

8.4.11.3. Opportunistic infections

In the IS, two subjects (0.4%) in the placebo group experienced opportunistic infections (one event each of cytomegalovirus colitis and oral candidiasis). In the ADA 160/80/40 treatment group, five subjects (1.0%) experienced opportunistic infections. No subject in the ADA 80/40 treatment group experienced an opportunistic infection.

In the MS, one subject (0.4%) in the placebo group experienced an opportunistic infection of oral candidiasis. In the ADA 160/80/40 treatment group, two subjects (0.9%) experienced opportunistic infections of oral candidiasis and candidiasis.

As reported in the original ISS, two subjects (Subject **[Redacted information]** and Subject **[Redacted information]**) had events of cytomegalovirus infections. In both cases, the event was reported as serious. Subject **[Redacted information]** was using concomitant prednisolone and AZA. Subject **[Redacted information]** was receiving concomitant prednisolone and also had dose-escalated to 40mg ew ADA. One other event of cytomegalovirus is reported (Subject **[Redacted information]**), but this was not reported as serious. The vast majority of opportunistic infections (excluding TB) represented non-serious, non-systemic candidiasis.

8.4.11.4. Malignancies

In the IS, treatment-emergent malignancies were reported by two subjects (0.4%) in the placebo group (basal cell carcinoma and breast cancer) and one subject (0.2%) in the ADA 160/80/40 group (squamous cell carcinoma).

In the MS, one ADA-treated subject (0.4%) had a treatment-emergent malignancy. Subject **[Redacted information]**, a 61-year-old male with a history of smoking (25 years, one pack/day) and light drinking, and concomitant intake of AZA, was diagnosed with gastric cancer on Day 201 of ADA treatment. The event was serious and considered by the Investigator to be probably not related to study drug. Due to this SAE, the subject prematurely discontinued study drug. No placebo-treated subjects reported malignancies.

In the AAS, there were three new reports of NMSC (two reports of squamous cell carcinoma and one report of basal cell carcinoma), however the event rate (0.32 events/100 PY versus 0.19 events/100 PY) is lower than that of ADA controlled trials across all indications and closer to the rate among control-treated patients. New cases (one subject each) of bladder cancer, cervix carcinoma stage 0, and gallbladder cancer were also reported. There was one new case of colon cancer reported in the AAS (Subject **[Redacted information]**, a 49-year-old female with a 12-year history of UC) that was reported as serious and possibly related to ADA.

Nine (9) subjects prematurely discontinued study drug due to malignancies, all of which were SAEs: three subjects were diagnosed with B-cell lymphoma, and one subject each were diagnosed with breast cancer, breast cancer in situ, bladder cancer, gastric cancer (in a male subject with a history of smoking), spindle cell sarcoma, and malignant melanoma (in a subject with a history of repeated prolonged sun exposure).

Of the 19 subjects with malignancies, 4/19 (21.1%) were receiving concomitant IMMs at baseline and 16/19 (84.2%) had a history of smoking. No malignancies were identified in the three patients who erroneously started the study with evidence of dysplasia during the screening biopsy.

Two neoplasms were adjudicated as benign based on clinical information available, but were categorised as malignancies due to coding conventions.

No subject had an event that was considered probably related to study drug by the Investigator; most subjects with malignancies had events that were considered probably not related or not related to study drug by the Investigator. Almost all the malignancies were serious; most subjects had events that were moderate to severe in intensity.

8.4.11.5. Injection site reactions

In the IS, injection site reactions were reported by a statistically significantly greater proportion of subjects in the ADA 160/80/40 group compared with the placebo group (6.3% versus 3.1%; p=0.022).

In the MS, injection site reactions were reported by a statistically significantly smaller proportion of subjects in the placebo group compared with the ADA 160/80/40 group (1.3% versus 6.8%, p=0.004). The incidence of injection site reactions was 31.67 events/100 PYs in the ADA group compared to 6.10 events/100 PYs in the placebo group.

In the AAS, 10.7% of subjects had injection site reactions. The event rate of injection site reactions was 11.55 events/100 PYs among subjects who dose escalated compared to 13.53 events/100 PYs for subjects who remained on the 40mg eow regimen. None were serious but four lead to study drug discontinuation. One subject had a severe event of injection site pruritus, and two had severe events of injection site reaction; all other injection site reaction AEs were mild or moderate in severity.

