26 May 2016
EMA/501143/2016
Committee for Medicinal Products for Human Use (CHMP)

Extension of indication variation assessment report

Invented name: Humira

International non-proprietary name: adalimumab

Procedure No. EMEA/H/C/000481/II/0146

Marketing authorisation holder (MAH): AbbVie Ltd.

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Table of contents

List of abbreviations

AAA	Anti-adalimumab antibodies
AC	Anterior chamber
ADR	Adverse drug reaction
AE	Adverse event
AESIs	Adverse events of special interest
ALS	Amyotrophic lateral sclerosis
AMD	Age related macular degeneration
ANOVA	Analysis of Variance
AS	Ankylosing spondylitis
AUC	Area under the curve
BCVA	Best corrected visual acuity
CD	Crohn's disease
CHF	Congestive heart failure
CHMP	Committee for Medicinal Products for Human Use
CL/F	Clearance
CRT	Central retinal thickness
CS	Corticosteroids
CVA	Cerebrovascular accident
DME	Diabetic macular oedema
E	Events
EAU	Experimental autoimmune uveitis
EEA	European Economic Area
ELISA	Enzyme-linked immunosorbent assay
eow	Every other week
EQ-5D	EuroQol-5D Questionnaire
ETDRS	Early Treatment Diabetic Retinopathy Study
ERA	Environmental Risk Assessment
EU	European Union
GBS	Guillain-Barré syndrome
HADS	Hospital Anxiety and Depression Scale
HR	Hazard Ratio
HRU	Health Resource Utilization Questionnaire
HS	Hidradenitis suppurativa
HSTCL	Hepatosplenic T-cell lymphoma
IC_{50}	Half maximal inhibitory concentration
IgG	Immunoglobulin G
ILD	Interstitial lung disease
Imax	maximum inhibitory effect
IMM	Immunomodulatory
IOP	Intraocular pressure
IRBP	Interphotoreceptor retinoid-binding protein peptide
ITT	Intention to treat
JIA	Juvenile idiopathic arthritis
LLOQ	Lowest limit of quantification
LOCF	Last observation carried forward
logMAR	Logarithm of the minimum angle of resolution
mITT	Modified intention to treat
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
MMF	Mycophenolate mofetil
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
MTX	Methotrexate
NEI	National Eye Institute
NMSC	Non-melanoma skin cancer
NPDR	Non-proliferative diabetic retinopathy
nr-axSpa	Non-radiographic axial spondyloarthritis

OCT	Optical coherence tomography
OFV	Objective function value
ON	Optic neuritis
PBS	Phosphate-buffered saline
PD	Pharmacodynamic
pedERA	Paediatric enthesitis-related arthritis
PK	Pharmacokinetic
PML	Progressive multifocal leukoencephalopathy
PP	Per protocol
PPK	Population pharmacokinetic
PRO	Patient reported outcome
PS	Psoriasis
PsA	Psoriatic arthritis
PT	Preferred Term (MedDRA)
PY	Patient years
RA	Rheumatoid arthritis
RCT	Randomised controlled trial
RPLS	Reversible posterior leukoencephalopathy syndrome
SC	Subcutaneous
SD	Standard Deviation
SJS	Stevens-Johnson syndrome
SOC	System Organ Class (MedDRA)
SUN	Standardization of Uveitis Nomenclature
TB	Tuberculosis
TEAE	Treatment Emergent Adverse Event
TNF	Tumour necrosis factor
UC	Ulcerative colitis
USA	United States of America
V2/F	Volume of distribution of central compartment
VEGF	vascular endothelial growth factor
VFQ-25	Visual Functioning Questionnaire-25
VPC	Visual predictive checks
VH	Vitreous haze
VKH	Vogt Koyanagi Harada
WPAI-SHP	Work Productivity and Activity Impairment, Questionnaire: Specific Health Problem Questionnaire

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, AbbVie Ltd. submitted to the European Medicines Agency on 2 September 2015 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II, IIIA and IIIB

Extension of Indication to include treatment of non-infectious intermediate, posterior and panuveitis in adult patients for Humira; as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC were proposed to be updated for the pre-filled syringe and pen formulations. The Package Leaflet was proposed to be updated in accordance. Furthermore, the PI is being brought in line with the latest QRD template version 10 and the MAH took the opportunity to make editorial amendments throughout the PI.

The requested variation proposed amendments to the Summary of Product Characteristics, Annex II, Labelling and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0070/2014 on the agreement of a paediatric investigation plan (PIP) and the granting of a (product-specific) waiver.

At the time of submission of the application, the PIP was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH received Scientific Advice from the CHMP on 22 October 2009 (EMEA/H/SA/127/7/2009/II). The Scientific Advice pertained to non-clinical and clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

CHMP Rapporteur: Kristina Dunder
CHMP Co-Rapporteur: Daniela Melchiorri
PRAC Rapporteur: Ulla Wändel Liminga

Timetable	Actual dates
Submission date	2 September 2015
Start of procedure	19 September 2015
CHMP Rapporteur's preliminary assessment report circulated on	13 November 2015
CHMP Co-Rapporteur's preliminary assessment report circulated on	24 November 2015
PRAC Rapporteur's preliminary assessment report circulated on	13 November 2015
PRAC RMP advice and assessment overview adopted by PRAC	3 December 2015
Joint CHMP Rapporteurs' updated assessment report circulated on	11 December 2015
Request for supplementary information and extension of timetable adopted by the CHMP on	17 December 2015
MAH's responses submitted to the CHMP on	25 February 2016
Joint CHMP Rapporteurs' preliminary assessment report on the MAH's responses circulated on	29 March 2016
PRAC Rapporteur's preliminary assessment report on the MAH's responses circulated on	29 March 2016
Ad-hoc Expert group experts meeting to address questions raised by the CHMP	5 April 2016
PRAC RMP advice and assessment overview adopted by PRAC	14 April 2016
Joint CHMP Rapporteurs' updated assessment report on the MAH's responses circulated on	21 April 2016
2nd request for supplementary information and extension of timetable adopted by the CHMP on	28 April 2016
MAH's responses submitted to the CHMP on	04 May 2016
Joint CHMP Rapporteurs' preliminary assessment report on the MAH's responses circulated on	11 May 2016
Joint CHMP Rapporteurs' updated assessment report on the MAH's responses circulated on	N/A
CHMP Opinion	26 May 2016

2. Scientific discussion

2.1. Introduction

Humira contains the active substance adalimumab, a recombinant human immunoglobulin 1 monoclonal antibody specific for human tumour necrosis factor-alpha (TNF-α). Adalimumab contains exclusively human sequences and is a 1,330 amino acid macromolecule with a molecular weight of approximately 148 kilodaltons. Adalimumab binds specifically to TNF-α and blocks its interaction with the p55 and p75 cell surface TNF-α receptors. Adalimumab also modulates biological responses that are induced or regulated by TNF, including changes in the levels of adhesion molecules responsible for leukocyte migration. TNF is a naturally occurring cytokine involved in normal inflammatory and immune responses. Elevated levels of TNF-α are thought to play an important role in autoimmune disorders and immune-mediated disorders.

Humira was first approved in the European Union (EU)/European Economic Area (EEA) through the centralised procedure by Commission Decision in September 2003 for the treatment of rheumatoid arthritis (RA). Since then, Humira was approved in a number of other (adult and paediatric) autoimmune conditions including psoriasis (PS), psoriatic arthritis (PsA), Crohn's disease (CD) and ulcerative colitis (UC). In addition to the EU/EEA, adalimumab is approved in the United States of America (USA), Japan and numerous other countries throughout the world. It has been studied in clinical trials that together include more than 9,000 patients.

In this variation application, the MAH seeks an extension of the indication to the treatment of non-infectious intermediate, posterior and panuveitis in adult patients. The application is based on 3 clinical studies: two completed pivotal phase 3 double-blind, placebo-controlled trialss (studies M10-877 in patients with active uveitis and M10-880 as maintenance treatment in patients controlled with corticosteroids), and an ongoing phase 3 open-label extension study (study M11-327). The MAH also provided the data of one non-clinical pharmacodynamic study.

The proposed posology consist of an initial subcutaneous (SC) dose of 80 mg followed by 40 mg every other week (eow) starting one week after the initial dose.

Background information on the disease

Uveitis is a serious and debilitating disease concerning some or all ocular tissues comprising the uveal tract (iris, ciliary body, and choroid). It includes symptoms of severe intraocular inflammation, vision impairment and pain and patients are at risk of developing permanent visual impairment and blindness.