8.4.11.6. Congestive heart failure

No subject in the IS reported a CHF-related TEAE. In the MS, Subject **[Redacted information]** in the ADA 160/80/40 group experienced a TEAE of right ventricular failure but continued treatment.

Three CHF-related events were reported in the AAS: Subjects 63952 (a 52 year-old female in the ADA 80/40 treatment group: subject lost to follow-up) and 81204 (a 40 year-old male on ADA 160/80/40 treatment in the IS and MS: continued in the Study 827) were considered mild in severity and unrelated to study drug by the Investigator whereas Subject **[Redacted information]** experienced right ventricular failure that lead to death, but the event was considered unrelated to study drug (see Section 8.3.3.1.1).

8.4.11.7. Demyelinating disorders

No subjects in the IS or MS reported a demyelinating disease. In the AAS, Subject **[Redacted information]** from the ADA 80/40 treatment group in Study 826 experienced an SAE of leukoencephalopathy. The event was considered resolved in 40 days and was assessed by the Investigator as mild in severity and possibly related to study drug. Subject **[Redacted information]** from the placebo treatment group in Study 827 experienced an SAE of demyelination while in OL Study 223. The event was assessed by the Investigator as mild in severity and probably related to study drug.

8.4.11.8. Hepatic-related TEAEs

In the IS, hepatic events were reported for a greater proportion of subjects in the ADA 160/80/40 group (2.1%) compared with the other two treatment groups (0.6% for placebo, 0.8% for ADA 80/40); this difference was not statistically significant. Of the 11 adalimumab-treated subjects who had hepatic TEAEs, six were receiving concomitant IMMs at baseline. One subject (Subject **[Redacted information]**) was also receiving TB prophylaxis. No hepatic event in the IS was reported as serious or resulted in study drug discontinuation.

In the MS, hepatic events were reported in 2.2% and 2.1% of subjects in the placebo and ADA 160/80/40 groups, respectively. Event rates were 9.77 events/100 PYs and 7.45 events/100 PYs in the placebo and ADA 160/80/40 treatment groups, respectively. Of the five adalimumab-treated subjects with hepatic TEAEs in the MS, four were receiving concomitant IMMs. One hepatic event, cholelithiasis in the ADA 160/80/40 group, was reported as serious. One event resulted in study drug discontinuation (hepatic enzyme increased in the placebo group). Neither of these subjects was receiving concomitant IMM treatment.

The proportion and event rate of hepatic events in the AAS was lower among subjects who dose escalated, 261 (4.8% and 4.25 events/100 PYs) than among those who did not dose escalate (5.7% and 4.57 events/100 PYs). The most frequently reported hepatic events were AST increased (1.7%) and ALT increased (1.6%). All other events were experienced by <1% of subjects. Four subjects had five serious hepatic events (cholelithiasis in two subjects [one subject had two separate SAEs] and cholecystitis, portal hypertension, and portal vein thrombosis in one subject each). None of these SAEs resulted in study drug discontinuation; although one subject prematurely discontinued due to a non-serious case of autoimmune hepatitis. Of the 54 subjects with hepatic events, 27 (50%) were receiving concomitant IMMs at baseline. Two subjects (Subject **[Redacted information]** and Subject **[Redacted information]**)

were on TB prophylaxis. Most events were ALT and/or AST elevations that resolved. No subjects met criteria for Hy's Law.

8.4.11.9. Allergic reactions

In the IS, allergic reaction TEAEs were reported by one subject (0.2%) in the placebo group (drug hypersensitivity) and four subjects (0.8%) in the ADA 160/80/40 group (urticaria in two subjects, and swelling face and drug hypersensitivity in one subject each). No subjects in the ADA 80/40 treatment group had allergic reaction TEAEs. None of the allergic reaction events were serious, although drug hypersensitivity in one subject in the ADA 160/80/40 treatment group led to study drug discontinuation.