According to the Standardization of Uveitis Nomenclature (SUN) working group (Jabs et al., 2005), uveitis can be classified according to the primary anatomical location of the inflammation into anterior uveitis, intermediate uveitis, posterior uveitis, or panuveitis (affecting all 3 eye segments). The location of the inflammation dictates the prognosis and therapy for the disease. As an example, there is a higher risk of vision loss and blindness in subjects with posterior and pan-uveitis. Uveitis can also be categorised by the aetiology of the inflammatory process into infectious or non-infectious uveitis. Non-infectious uveitis can be further classified as to whether it is an isolated ocular syndrome (i.e., Birdshot choroidopathy) or if there is accompanying extra-ocular or systemic inflammation (i.e., sarcoidosis, Vogt Koyanagi Harada [VKH] disease, Behçet's disease, ankylosing spondylitis [AS], juvenile idiopathic arthritis [JIA], psoriatic arthritis [PsA], etc). Subjects with non-infectious uveitis,

who have no characteristic disease pattern, or systemic involvement that indicates a specific diagnosis, are often referred to as having 'idiopathic' uveitis.

Non-infectious uveitis affecting the posterior segment usually has an early onset in life. The incidence of uveitis is greatest among people in the working age group of 20 to 50 years (Durrani et al., 2004), which adds to the socioeconomic burden of the disease. There is likelihood of progression to severe visual impairment if left untreated, with a substantial impact on day-to-day functioning and overall quality of life.

The global annual incidence of uveitis (infectious and non-infectious) has been estimated at 17 to 52 per 100,000 with a prevalence of 38 to 714 cases per 100,000 subjects. In Europe, up to 26% of total uveitis cases are intermediate, posterior or panuveitis (Wakefield and Chang, 2005). In the United States (US) and Western countries, it is estimated that approximately 10% to 20% of preventable blindness is caused by non-infectious uveitis and associated complications (Rothova et al., 1996; Miserocchi et al., 2013; Nguyen et al., 2011).

Current treatment options

At the time of this report, the established treatment for non-infectious uveitis was corticosteroids (CS, either topical, oral, periocular or intraocular). The type and severity of the disease dictate the route of administration of CS and the likelihood of requiring other immunosuppressive therapy to control the disease.

Topical CS eye drops are often sufficient to control anterior uveitis, while for inflammation involving the posterior segment of the eye (intermediate, posterior or panuveitis), systemic or intraocular CS are required. Periocular CS injections can also be used in both anterior and posterior uveitis.

Dexamethasone, 700 µg implants, and fluocinolone acetate, 190 µg implants, are approved in the EU for intravitreal use in the treatment of uveitis of the posterior eye segment. Both treatments have been shown to be effective in reducing inflammation and improve visual acuity. However, their use is associated with ocular complications, mainly increased intraocular pressure (IOP) and cataract, but also with rare sight-threatening events including endophthalmitis as a consequence of the intravitreal injection.

Systemic CS are usually effective in the treatment of uveitis, although some patients, e.g., those with Behçet-associated uveitis, are known to be poor responders. Despite their benefit in the treatment of uveitis, the risk of adverse effects of long-term systemic CS therapy, including cataract development, osteoporosis, glucose intolerance, and weight gain, limit their use in the treatment of non-infectious uveitis. The acceptability of CS-associated side effects differs between countries. However, for chronic suppression of uveitis, it is generally accepted in clinical practice that a CS sparing agent should be considered if > 10 mg per day of prednisone or its equivalent are required to achieve quiescence to avoid exposing patients to risk of adverse effects of CS.

Immunosuppressive and –modulating agents are also used for the treatment of non-infectious uveitis in clinical practice. Ancillary studies indicate that immunosuppressants may be efficacious. However, efficacy and safety in this indication have not been established in well-controlled studies. The most commonly used immunosuppressive agents are azathioprine, methotrexate (MTX), mycophenolate mofetil (MMF), ciclosporin and tacrolimus. At the time of this report, only ciclosporin was approved in the EU for uveitis treatment. However, its onset of action is rather slow and its use is associated with substantial side effects. In general, use of immunosuppressive agents has limitations related to safety.

Anti-TNF agents are also used in the treatment of various types of uveitis in clinical practice. However, with the exception of infliximab, which is approved in Japan for the treatment of refractory uveitis associated with Behçet's disease, no anti-TNF agent has been approved in this indication.

Globally, there is a clear demand for additional effective and possibly steroid–sparing therapies in patients with non-infectious intermediate uveitis, posterior uveitis, and panuveitis.

2.2. Non-clinical aspects

2.2.1. Introduction

The pharmacology of adalimumab has been extensively studied and was described in previous applications. Non-clinical data available at the time of this report revealed no special hazard for humans based on studies of single dose toxicity, repeated dose toxicity, and genotoxicity.

For the purpose of this application, a study in the Experimental Autoimmune Uveoretinitis (EAU) mouse model mice (study R&D/09/1420) was conducted using a mouse anti-mouse TNF monoclonal antibody. This study had been recommended in a Scientific Advice by the CHMP for clinical dose selection purposes. No other non-clinical studies were conducted in support of this application.

2.2.2. Pharmacology

Primary pharmacodynamic (PD) studies

Study R&D/09/1420: A Role for Tumor Necrosis Factor (TNF) in a Preclinical Model of Autoimmune Uveitis

Method

Interphotoreceptor retinoid-binding protein peptide (IRBP) 161-180 and Complete Freund's adjuvant were used to immunise female mice. The day after immunisation the mice were treated with mouse anti-mouse TNF antibody A-846889.0 in 200 µl phosphate-buffered saline (PBS) for a total of three doses (one per week). In the first part of the study all animals were administered a dose of 15 mg/kg/week, however in the latter part animals were dosed ascending doses (0.15, 0.5, 1.5, 5 and 15 mg/kg/week). The control group was injected with 200 µl IgG control. On Day 21 animals were euthanized and eyes prepared. Left and right eyes were scored separately for each animal. Severity of EAU was scored based on a system modified from Caspi et al. (1988). Total EAU histologic scores were based on photoreceptor damage (photoreceptor cell loss, retinal folds and detachment) and inflammatory infiltrates (vitreous, retina, retinal pigment epithelium and choroid). An additional scoring category was Dalen Fuchs-type nodules between the retina and the choroid which are characteristic features of chronic human uveitis.

Results

Group mean EAU scores are presented in Table 1.

Table 1 - Study R&D/09/1420 – Overview of EAU score

Dose (mg/kg)	Score	
	Left eye	Right eye
IgG control part 1	3.4 (combined)	
IgG control part 2	3.4	3.6
0.15, part 2	3.4	2.8
0.5, part 2	2.0	2.2
1.5, part 2	2.0	2.0
5, part 2	3.0	2.3
15, part 2	0.5	1.5
15, part 1	0.8 (combined)	

2.2.3. Ecotoxicity/environmental risk assessment

Adalimumab is a human anti-human TNFα monoclonal antibody (IgG1), a composite of 100% human antibody sequences. In accordance with the CHMP Guideline on the Environmental Risk Assessment of Medicinal Products for Human use (EMEA/CHMP/SWP/4447/00), proteins are unlikely to result in a significant risk to the environment. Hence, the CHMP agreed that no environmental risk assessment (ERA) studies were needed.

2.2.4. Discussion on non-clinical aspects

The applicant has performed a PD study as previously recommended by the CHMP. The data show that murine anti-TNF is able to reduce inflammation in a murine IRBP-induced EAU model. A dose-relationship in the decrease of photoreceptor damage was observed. However, a substantial reduction was only seen for the highest dose selected. The CHMP furthermore noted that an anti-TNF murine surrogate antibody (A-846889) was used in the tests. The MAH explained the use of A-846889 as the potency of TNF neutralization with adalimumab is about 3 orders of magnitude lower in mice compared to humans. No further explanation was available to clarify possible functional differences of the two antibodies, and to discuss the clinical relevance of adalimumab-mediated TNF-α blockade in the model. However, the CHMP was reassured by the lack of toxicity observed. All findings were consistent with the pharmacological mode of action of A-846889, which overlaps with that of adalimumab in humans. This supports the conclusion that there was no change to the pharmaco-toxicological profile of adalimumab.

No other non-clinical studies were conducted, which was considered acceptable by the CHMP.

The CHMP agreed that no ERA studies were needed as adalimumab is a protein.

2.2.5. Conclusion on the non-clinical aspects

The CHMP concluded that the non-clinical data provided by the MAH were adequate to support this application.