In the MS, one placebo-treated subject (0.4%) had an allergic reaction event (drug hypersensitivity to a non-study drug) and two ADA-treated subjects (0.9%) had allergic reactions (drug hypersensitivity and urticaria that was deemed not related to study drug). None of the events were serious or led to study drug discontinuation. All three subjects were AAA negative at baseline.

In the AAS, none of the allergic reaction events were regarded as serious, although events in two subjects in the ADA 160/80/40 treatment group led to study drug discontinuation (drug hypersensitivity in both subjects). Of the five events of drug hypersensitivity in four subjects (four events were considered by the Investigator to be probably related to ADA), three were an itching response and one was a skin reaction to ADA. Antibody data are available for two of the four subjects from Study 827 who had allergic reaction TEAEs; one was HACA positive at baseline (Subject **[Redacted information]**), and none were AAA positive at baseline. One ADA-treated subject with an allergic reaction TEAE developed AAA on treatment.

8.4.11.10. Lupus-like syndrome

No subject in the IS reported lupus-like syndrome TEAEs. In the MS, one subject in the ADA 160/80/40 treatment group had a non-serious lupus-like syndrome event. The subject was discontinued from study drug, and the event remained unresolved. The Investigator assessed the event as probably related to study drug. No placebo-treated subjects had lupus-like syndrome.

In the AAS, Subject **[Redacted information]**, a 47-year-old white male, had a serious and severe event of lupus-like syndrome. The subject was prematurely discontinued from study drug and started on CS, and the event was reported to be resolved after 67 days. The event was assessed as probably related to study drug by the Investigator.

8.4.11.11. Haematology-related AEs

In the IS, haematological TEAEs were experienced by one subject (0.2%) in the placebo treatment group (thrombocytopenia), two subjects (1.5%) in the ADA 80/40 group (both leukopenia), and six subjects (1.3%) in the ADA 160/80/40 treatment group (five subjects with leukopenia, one subject with neutropenia). There was one serious haematological TEAE: leukopenia in Subject **[Redacted information]** in the ADA 160/80/40 treatment group was assessed by the Investigator as not related to study drug (attributed as possibly related to concomitant 6-MP treatment). In the MS, one subject (0.4%) in the ADA 160/80/40 treatment group experienced a non-serious haematological TEAE (leukopenia); no subjects in the placebo group had a haematological event.

The event rate of haematologic events was similar between subjects who dose escalated and those who did not (1.46 versus 1.05 events/100 PYs) in the AAS. Of the 21 subjects (2.1%) who experienced haematological events, 20 were receiving concomitant AZA and/or 6-MP at baseline. Two subjects discontinued study drug due to leukopenia. One SAE was reported, the majority of subjects had haematology-related TEAEs that were not related to study drug, and all events resolved during the study.

8.4.11.12. Vasculitis

No events of vasculitis were reported in any analysis set.

8.4.11.13. Diverticulitis

No event of diverticulitis were reported in the IS or MS. Three cases of treatment-emergent diverticulitis were reported in the AAS (0.3%). The Investigator considered all diverticulitis events not related or probably not related to study drug. One of the three subjects was receiving concomitant CS at baseline and two subjects were obese. Subject **[Redacted information]** experienced a serious event of diverticulitis on Day 894 (Study 223, Day 529), which led to the subject's discontinuation of study drug.

8.4.11.14. Intestinal perforation

In the IS, one subject in the placebo group experienced an SAE of rectal perforation. No ADA-treated subjects experienced intestinal perforations. No subject in the MS experienced an intestinal perforation. Six ADA treated subjects (all reported as SAEs; in the AAS) experienced intestinal perforations, three of which were large intestine perforations, one duodenal, one rectal and one appendix.

8.4.11.15. Interstitial lung disease

No events of interstitial lung disease were reported in any analysis set.

8.4.11.16. Stevens-Johnson syndrome

No events of Stevens-Johnson syndrome were reported in any analysis set.

8.4.11.17. Pancreatitis

No subject in the IS had a treatment-emergent pancreatitis event. In the MS, one placebo-treated subject (0.4%) had a SAE of pancreatitis acute. There was no pancreatitis events among subjects treated with ADA. In the AAS, Subject **[Redacted information]**, a 32-year-old white male with a history of alcohol-induced pancreatitis, experienced a non-serious event of pancreatitis on OL ADA treatment.

8.4.11.18. Ulcerative colitis worsening/flare

In the IS, UC worsening or flare, defined as TEAEs of colitis ulcerative, was reported by a statistically significantly greater proportion of subjects in the placebo group compared with the ADA 160/80/40 group (12.2% versus 7.3%, p=0.012). Most events were assessed by the Investigator as probably not related or not related to study drug. In the MS, UC worsening or flare was reported by 16.6% of subjects in the placebo group and 16.7% of subjects in the ADA 160/80/40 group. Most events were assessed by the Investigator as probably not related or not related to study drug. Higher proportions of subjects who were prior anti-TNF users had UC worsening/flare (21.4% in the placebo group and 18.8% in the ADA 160/80/40 group) compared with anti-TNF naive subjects (13.7% and 15.4%, respectively).

In the AAS, 35.9% of subjects experienced UC worsening/flare during ADA treatment overall, with dose-escalators experiencing proportionately higher rates of UC worsening than those who received the eow regimen.

> **Comment**: Worsening UC or flare may be considered as part of the disease process rather than as a TEAE per se. Hence, the high rates of this TEAE reported here may reflect a lack of ADA efficacy. Furthermore prior anti-TNF exposure tended to result in higher rates of UC worsening/flare, indicative of reduced efficacy in this subgroup of subjects. . Duration of studies makes detection of increased incidence of AEs that have a long lead in time difficult. The relative contribution of a specific agent to an AE with a long lead in time is also difficult to assess in either pre or post-market studies.

8.5. Post-marketing experience

From the ISSU:

> ADA was first approved for treatment of RA on 31 December 2002 (international birth date). Through 30 December 2011, ADA was approved in 89 countries with an estimated cumulative exposure of 1,875,014 patient treatment years. Post-marketing experience has confirmed the favourable benefit/risk profile of ADA originally characterised in clinical studies with the type and severity of AEs generally consistent with those observed in these trials. The following new safety information has been obtained based on Abbott Laboratories' ongoing post approval safety surveillance program for ADA, which includes monitoring of clinical studies, spontaneous AE reports and literature reports since the international birth date:
>
> Serious allergic reactions including anaphylaxis; cutaneous vasculitis; fatal cases of TB; new onset demyelinating disease; Angioedema; reactivation of hepatitis B; Guillain-Barré syndrome; diverticulitis; intestinal perforation; Stevens-Johnson syndrome; Hepatosplenic T-cell lymphoma (HSTCL); pancreatitis; myocardial infarction; cerebrovascular accident new onset or worsening of psoriasis (Ps) (including palmoplantar pustular Ps); leukaemia; pulmonary embolism; pleural effusion; erythema multiforme; alopecia; lupus-like syndrome; higher risk for infections in patients ≥65 years of age; sarcoidosis; liver failure and Legionella.

Furthermore, on 21 March 2012, Abbott Laboratories established a long-term non-interventional registry (REGISTRY PROTOCOL P11-282) to assess the safety and effectiveness of ADA treatment in patients with moderately to severely active UC. Approximately 8,250 patients (approximately 5,500 patients prescribed ADA and approximately 2,750 patients prescribed IMM) in the US and Europe will be enrolled after Market Authorisation is obtained in these regions and a decision to prescribe registry drug is made. Patients from additional countries will be added after Market Authorisation is obtained in these regions and a decision to prescribe registry drug is made. The registry observation period will be six years based on the sample size calculation. The physician will monitor each patient for SAEs and pre-defined AEs of interest on a routine basis throughout the registry.

8.6. Safety issues with the potential for major regulatory impact

8.6.1. Unwanted immunological events

In Study 827, 19 of 487 (3.9%) of subjects were identified as AAA+ by the end of the study. TEAEs were stratified by AAA status into DB and OL.