2.3. Clinical aspects

2.3.1. Introduction

Good Clinical Practice (GCP)

The applicant confirmed that all clinical trials were performed in accordance with GCP.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Tabular overview of clinical studies

Study ID	No. of study centres / locations	Design	Study Posology	Study Objective	Subjects randomised / completed[a]	Duration	Gender M/F Mean Age[b]	Diagnosis	Primary Endpoint
M10-877 (VISUAL I)	67/ global incl. EU	Double-masked, RCT, superiority	Adalimumab: 80mg loading dose, followed by 40mg eow vs. placebo. Initial prednisone 60mg/day in both arms	Efficacy, safety	239/214 Main study (excluding Japanese substudy): 223/198	Up to 80 weeks	M: 93 F: 124 43 y	Active uveitis involving posterior segment despite CS 10-60mg/day	Time to treatment failure
M10-880 (VISUAL II)	62/ global incl. EU	Double-masked, RCT, superiority	Adalimumab: 80 mg loading dose, followed by 40mg eow vs. placebo.	Efficacy, safety	261/229 Main study (excluding Japanese substudy): 229/199	Up to 80 weeks	M: 88 F: 138 42 y	'Inactive' uveitis involving posterior segment, controlled on CS 10-35mg/day	Time to treatment failure
M11-327 (VISUAL III)	Up to 102/ global incl. EU	Open-label extension of M10-877 and -880	Adalimumab 40 mg eow.	Long-term safety, efficacy	423/ ongoing (to be terminated in March 2018)	Until March 2018, i.e. up to ~5-6 years		Active and 'inactive' uveitis	*1. Safety* *2. Efficacy*

RCT: randomised controlled trial, eow: every other week, CS: corticosteroids (prednisolone equivalent)
[a] Prematurely discontinued study drug
[b] Main study

2.3.2. Clinical Pharmacology

The clinical pharmacology and immunogenicity of adalimumab are well characterized in healthy subjects as well as in subjects in the approved indications (RA, CD, UC, PS, PsA, and AS).

The pharmacokinetics (PK) and immunogenicity of adalimumab were evaluated in subjects with non-infectious uveitis in the two pivotal phase 3 studies (studies M10-877 and M10-880, see section 2.4. for a detailed description of study design and methods). The population PK of adalimumab was evaluated in uveitis subjects using a non-linear mixed effects modeling approach in NONMEM. Furthermore, exposure-response analyses were conducted to evaluate the relationship between serum concentrations and efficacy of adalimumab in the phase 3 studies.

Blood samples were taken at the following time points:

Adalimumab serum concentration: at Baseline and Weeks 1 (Study M10-877 only), 2 (Study M10-880 only), 8, 12, 27, 36, and 52; furthermore at the final/early termination visit when the subject terminated prior to Week 52, an unscheduled visit before Week 52 if applicable. Baseline, Week 1, and Week 27 blood samples were also drawn prior to study drug (placebo and adalimumab) administration.

Anti-adalimumab antibodies (AAA) serum concentration: at Baseline, Weeks 12, 27, 36, and 52; and at the final/early termination visit when the subject terminated prior to Week 52, an unscheduled visit before Week 52 if applicable. Baseline and Week 27 samples were also drawn prior to study drug (placebo and adalimumab) administration.

Methods

- **Analytical methods**

Adalimumab concentrations in serum were determined using a validated enzyme-linked immunosorbent assay (ELISA) method. Serum samples were analysed for screening and confirmatory AAA assay using a validated double antigen immunoassay which detects antibodies directed against epitopes on the entire adalimumab molecule.

- **PK data analysis**

Descriptive statistics of adalimumab concentrations are presented for within and between study comparisons. In addition, a population pharmacokinetic (PPK) analysis has been performed.

PPK and exposure-response models were built using nonlinear mixed effect modeling implemented in NONMEM 7.3. The PK model was fit to the data using the first-order conditional estimation method with interaction and the exposure-response models using the Laplacian Conditional Estimation method within NONMEM.

The models describing the relationships between adalimumab dose, exposure and response were built in a sequential manner. First, a PPK model was constructed to describe the relationships among adalimumab dose, serum concentration time profiles and covariates. Next, individual *post hoc* PK parameters generated from the final PPK model were used to predict adalimumab concentration-time profiles, which were applied as input functions of the PD models to describe the relationship between adalimumab exposure and its effects on efficacy (primary efficacy end point, i.e. time to treatment failure).

2.3.2.1. Pharmacokinetics

- Adalimumab serum concentrations

A summary of the serum adalimumab concentrations from all subjects in studies M10-877 and M10-880, who received adalimumab treatment is presented in Table 2.

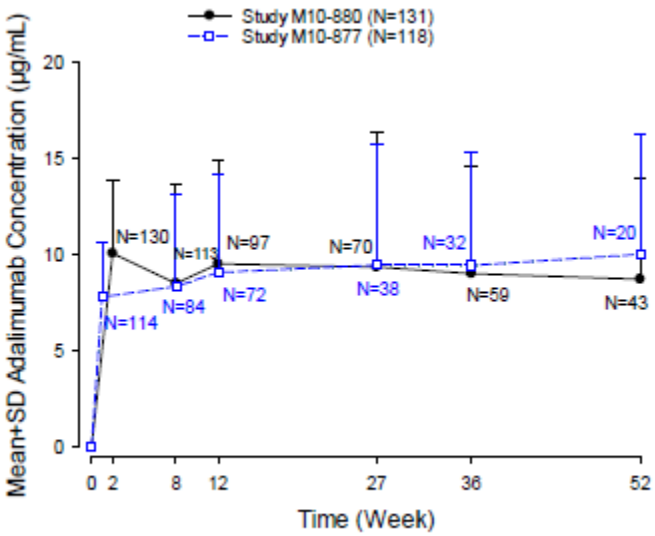
Table 2 - Summary of Serum Adalimumab Concentrations (µg/mL) for Subjects with Uveitis (Studies M10-877 and M10-880)

	Mean ± SD (Range), N						
	Week						
Study	0	1 or 2[a]	8	12	27	36	52
M10-877 (N = 118)	0 ± 0 (0 – 0), 117	7.80 ± 2.87 (1.47 – 18.4), 114	8.34 ± 4.86 (0 – 21.2), 84	9.09 ± 5.12 (0 – 23.0), 72	9.46 ± 6.25 (0 – 31.4), 38	9.45 ± 5.90 (0 – 21.3), 32	10.0 ± 6.25 (0 – 22.0), 20
M10-880 (N = 131)	0 ± 0 (0 – 0), 131	10.1 ± 3.79 (0.311 – 21.0), 130	8.50 ± 5.17 (0 – 25.0), 113	9.53 ± 5.36 (0 – 23.9), 97	9.36 ± 7.00 (0 – 46.8), 70	9.01 ± 5.63 (0 – 28.8), 59	8.72 ± 5.28 (0 – 27.1), 43

a. Week 1 for Study M10-877 and Week 2 for Study M10-880.

All subjects (non-Japanese and Japanese) included in the analysis.

The mean (SD) serum adalimumab concentration in the adalimumab treatment group in studies M10-877 and M10-880 is shown in Figure 1.



Note: The numbers next to the standard deviation bars are total N at that time point.

Figure 1 - Mean (+SD) Serum Adalimumab Concentrations Versus Time in Subjects with Uveitis (Studies M10-877 and M10-880)

In the phase 3 studies M10-877 and M10-880, following adalimumab 80 mg at Baseline and 40 mg eow starting at Week 1, the mean serum adalimumab concentrations reached steady state levels (8-10 µg/mL) after the initial dose and remained constant through Week 52 during adalimumab 40 mg eow treatment. Adalimumab exposure was comparable between studies M10-877 and M10-880.

- Anti-adalimumab antibody (AAA) formation

In the phase 3 studies M10-877 and M10-880, the percentage of subjects who received adalimumab 40 mg eow and tested positive for AAA was 4.8% (12/249) as shown in Table 3.

Table 3 - AAA Positive Rates (Studies M10-877 and M10-880)

Treatment Population	Study M10-877	Study M10-880	Total
Non-Japanese only (Main study)	2.7 % (3/110)	5.2% (6/115)	4.0% (9/225)
Japanese only (Japan sub-study)	12.5% (1/8)	12.5% (2/16)	12.5% (3/24)
All subjects non-Japanese and Japanese (Integrated study)	3.4% (4/118)	6.1% (8/131)	4.8% (12/249)

Overall, mean adalimumab concentrations were lower in AAA+ subjects compared to those in AAA– subjects, starting at Week 8 and remained lower throughout the study (see Figure 2).

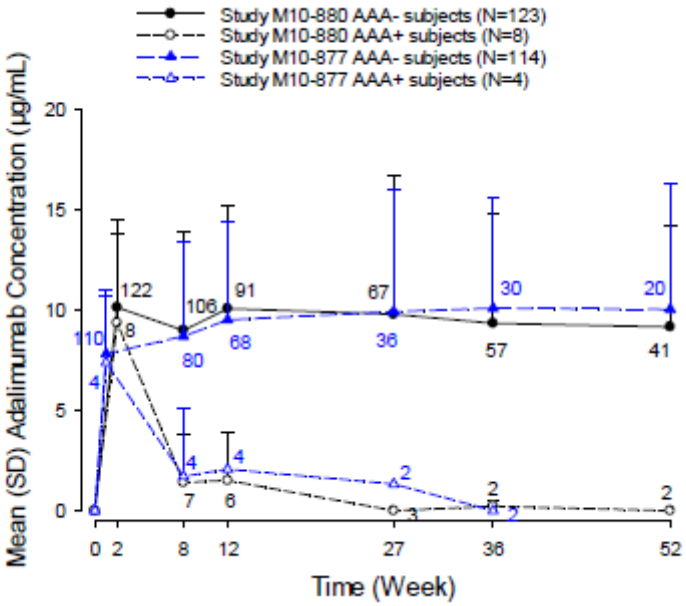


Figure 2 - Mean (SD) Serum Adalimumab Concentrations Versus Time by AAA Status

Population PK analysis

The PPK analysis was performed for subjects with at least one measurable adalimumab concentration in studies M10-877 and M10-880. A total of 248 uveitis subjects were included. Adalimumab concentration values below the lower limit of quantification (LLOQ) during treatment were set to LLOQ/2. This approach was considered acceptable by the CHMP as the number of observations below limit of quantification was small with 54/1078 (5%).

The demographic data for the subjects included in the PPK analyses are presented below.

Table 4 - Summary of patient characteristics

Demographic Characteristic		Total (N = 248)
Sex, N (%)	Male	109 (44.0%)
	Female	139 (56.0%)
Race, N (%)	White	154 (62.1%)
	Black	17 (6.9%)
	Asian	31 (12.5%)
	Other	46 (18.5%)
Japanese, N (%)	Non-Japanese	223 (89.9%)
	Japanese	25 (10.1%)
Age (years)	Mean ± SD (Range)	43.2 ± 13.93 (18 – 81)
Baseline Body Weight (kg)	Mean ± SD (Range)	78.3 ± 19.25 (38 – 174)

Cross reference: Table 13.1__2

Residual unexplained variability was explored using an additive, proportional or combined residual error model. Between-subject variability was described assuming a log-normal distribution.

Model evaluation and selection was based on the objective function value (OFV, P < 0.01), goodness of fit plots and precision of the parameter estimates. The predictive performance was assessed by visual predictive checks (VPC). Confidence intervals (95% CI) around the parameter estimates were obtained from a nonparametric bootstrap (n=1000).

Covariate evaluation was performed by a forward inclusion (P <0.01) backward elimination (P <0.001) procedure. Continuous covariates were included in the model using a power function centred around the median value and for categorical covariates, different parameter values were estimate for each category. The covariates that were evaluated were demographics such as age, weight, sex race etc. In addition, presence of AAA and some Baseline disease characteristics was evaluated on the apparent clearance (CL/F).

The final PPK model included a one-compartment model with first order absorption and elimination and inter-individual variability on CL/F and apparent volume of distribution of central compartment (V2/F), and a combined residual error model. The provided goodness of fit plots indicate some model misspecifications both at higher and lower exposures. The M3 method was tested but did not significantly improve the VPCs at the lower exposures. A two-compartment model, additional Michaelis-Menten elimination pathway, and alternative ETA structure did not resolve the issue either.

The mean CL/F and V2/F of adalimumab were estimated to be 16.0 mL/hr (0.384 L/day) and 7.95 L, respectively, in subjects with non-infectious uveitis. The η-shrinkage for CL/F was 13% and for V/F 58%. The shrinkage in V/F was high. However, no relevant differences in the estimated drug effect parameter values were found when removing eta on V/F, suggesting that the η-shrinkage did not have a significant impact on the outcome of the exposure-response analyses.

Impact of covariates

AAA, MTX and MMF use, and Baseline body weight were identified as significant covariates for CL/F of adalimumab. Adalimumab CL/F was approximately 3 times higher in the AAA+ subjects when compared to the AAA– subjects whereas concomitant MTX or MMF use were associated with reduced adalimumab CL/F by 38.4%. The increased clearance in AAA+ subjects in the PPK model was

consistent with the lower adalimumab concentrations observed in studies M10-877 and M10-880 in this group of patients (see Figure 2) compared to AAA- subjects.

There was a ~58% increase in median adalimumab CL/F in subjects with the highest weight quartile of 87-174 kg compared to subjects with the lowest weight quartile of 38-65 kg. Baseline body weight was also identified as a significant covariate for V2/F. A stratification per body weight was requested by the CHMP to obtain reassurance of comparable exposure across the different patients weight-ranges. From the estimates provided by the MAH by weight range (66-86 kg, 38-65kg, and 87-174 kg), a difference of almost ±20% change in CL/F and V/F can be observed in the lowest and highest weight quartiles when compared to patients in the weight range of 66-86 kg. These results supported that patients in the weight range 66-86 kg were not underexposed.

Comparison of PK across indications

Subjects in the phase 3 studies with uveitis received 80 mg adalimumab at Week 0 and the same initial dose was tested in subjects with chronic plaque psoriasis (study M02-528). Furthermore, mean steady-state serum adalimumab concentrations following 40 mg eow treatment in subjects with uveitis were compared to those observed in subjects with CD (study M02-433), UC (study M06-827), RA (study DE019), and PS (studies M02-528 and M03-656) using the same maintenance regimen (see Figure 3).

Based on the mean steady-state serum adalimumab concentrations, similar exposure was observed in uveitis patients compared to other patient population using the same dose.

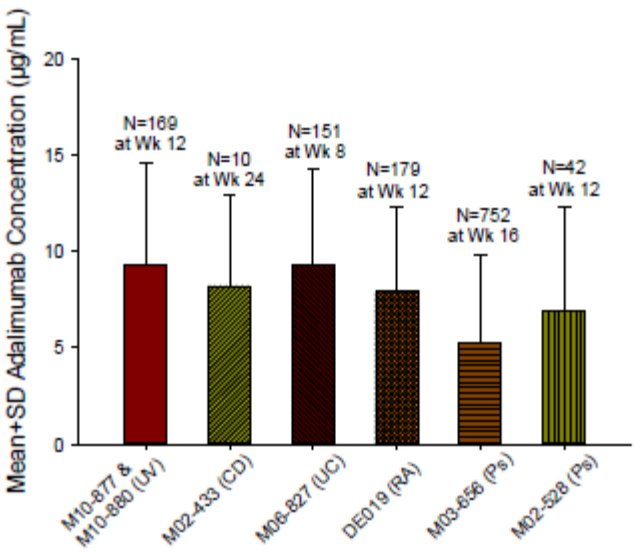


Figure 3 - Comparison of Mean (+SD) Steady-State Serum Adalimumab Concentrations in Subjects with Uveitis and Subjects with CD, UC, RA and Ps during Maintenance Dosing (Adalimumab 40 mg eow)

2.3.2.2. Pharmacodynamics

No clinical PD studies have been conducted.

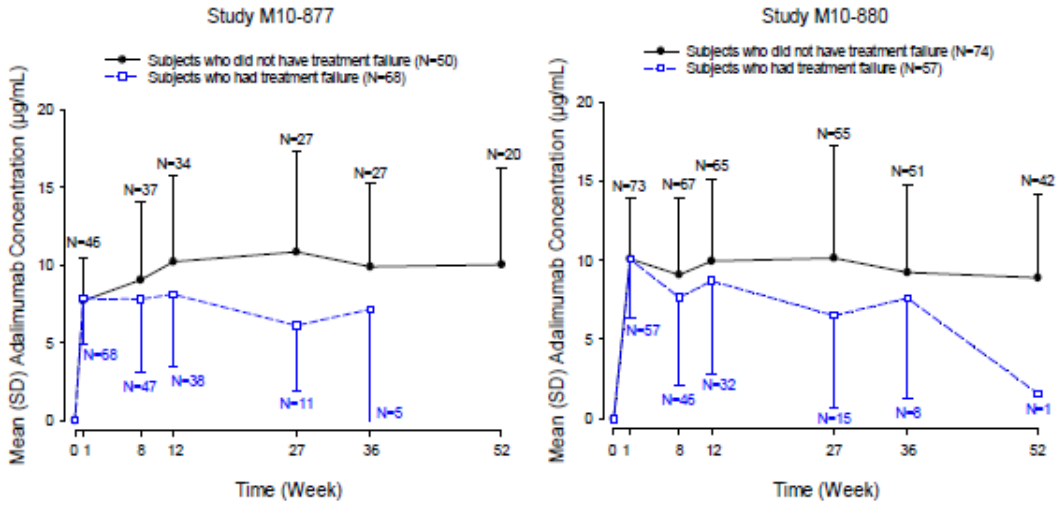
Mechanism of action

The mechanism of action of adalimumab in non-infectious uveitis is the same as for other immune mediated disorders, i.e. blockage of TNF-α. Elevated levels of TNF-α are thought to play an important role in pathologic autoimmune disorders and immune-mediated disorders. Reports in the scientific literature suggest that non-infectious uveitis is mediated by T helper type 1 CD4+ T cells. TNF-α, a pro-inflammatory cytokine produced mainly by macrophages and T cells, has also been shown to play a role in the perpetuation of inflammation in uveitis by facilitating further leukocyte infiltration via adhesion molecule upregulation, macrophage activation, and dendritic cell maturation/survival (Dick et al., 2004). This has been supported by both laboratory and clinical studies showing elevated levels of TNF-α in peripheral CD4+ T cells of patients in both idiopathic and sarcoid intermediate uveitis and intraocularly in EAU rats (Okada et al., 1998, Murphy et al., 2004).