For the DB period, the percentage of TEAEs was lower in AAA- subjects (82.6%, 200/242) than AAA+ (100.0%, 13/13) subjects. Apart from a higher incidence of injection site reactions in the AAA+ group (23.1%, n=3/13) compared with the AAA- group (11.6%, n=28/242), the overall incidence rates in SAEs, severe AEs and AEs leading to discontinuation was lower in the AAA+ group. However, the number of AAA+ subjects in each category was too small to make any meaningful assessment. The rate difference between AAA statuses in AEs of special interest was comparable (less than 10%). No incidence of demyelinating diseases, lymphomas, AEs leading to death and deaths were reported during the DB period.

For the OL period, the overall percentage of AEs was comparable between AAA- subjects (73.3%, 178/243) and AAA+ (78.6%, 11/14) subjects. The percentage of AE at least possibly drug related was higher in the AAA+ group (57.1%. 8/14) than the AAA- group (30.9%, 75/243), however, the overall percentage of AE at least possibly drug related was similar in placebo (33.6%, 47/140) and ADA treatment group (30.8%, 36/117). The percentage of injection site related AE appeared to be higher in the AAA+ group (14.3%, 2/14) than the AAA- group (6.6%, 16/243); however, the overall percentage was higher in the placebo (9.3%,

13/140) than the ADA treatment group (4.3%, 5/117). A comparison of the rate of severe AE, serious AE, AE leading to discontinuation of study drug, serious infection and hematologic related AE between the AAA+ and AAA- group was inconclusive as the number of AAA+ subjects (n ≤ 2) in each category was too small. The rate of infectious AE was similar between AAA+ (42.9%, 6/14) and AAA- (38.7%, 94/243) subjects. The rate of allergic reaction related AE, opportunistic infection related AE (excluding TB), malignant AE, non-melanoma skin cancer (NMSC) AE and hepatic related AE was less than 10% in both AAA- and AAA+ groups. No incidence of demyelinating disease, CHF related, lupus-like syndrome, lymphomas, malignant (excluding NMSC and lymphomas), malignant (including lymphomas, excluding NMSC) and AEs leading to deaths and deaths were reported during the OL period.

> **Comment**: Generally, AAA status did not appear to affect the tolerability to ADA other than consistently higher injection site reactions observed in AAA+ subjects (DB and OL). Given the small numbers of subjects in each category a meaningful assessment of AAA status cannot be made. However the plausibility of an immunologic component to the higher injection site reaction rates observed across the studies in this submission cannot be discounted. Furthermore, the detection level of the ADA-specific ELISA assay may have underestimated the true number of subjects who were AAA+ and therefore any true effect of AAA+ status.

8.7. Evaluator's overall conclusions on clinical safety

Overall, ADA 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 ADA was consistent with the known profile established in other indications, including CD, with the exception of a higher lymphoma rate. 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, prior AZA/IMM treatment). Lymphoma will continue to be monitored in pharmacovigilance activities detailed in the 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.

Subjects who received prior anti-TNF treatment tended to have higher rates of some TEAEs e.g. SAEs and study discontinuations. UC worsening/flare (most common AE) rates were higher in anti-TNF experienced subjects compared with naive 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 ADA 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.

ADA 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.

9. First round benefit-risk assessment

9.1. First round assessment of benefits

The benefits of ADA in the proposed usage are:

- An alternative to infliximab in terms of medication and route of administration (SC versus IV);
- If approved, ADA would be the only self-administered monoclonal antibody therapy for UC (and hence hospitalisation is not required);
- The PK of ADA in UC is very similar to other ADA indications, particularly CD;
- The alternative 160/80/40 ADA regimen (160mg 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 ADA 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 ADA 160/80/40 group, adding robustness to the results;
- Subjects who were anti-TNF naive tended to benefit more than those subjects who had prior anti-TNF exposure;
- Early responders to ADA treatment appeared to derive the greatest benefit of treatment;
- Most endpoints/parameters examined tended to favour ADA 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 ADA treatment (but no autopsy reports were available);
- No case of colon carcinoma was identified in this submission;
- 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 ADA in UC);
- Study M10-223 and the ongoing controlled Japanese study (DB for 52 weeks) using two ADA induction regimens (160/80/40 and 80/40) will provide much more efficacy data (particularly for maintenance treatment) and safety data.