Primary and Secondary pharmacology

There are numerous publications on the clinical use of anti-TNF agents in the treatment of various types of uveitis. Several of these publications report on the effectiveness of adalimumab (Callejas-Rubio et al., 2008; Mushtaq et al., 2007; Diaz-Llopis et al., 2008) and also the TNF-alpha blocker infliximab. There have been also reports on the efficacy of adalimumab in paediatric patients with JIA-associated or idiopathic uveitis (Vazquez-Cobian et al. 2006; Biester et al. 2007).

In both phase 3 studies conducted with adalimumab in patients with non-infectious uveitis, the exposure-response relationship was explored for subjects in the adalimumab treatment arm using the primary endpoint, time to treatment failure. As shown in Figure 4, mean adalimumab concentrations were slightly higher in patients who did not experience treatment failure (9-11 µg/mL) compared to those with treatment failure (6–9 µg/mL), starting from Week 8 (see also PK/PD model in section 2.3.2.3.).



Note: The numbers next to the standard deviation bars are total N at that time point. For the treatment failure subjects, none had Week 52 samples for Study M10-877.

Figure 4 - Mean (SD) Serum Adalimumab Concentrations versus Time by Occurrence of Treatment Failure (Studies M10-877 and M10-880)

2.3.2.3. PK/PD Model

Graphical analyses and parametric time-to-event analyses were performed for a preliminary assessment of the exposure-response relationship for the efficacy of adalimumab in subjects with non-

infectious uveitis using the primary efficacy end point, time to treatment failure assessed at or after Week 6 (study M10-877) or Week 2 (study M10-880). The observed time to treatment failure in studies M10-877 and M10-880 was furthermore plotted versus time stratified by placebo and different simulated adalimumab concentration quartile groups (at week 24).

The PK-PD modeling was performed separately for each study because of the differences in the population between the two studies (adult subjects with active non-infectious uveitis in study M10-877 versus adult subjects with inactive, non-infectious uveitis controlled with corticosteroids (CS) in study M10-880). A model was developed first to describe the observed time-to-treatment-failure in the placebo arm. Next, parameters of the placebo model were fixed and a concentration-effect model was developed for adalimumab concentration as a predictor of treatment failure. At last, a covariate evaluation for the drug effect parameter was performed.

The concentration time profile of adalimumab was described by individual *post-hoc* PK parameters generated from the final population PK model.

Model development was guided by the NONMEM objective function value (OFV). Predictive performance was evaluated by VPC where simulated predictions were compared in Kaplan-Meier plots with the observed data superimposed with the 95% prediction interval.

The following covariates were investigated as significant covariates for Baseline hazard in placebo patients and for the drug effect parameter: age, sex, race, Japanese origin, bodyweight, co-medications (prednisolone, azathioprine, MTX, ciclosporin and MMF) and baseline disease characteristics.

Several baseline hazard distribution functions were tested and a constant baseline hazard function resulted in an adequate description of the observed time to treatment failure for the placebo arms in both studies and was hence used in the model.

In study M10-877, visual acuity at baseline [best corrected visual acuity (logMAR BCVA) of left/right eye categorized as < 0.3 and ≥ 0.3] was identified as a significant covariate on the basal hazard rate for placebo. Subjects with logMAR BCVA ≥ 0.3 resulted in a higher probability of an event of treatment failure. None of the evaluated covariates on the drug effect parameter were significant.

In study M10-880, number of flares in the past 12 months, type of uveitis, and Japanese population were identified as significant covariates on the basal hazard rate for placebo. Higher number of flares in the past 12 months resulted in a more likely event of treatment failure. The subjects with posterior uveitis had a lower probability of having treatment failure when compared to intermediate uveitis or panuveitis, whereas Japanese subjects had a higher probability of having treatment failure compared to the non-Japanese subjects within the placebo population. None of the evaluated covariates on the drug effect parameter were significant.

The results from the exposure-response analyses showed that adalimumab treatment resulted in reduced risk of treatment failure when compared to the placebo group in both studies. Higher adalimumab concentrations were associated with lower probability of treatment failure. The estimated IC_{50} values for the inhibition of event of treatment failure were 9.7 µg/mL (95% CI 5.5-17.4 µg/mL) and 6.4 µg/mL (95% CI 3.8-10.8 µg/mL) in studies M10-877 and M10 880, respectively. No significant covariates were identified for IC_{50} of adalimumab. The model predicted IC_{50} values are based on the assumption that the maximum inhibitory effect is 100%. The assumption was evaluated by estimating the IC_{50} value when fixing the maximum inhibitory effect to different values. The assumed maximum effect has a significant influence on the IC_{50} estimate in the model and the assumption of 100% inhibitory effect provides the highest IC_{50} estimate. An additional sensitivity analysis (i.e. objective function values) and VPC showed only minor differences in the model fits.

Furthermore, in response to a request by the CHMP to evaluate alternative dosing regimens, clinical trial simulations were performed by the MAH. The final PK/PD model was used for a more frequent dosing regimen for adalimumab, i.e., 80 mg loading dose at baseline followed by 40 mg every week starting at Week 1 under 3 different assumptions of the maximum inhibitory effect (Imax = 0.6, 0.8, and 1). The results of these simulations indicated a potentially higher benefit of adalimumab 40 mg every week. Given the assumption of Imax=1, there is an increased benefit with a 40 mg every week. The PK/PD model suggests a decreased treatment failure of approximately 15%.

2.3.2.4. Discussion on clinical pharmacology

The PK properties of adalimumab have been previously characterised in healthy subjects as well in the approved indications. PK, immunogenicity and exposure-response relationship of adalimumab in patients with non-infectious uveitis were evaluated in the two pivotal phase 3 clinical trials (studies M10-877 and M10-880). In addition, PPK and PK-PD modelling was performed.

No specific PD data have been submitted to support this application. However, non-clinical data support a role of TNF-α in uveitis and there are some smaller clinical trials/case series that indicate an effect of anti-TNF agents in this disease. No further data was considered necessary by the CHMP.

In the phase 3 studies, a range of steady-state serum adalimumab concentrations from 8-10 µg/mL was achieved. This exposure range was similar to what has been observed in other patients groups (CD, UC, RA, and PS) studied with the same initial and maintenance dose (studies M02-528 and M03-656).

The final PPK model included a one-compartment model with first order absorption and elimination. This approach was similar to previous applications for Humira. However, the CHMP remarked that in light of the limited data in uveitis patients, use of exposure data of adalimumab in other indications would have helped to strengthen the model.

In the PK and PPK analyses, AAA, MTX and MMF use, and Baseline body weight were identified as significant covariates of adalimumab clearance. Particularly AAA+ had a significant impact on adalimumab exposure, whereby patients with a positive AAA status had lower adalimumab serum concentrations compared to AAA– subjects. The effect of AAA was already reflected in the SmPC of Humira. Further discussion on the development of AAA in patients with and without concomitant IMM use is provided in section 2.4.4. Likewise, the impact of body weight is further discussed in section 2.4.4. based on subgroup analyses by weight categories.

The estimated IC_{50} values for the inhibition of event of treatment failure were 9.7 µg/mL (95% CI 5.5-17.4 µg/mL) and 6.4 µg/mL (95% CI 3.8-10.8 µg/mL) in studies M10-877 and M10 880, respectively, indicating that steady-state serum adalimumab concentrations at 8-10 µg/mL were on the lower side of the therapeutic dose range. The exposure-response analyses further indicated that patients with treatment failure had lower adalimumab exposure compared to those without treatment failure in both studies. This suggests that the doses used were too low or that the dosing frequency should be increased. As no dose-response studies have been performed the rationale for the chosen dosing regimen was not clear. In fact, clinical trial simulations indicated that there may be a potential benefit of a maintenance dose of 40 mg every week. For this regimen, an additional 15% reduction in treatment failures was estimated by the model compared to the 40 mg eow regimen. The CHMP recommended that the weekly dosing regimen should be further explored in the clinical setting post-approval.

Finally, the CHMP noted that the population PK model over predicted low exposures. However it was expected that this issue will have no considerable impact on the efficacy and safety of the adalimumab

treatment of non-infectious uveitis and for this reason, the CHMP decided not to further pursue the issue in the present application. Nevertheless, it is expected that this feature of the population PK model is improved for future use of the model.

2.3.2.5. Conclusions on clinical pharmacology

Overall, the CHMP considered that the clinical pharmacology data provided with this application were adequate to support this application. The population PK model was found to over predict low exposures and the MAH is expected to improve this feature if the model is used in future applications. Furthermore, the CHMP recommended that post-approval, a weekly dosing regimen of 40 mg adalimumab is further explored in the clinical setting.