9.2. First round assessment of risks

The risks of ADA in the proposed usage are:

- The first ranked secondary efficacy endpoint in Study 826 for DB ADA 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 ADA 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 ADA 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;

- 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 ADA 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 ADA treatment remain unknown;
- Maintenance effect was not adequately demonstrated (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);
- The ADA 80/40 induction regimen did not demonstrate efficacy over placebo;
- Dose-escalation to once weekly ADA treatment was not associated with greater efficacy;
- Autopsy reports were not provided for at least two subject deaths so no assessment could be made;
- AEs related to worsening UC/flare (overall and SAEs) were frequently reported in placebo and ADA-treated subjects (placebo > ADA), as well as the most common AE leading to premature discontinuation from the studies, which suggests ADA dosing may be sub-optimal in subjects with moderately severe to severely active UC;
- Due to the small numbers of subjects in the pivotal studies it remains unknown whether ADA 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 ADA 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 ADA ELISA assay may be inadequate in detecting those subjects who develop AAA.

9.3. First round assessment of benefit-risk balance

While the safety profile of ADA in UC was consistent with the established toxicity 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 ADA 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 ADA to maintain remission. Furthermore, few subjects who had prior anti-TNF exposure achieved a benefit from ADA treatment in this submission and the anti-TNF naive subjects achieved only half the CR rates demonstrated with infliximab in the induction and maintenance periods, questioning the role of ADA for Australian patients.

Many of the serious risks associated with ADA are rare (e.g. demyelination) or take many years to develop (e.g. 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 ADA 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 ADA 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, given the high rates of UC worsening/flare across studies for ADA (and placebo), including SAEs and premature discontinuations secondary to these events, provides additional evidence that the ADA 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 ADA 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 ADA 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. While the recommendation to cease treatment after 8 weeks, if inadequate response to ADA treatment occurs, will result in a more favourable benefit-risk balance, most subjects will still not benefit from ADA treatment.

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

10. First round recommendation regarding authorisation

The provisional recommendation is to approve ADA in UC only for anti-TNF naive patients. However, this opinion may change upon review of the answers to the Clinical Questions (see Section 11).

11. Clinical questions

11.1. Pharmacokinetics

Question 1: What are the mean serum adalimumab trough concentrations for the anti-TNF naive and anti-TNF experienced groups at Weeks 32 & 52 (by randomised treatment group and by weekly or fortnightly Humira 40mg regimen) as cited in Table 6 in document R&D/10/462 that pertains to Study M06-827?

Sponsor's response:

In Table 1 of its response, the Sponsor provided mean serum adalimumab concentrations for Weeks 32 and 52 for double-blind ADA 160/80mg eow treatment by previous anti-TNF treatment status. This data extends the information provided in Table 6 of document R&D/10/462, as part of Study MO6-827. The Sponsor provided mean serum adalimumab concentrations for those subjects who remained on double-blind eow treatment throughout the study duration and those who dose-escalated to adalimumab 40mg once-weekly dosing.

Clinical comment on response:

For those subjects who completed double-blind ADA eow treatment there was an 11% difference in mean serum adalimumab concentration at Week 52, which favoured anti-TNF naive 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 naive subjects. These results suggest prior anti-TNF exposure may lower the mean serum adalimumab concentration, and potentially adversely affect efficacy for this group.

11.2. Immunogenicity

Question 1: 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.

Sponsor's response:

HACA status was not measured for subjects who entered Study M10-223 from Study MO6-827. AAA was measured every 12 weeks starting at Week 108 through to Week 292 following a protocol amendment. The serum samples collected in this study will be analysed for AAA when the study is completed.

Clinical 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.

11.3. 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?

Sponsor's response:

An integrated summary of efficacy was not included in Module 5. All efficacy table references in the summary of clinical efficacy are attached to the Module 2 document.

Clinical 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?

Sponsor's response:

In Table 2 of its response, the Sponsor listed the reasons for screening failure in Study MO6-826. Of 159 total screen failures, 63 (25.3%) of pre-amendment 3 subjects failed screening compared with 96 (19.8%) post-amendment 3 subjects.

Clinical 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?

Sponsor's response:

In Table 3 of its response, the Sponsor listed the reasons for screening failure in Study MO6-827. 23.3% of subjects failed screening. Endoscopy results accounted for most screen failures.

Clinical 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 (i.e. for the 93 subjects receiving adalimumab 160/80/40 and 92 placebo subjects)?

Sponsor's response:

In Table 4 of its response, the Sponsor provided comparative baseline demographic and disease data for the pre-amendment 3 and post-amendment 3 (ITT-A3) populations in Study MO6-826.

Clinical 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 ADA 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, 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.

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

Sponsor's response:

In Table 5 of its response, the Sponsor has detailed the primary efficacy analyses of subjects enrolled into Study Mo6-826 prior to amendment 3.

Clinical comment on response:

The ADA 160/80 group did not demonstrate statistical separation from placebo at Week 8 (unlike the ITT-A3 analysis), which may reflect the selection of more severe subjects pre-amendment 3. 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 naive subjects (versus anti-TNF experienced subjects).

Question 6

No question 6 was submitted to the Sponsor.

Question 7: Subjects randomised to receive adalimumab 160/80/40mg 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?

Sponsor's response:

In Table 7 of its response, the Sponsor listed the primary reasons for the pre-amendment 3 and post-amendment 3 discontinuations by Week 8 in Study MO6-826 by treatment group.

Clinical comment on response:

Pre-amendment 3 adalimumab 160/80mg 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 adverse effects. 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 80/40mg adalimumab induction regimen in Study M06-826?

Sponsor's response:

The Sponsor provided a detailed explanation in terms of biologic activity of the adalimumab 80/40 induction regimen, lower hospitalisation rates of adalimumab 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.

Clinical comment on response:

The Sponsor's response is satisfactory.

Question 9: In respect of the early responder analyses, and to place these results in a more meaningful clinical context, this 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?*

Sponsor's response:

The Sponsor provided four tables of data on baseline characteristics of early responders to ADA treatment in Study MO6-827 versus non-responders.

Clinical comment on response:

On the information provided, there were no meaningful differences between early responders to ADA 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 naive subjects achieved early response. Further investigation to identify the early responder group is required but anti-TNF naive subjects appear to have a greater chance of a response to ADA treatment than those with prior anti-TNF exposure.

11.4. Safety

No questions.

11.5. 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?

Sponsor's response:

The Sponsor provided further details of the three sites that failed GCP compliance in Study MO6-827.

Clinical 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)?

Sponsor's response:

In Table 14 of its response, the Sponsor provided a summary of serum adalimumab trough concentrations by dose in all subjects with ulcerative colitis i.e. including the 24 non-GCP compliant subjects.

Clinical 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?

Sponsor's response:

In Table 15 of its response, the Sponsor has provided the results of the co-primary and ranked secondary efficacy endpoints of Study MO6-827 which included the 24 non-GCP compliant subjects.

Clinical 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)?

Sponsor's response:

In Table 16 of its response, the Sponsor provided the results of baseline AAA, HACA and anti-TNF status for the 24 non-GCP subjects by randomised treatment group versus the ITT population. One of the anti-TNF naive subjects developed AAA (measured at Week 32).

Clinical 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.

Note: Questions and evaluation of responses regarding the PI and CMI are not included in this Extract from the Clinical Evaluation Report

12. Final round evaluation of clinical data submitted in response to questions

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

13. Final round benefit-risk assessment

13.1. Final round assessment of benefits

The clinical information submitted in the Sponsor's s31 response does not change the assessment of benefits in the original clinical evaluation report (Section 9.1).

13.2. Final round assessment of risks

The clinical information submitted in the Sponsor's s31 response does not change the assessment of risks in the original CER (Section 9.2).

13.3. Final round assessment of benefit-risk balance

The clinical information submitted in the Sponsor's s31 response does not change the assessment of the benefit-risk balance provided in the original clinical evaluation report (Section 9.3).

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 ADA treatment.

14. Final round recommendation regarding authorisation

The clinical information submitted in the Sponsor's s31 response 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.

15. References

- Guideline on the Development of New Medicinal Products for the Treatment of Ulcerative Colitis (CHMP/EWP/18463/2006)
- Remicade PI

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
http://www.tga.gov.au