2.4. Clinical efficacy

2.4.1. Dose response study(ies)

No clinical dose response studies were performed in support of this application. The adalimumab dose regimen in the pivotal phase 3 placebo-controlled studies consisted of an 80 mg SC loading dose, followed by 40 mg eow starting at Week 1. The purpose of the initial loading dose of 80 mg was to achieve steady-state adalimumab concentrations and efficacy earlier during treatment. This dose was previously studied in psoriasis and has been shown to be an appropriate loading dose for the 40 mg eow maintenance regimen.

Exposure-response analyses including a PK-PD model are summarised in section 2.3.2.

2.4.2. Main study(ies)

The results of two pivotal phase 3 studies investigating the use of Humira in active uveitis (M10-877) and in corticosteroid depended patients with 'inactive' uveitis (M10-880) were provided. Both studies consisted of a main study and a sub-study in Japanese subjects. Efficacy outcomes from the Japanese sub-studies are summarised among the ancillary analyses (section 2.4.2.3.) and as part of the integrated analyses of the primary endpoint.

2.4.2.1. Methods

- **Study M10-877 (VISUAL I)**

Title: A Multicenter Study of the Efficacy and Safety of the Human Anti-TNF Monoclonal Antibody Adalimumab as Maintenance Therapy in Subjects Requiring High Dose Corticosteroids for Active Non-infectious Intermediate Uveitis, Posterior Uveitis, or Panuveitis – Including a Sub-study in Japanese

The study was a randomised (1:1), double-masked, placebo-controlled multicentre study in subjects requiring ≥10 to ≤60 mg prednisolone (or equivalent) per day for active non-infectious intermediate, posterior, or pan-uveitis. Baseline immunomodulatory (IMM) therapy was used as stratification factor. The study included a sub-study in Japanese patients randomised in a separate stratum. Subjects needed to be on oral prednisone 10 to 60 mg/day (or oral CS equivalent) at Baseline.

The study was to continue up to 80 weeks or to be ended when the 138th event of treatment failure (excluding Japan subjects) had occurred. Visits were scheduled at Baseline, Week 1, 3, 6 and 8, thereafter every 4 weeks.

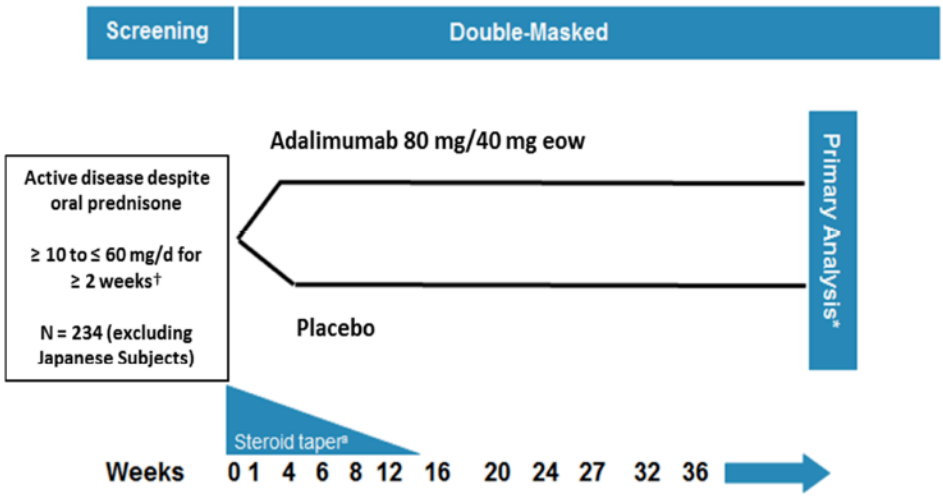


Figure 5 - Schematic Study Design for M10-877

* The study ended when the 138th event of treatment failure (excluding Japan subjects) had occurred.
† May have been on 1 immunosuppressive therapy and/or topical steroids at pre-defined stable doses.
[a] Prednisone 60 mg per day was given at Baseline followed by a taper from Weeks 2 – 15. Topical steroids were allowed at study entry, but subjects were to undergo a mandatory taper schedule from Weeks 1 – 9.

Study participants

Both of the subject's eyes were to be evaluated for the purpose of determining eligibility based on inclusion and exclusion criteria, and for the purpose of assessing treatment failure. There was no designated "study eye."

Main inclusion criteria

- Diagnosed with non-infectious intermediate uveitis, posterior uveitis, or pan-uveitis.
- Subject must have had active disease at the Baseline visit as defined by the presence of at least 1 of the following parameters in at least 1 eye despite at least 2 weeks of maintenance therapy with oral prednisone of ≥ 10 mg/day to ≤ 60 mg/day (or oral CS equivalent):
    - Active, inflammatory, chorioretinal, and/or inflammatory retinal vascular lesion.
    - ≥ 2+ anterior chamber (AC) cells (Standardization of Uveitis Nomenclature [SUN] criteria).
    - ≥ 2+ vitreous haze (VH) (National Eye Institute [NEI]/SUN criteria).
- On oral prednisone at a dose of ≥ 10 mg/day to ≤ 60 mg/day (or oral corticosteroid equivalent) for at least 2 weeks prior to screening and remained on the same dose from Screening to Baseline visit.
- Documented adequate response to oral CS (equivalent of oral prednisone up to 1 mg/kg/day).
- Subject did not have previous, active, or latent tuberculosis, i.e. negative Purified Protein Derivative or QuantiFERON®-Tuberculosis Gold test.

- In addition, subjects should be in an overall good health and being able and willing to self-administer SC injections.

Main exclusion criteria

- Isolated anterior uveitis.
- Confirmed or suspected infectious uveitis, including presumed ocular histoplasmosis syndrome.
- Masquerade syndromes or serpiginous choroidopathy.
- Contraindication to pupil dilation with mydriatic eyedrops.
- Corneal or lens opacity that precluded visualization of the fundus or likely required cataract surgery during the duration of the study.
- Subject had intraocular pressure (IOP) of ≥ 25 mmHg and on ≥ 2 glaucoma medications or evidence of glaucomatous optic nerve injury.
- Best Corrected Visual Acuity (BCVA) < 20 letters (Early Treatment Diabetic Retinopathy Study [ETDRS]) in at least 1 eye at the Baseline visit.
- Intermediate uveitis or panuveitis with signs of intermediate uveitis and symptoms and/or magnetic resonance imaging (MRI) findings suggestive of a demyelinating disease, e.g. multiple sclerosis (MS).
- Previous exposure to anti-TNF therapy or any biologic therapy with a potential therapeutic impact on non-infectious uveitis.
- More than 1 immunosuppressive therapy (not including CS) at Baseline. Increase in dose during the 28 days prior Baseline.
- On concomitant therapy other than stable doses of MTX (≤25 mg/week), ciclosporin (≤ 4 mg/kg/day), MMF, ≤ 2g/day), or an MMF equivalent, azathioprine (≤175 mg/day), or tacrolimus (≤ 8 mg/day) at Baseline.
- Prior or current use of chlorambucil.
- Retisert (glucocorticosteroid implant) within 3 years, or in case of complications related to the device removal within 90 days prior to the Baseline visit, or Ozurdex, intraocular/periocular CS or intravitreal MTX within 6 months, 30 days or 90 days, respectively prior the Baseline visit.
- Subject had received intravitreal anti-vascular endothelial growth factor (VEGF) therapy within 45 days of the Baseline visit for Lucentis (ranibizumab) or Avastin(bevacizumab), or within 60 days of the Baseline visit for Eylea (aflibercept).
- Severe non-proliferative diabetic retinopathy (NPDR), diabetic macular oedema (DME), neovascular age-related macular degeneration (AMD) or abnormality of the vitreo-retinal interface.
- Prior exposure to biologics that have a potential or known association with progressive multifocal leukoencephalopathy.
- History of demyelinating disease (including myelitis and optic neuritis) or neurologic symptoms suggestive of demyelinating disease.
- Chronic recurring infections, history of malignancies.

Treatments

Study drug: Humira was administered in pre-filled syringes containing adalimumab 40 mg/0.8 mL or matching placebo. Drug was administered SC as an 80 mg or placebo loading dose (2 syringes) at baseline followed by a 40 mg or placebo dose eow starting at Week 1. Treatment was administered by medical staff or self-administered (after training), the latter was recorded in a dosing diary.

Open label prednisone (from commercially available sources): All subjects were to receive a prednisone burst of 60 mg/day at randomisation. Beginning at Week 2, subjects were to undergo a standardised taper schedule (10 mg/week between Weeks 2 and 5, thereafter reductions in smaller steps) until all subjects were off oral prednisone by Week 15, see Table 5.

Table 5 - Study M10-877 Oral Prednisone Dosing and Taper Schedule

Study week	Prednisone Dose (mg/day)
0	60
1	60
2	50
3	40
4	30
5	20
6	15
7	12.5
8	10
9	7.5
10	5
11	4
12	3
13	2
14	1
15	Discontinue prednisone

Beginning at Week 1, subjects who entered the study on topical CS were to undergo a standardised taper schedule until all subjects were off topical CS by Week 9.

Objectives

To evaluate the efficacy and safety of adalimumab (80 mg loading dose at Baseline followed by a 40 mg dose given eow SC starting at Week 1) compared with placebo in subjects requiring high-dose systemic CS for treatment of active non-infectious intermediate uveitis, posterior uveitis, or panuveitis.

Outcomes/endpoints

The primary efficacy endpoint was the **time to treatment failure on or after Week 6**. Both of the subject's eyes were to be evaluated for the purpose of assessing treatment failure with no designated study eye and the first evaluation was conducted at Week 6. Criteria for treatment failure are summarised in the below table.

Table 6 - Study M10-877 Treatment Failure Criteria

	Treatment Failure*	
Parameter	**Week 6 Visit**	**All Other Visits After Week 6**
Inflammatory, chorioretinal, and/or inflammatory retinal vascular lesions	New active, inflammatory lesions relative to Baseline	New active, inflammatory lesions relative to Baseline
AC cell grade (SUN criteria)	Inability to achieve ≤ 0.5+	2-step increase relative to best state achieved**
VH grade (NEI/SUN criteria)	Inability to achieve ≤ 0.5+	2-step increase relative to best state achieved**
Visual acuity (ETDRS)	Worsening of BCVA by ≥ 15 letters relative to best state achieved	Worsening of BCVA by ≥ 15 letters relative to best state achieved

* To be considered a treatment failure, ≥ 1 of these 4 criteria had to be present in at least 1 eye.

** A 2-step increase was represented by a change of Grade 0 to Grade 2+; or Grade 0.5+ to Grade 3+.

The number of AC cells observed within a 1 mm × 1 mm slit beam was to be recorded (by the investigator) for each eye. VH scores were graded by the Investigator with the help of standardised photographs and descriptions. Independent sequential masked efficacy evaluations by a central reader were established for fundus photography and optical coherence tomography (OCT) measurements.

Secondary efficacy variables (ranked):

1. Change in AC cell grade in each eye from best state achieved prior to Week 6 to the final/early termination visit.
2. Change in VH grade according to NEI/SUN criteria in each eye from best state achieved prior to Week 6 to the final/early termination visit.
3. Change in logarithm of the minimum angle of resolution (logMAR) BCVA in each eye from best state achieved prior to Week 6 to the final/early termination visit.
4. Time to OCT evidence of macular oedema in at least 1 eye on or after Week 6.
5. Percent change in central retinal thickness in each eye from best state achieved prior to Week 6 to the final/early termination visit.
6. Change in NEI Visual Functioning Questionnaire-25 (VFQ-25) composite score from best state achieved prior to Week 6 to the final/early termination visit.
7. Change in VFQ-25 sub-score distance vision from best state achieved prior to Week 6 to the Final/Early Termination Visit
8. Change in VFQ-25 sub-score near vision from best state achieved prior to Week 6 to the Final/Early Termination Visit
9. Change in VFQ-25 sub-score ocular pain from best state achieved prior to Week 6 to the Final/Early Termination Visit

Other efficacy variables included analyses of mean changes (as well as area under the curve [AUCs]) of AC cell scores, VH scores, BCVA over time, time to failures for the individual components of the primary endpoint (*post hoc* for BCVA) and proportions of patients in quiescence/in steroid-free

quiescence. A number of patient reported outcomes (PROs) including VFQ-25 subscores, Hospital Anxiety and Depression Scale (HADS), Work Productivity and Activity Impairment, Questionnaire: Specific Health Problem Questionnaire (WPAI-SHP), and EuroQol-5D (EQ0-5D) Questionnaire were evaluated.

Post hoc analyses were conducted using a definition for macular oedema with different centre point thickness cut-offs for different brands of OCT machines, for time to treatment failure and failure rates based on BCVA only and for the percentage of subjects in disease control at Week 1 and 4 were analysed (definition according to Table 6).

Subgroup analyses based on e.g. duration and type of uveitis (location, aetiology), number of flares were conducted for the primary and ranked efficacy variables.

Safety was assessed by collection and monitoring of adverse events (AEs), physical examination assessments, vital signs assessments, and laboratory data.

Regarding blood samples for serum concentrations of adalimumab (PK and PK/PD analyses), see section 2.3.2.

Sample size

The placebo treatment failure rate at 6 months was assumed to be 70% and the adalimumab treatment failure rate at 6 months was assumed as 50%. For conservative purposes, it was assumed that failures would begin to occur after 2 months of study duration as the prednisone taper reached lower doses. In addition, a pooled dropout rate of 35% over 12 months was assumed.

Using these failure rate assumptions for a log-rank test and a 2-sided significance level of 5%, a total of 138 events were needed. The assumptions also included power of 90% and an average accrual rate of 4 subjects per month in the first 30 months and 7 subjects per month thereafter. To achieve 138 treatment failure events, it was anticipated that a sample size of approximately 234 subjects was needed.

Randomisation

Subjects who were eligible based on inclusion and exclusion criteria and had had all pre-randomization procedures performed were randomized in 1:1 double-masked fashion to the treatment groups using baseline IMM usage as the stratification factor. Randomization was not stratified by site due to the small expected number of subjects per site. Randomization was done using a block size of 4.

Japan sub-study: Due to the small sample size, no stratification by baseline IMM usage was to be used for subjects from Japan. Subjects from Japan were to be randomized in a separate stratum.

Blinding (masking)

Double-masked study drug was provided as a sterile, preservative-free solution for injection contained in 1 mL pre-filled syringes containing adalimumab 40 mg/0.8 mL or matching placebo. All MAH personnel with direct oversight of the conduct and management of the study (with the exception of the Drug Supply Management Team), the investigator, study site personnel, and the study subjects were to remain masked to treatment throughout the masked period of the study. Interactive Web and Voice Response Systems were used to provide access to masked subject treatment information in the case of a medical emergency.

Statistical methods

The intent-to-treat (ITT) set included all subjects who were randomized, excluding those for whom efficacy source data was incomplete and/or there were general GCP compliance issues at the sites. No per protocol analysis was planned.

The modified intent-to-treat (mITT) set includes all randomized subjects recruited outside Japan and was used for sensitivity analyses.

The safety set consisted of all subjects who received at least 1 dose of study drug.

The statistical test for the primary endpoint and ranked secondary endpoints as well as all other statistical tests were performed at a 2-sided significance level of 0.05. Descriptive statistics, including the number of observations, mean, standard deviation, minimum, first quartile, median, third quartile, and maximum for continuous variables; and counts and percentages for discrete variables, were provided. The analyses were performed using SAS® (SAS Institute Inc., Cary, NC, USA).

The 2-sided testing of ranked secondary endpoints were initiated only in case of statistically significant differences between the treatment groups for the primary endpoint. The statistical test for the ranked secondary variables was carried out in the hierarchical order shown. This means that statistically significant results for the higher ranked secondary variable were mandatory to initiate the testing of the next variable with a lower rank, thus controlling the multiple significance level of 5% two-sided.

Demographics and baseline characteristics as well as efficacy variables were summarized for each treatment group using descriptive statistics. Statistical tests were performed to assess the comparability of the treatment groups assigned by randomization. Continuous variables were analysed using analysis of variance (ANOVA) and discrete variables were analysed using Chi-square test. For the primary endpoint and the 4th ranked secondary endpoint, Kaplan-Meier estimates were calculated and Kaplan-Meier curves were plotted. The primary efficacy endpoint was analysed using a log-rank test. Treatment failures on or after Week 6 were counted as events. Dropouts due to reasons other than treatment failure at any time during the study were considered as censored observations at the time of dropping out.

In a sensitivity analysis, time to treatment failure was compared between the treatment groups in a proportional hazards model with treatment and baseline IMM usage as factors.

The ranked secondary endpoints were analysed as follows: Change in AC cell grade, change in VH grade, change in logMAR BCVA, and change in central retinal thickness were compared between treatment groups using ANOVA adjusted for clustered observations (i.e., observations from each of the subject's eyes). Change in VFQ-25 was compared between treatment groups using ANOVA. Subjects dropping out through Week 6 were excluded from the analysis of AC cells, VH, logMAR BCVA, central retinal thickness, and VFQ-25. Missing values were imputed by last observation carried forward (LOCF), the subject's value at the time of treatment failure, or as carrying forward the last observed value if a subject did not fail until completion of the study. Baseline values were not used to impute the missing post-baseline values and missing values after Rx Day 1 were imputed using the latest non-missing value after Rx Day 1 and prior to the missing value.

The time to OCT evidence of macular oedema on or after Week 6 was analysed in a proportional hazards model. OCT evidence of macular oedema on or after Week 6 was counted as an event. Dropouts due to reasons other than OCT evidence of macular oedema were considered as censored observations at the time of dropping out.

- **Study M10-880 (VISUAL II)**

Title: A Multicenter Study of the Efficacy and Safety of the Human Anti-TNF Monoclonal Antibody Adalimumab in Subjects with Inactive Non-infectious Intermediate Uveitis, Posterior Uveitis, or Panuveitis – Including a Sub-study in Japanese

The study was a randomised (1:1), double-masked, placebo-controlled multicentre study in subjects with 'inactive' non-infectious intermediate, posterior, or pan-uveitis while on oral prednisone 10 - 35 mg/day (or oral CS equivalent). Baseline IMM was used as the stratification factor. Also this study included a sub-study in Japanese patients randomised in a separate stratum. Subjects needed to be on 10 - 35 mg/day (or oral CS equivalent) at Baseline.

The study was of 80 weeks duration or ended when approximately 96 treatment failures (excluding Japanese subjects) had occurred. Visits were scheduled at Baseline, then eow up to Week 8 and thereafter every 4 weeks.

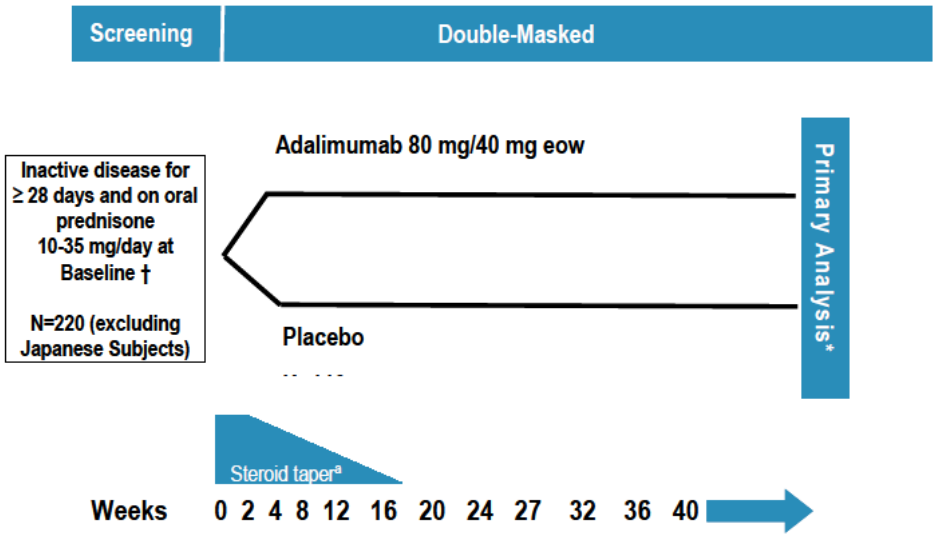


Figure 6 - Study Design Schematic for Study M10-880

* The study ended when the 96 (84 to 107) event of treatment failure (excluding Japan subjects) had occurred.
† May have been on 1 immunosuppressive therapy and/or topical steroids at pre-defined stable doses.
[a] Prednisone taper was to occur from Week 2 up to Week 19. Topical steroids were allowed at study entry, but subjects were to undergo a mandatory taper schedule from Week 1 to Week 9.

Study participants

The main selection criteria were as for study M10-877 except for:

Inclusion criteria

- Subject had inactive intermediate uveitis, posterior uveitis, or pan-uveitis for ≥ 28 days prior to the Baseline visit, was taking ≥ 10 mg of oral prednisone to maintain this inactive state, and fulfilled 3 of the following criteria (investigator's clinical judgment at screening and baseline visits) for both eyes:
    - Without active, inflammatory, chorioretinal, and/or inflammatory retinal vascular lesion
    - ≤ 0.5+ AC cells (SUN criteria)
    - ≤ 0.5+ VH; (NEI/SUN criteria)
- On oral prednisone at a dose of 10 to 35 mg/day (or oral CS equivalent) at Baseline and the dose had not been increased in the past 28 days or decreased in the past 14 days.

- Documented history of ≥ 1 disease flare within 18 months of the Screening visit. This flare had to occur during or up to a maximum of 28 days after tapering off the oral CS therapy.

Exclusion criteria

- Intraocular or periocular CS within 90 days prior to the Baseline visit.
- Cystoid macular oedema unless the retinal changes were persistent (> 3 months duration), residual, and stable as defined by SUN criteria.

Treatments

Adalimumab and placebo treatment was administered as in study M10-877, i.e. a loading dose of 80 mg or placebo, and thereafter 40 mg or placebo eow.

Beginning at Week 2, subjects were to undergo a standardised taper schedule (5 mg/week between weeks 2 and 5, thereafter reductions in smaller steps) until all subjects were off oral prednisone no later than Week 19.

Table 7 - Study M10-8807 Oral Prednisone Dosing and Taper Schedule

Prednisone (mg/day)	35 mg	30 mg	25 mg	20 mg	15 mg	12.5 mg	10 mg
35	Week 0-1						
30	2	Week 0-1					
25	3	2	Week 0-1				
20	4	3	2	Week 0-1			
15	5	4	3	2	Week 0-1		
12.5	6	5	4	3	2	Week 0-1	
10	7	6	5	4	3	2	Week 0-1
7.5	8	7	6	5	4	3	2
5	9	8	7	6	5	4	3
4	11	10	9	8	7	6	5
3	13	12	11	10	9	8	7
2	15	14	13	12	11	10	9
1	17	16	15	14	13	12	11
Discontinue	19	18	17	16	15	14	13

Objectives

To evaluate the efficacy and safety of adalimumab (80 mg loading dose followed by a 40 mg dose given eow SC starting at Week 1) compared with placebo in subjects requiring systemic CS (oral prednisone 10 to 35 mg/day) for inactive non-infectious intermediate uveitis, posterior uveitis, or panuveitis.

Outcomes/endpoints

The primary efficacy endpoint was the **time to treatment failure on or after Week 2**. As in study M10-877, both eyes were evaluated for treatment failure according to the below criteria.

Table 8 - Study M10-880 Treatment Failure Criteria

Parameter[a]	How Represented	When Assessed
New active, inflammatory, chorioretinal, and/or inflammatory retinal vascular lesions	New active, inflammatory lesions relative to baseline	Week 2 and all other visits after Week 2
AC cell grade (SUN criteria)	2-step increase in AC cell grade relative to baseline[b]	Week 2 and all other visits after Week 2
VH grade (NEI/SUN criteria)	2-step increase in VH grade relative to baseline[b]	Week 2 and all other visits after Week 2
Visual acuity (ETDRS)	Worsening of BCVA by ≥ 15 letters relative to baseline	Week 2 and all other visits after Week 2

a. To be considered a treatment failure, ≥ 1 of these 4 criteria had to be present in at least 1 eye.

b. A 2-step increase was represented by a change of Grade 0 to Grade 2+; or Grade 0.5+ to Grade 3+.

Secondary efficacy variables (ranked):

1. Change in AC cell grade in each eye from Baseline to the Final/Early Termination visit.
2. Change in VH grade (NEI/SUN criteria) in each eye from Baseline to the Final/Early Termination visit.
3. Change in logMAR BCVA in each eye from Baseline to the Final/Early Termination visit.
4. Time to OCT evidence of macular oedema based on central retinal thickness (CRT) in at least 1 eye on or after Week 2.
5. Percent change in CRT in each eye from Baseline to the Final/Early Termination visit.
6. Change in VFQ-25 composite score from Baseline to the Final/Early Termination visit.
7. Change in VFQ-25 sub-score distance vision from Baseline to the Final/Early Termination visit.
8. Change in VFQ-25 sub-score near vision from Baseline to the Final/Early Termination visit.
9. Change in VFQ-25 sub-score ocular pain from Baseline to the Final/Early Termination visit.

Other efficacy variables

- AUC of AC cell grades, VH grades, logMAR BCVA and VFQ-25 from Baseline to Final/Early Termination Visit.
- Time to failure (as per primary endpoint) based on active inflammatory lesions, AC cell grade, VH grade and logMAR BCVA.
- Proportion of subjects in quiescence (defined as no active inflammatory lesions and AC cell grade ≤ 0.5 and VH grade ≤ 0.5) at each visit between Baseline through Week 52 and in steroid-free quiescence at each visit between Week 20 through Week 52.
- Proportion of subjects with lack of inflammation (defined as no active inflammatory lesions and AC cell grade = 0 and VH grade = 0) at each visit between Baseline through Week 52 and in steroid-free quiescence (between Week 20 through Week 52)
- PROs including VFQ-25 sub-scores, Hospital Anxiety and Depression Scale, WPAI:SHP,

Subgroup analyses were conducted as in study M10-877.

Safety was assessed by collection and monitoring of AEs, physical examination assessments, vital signs assessments, and laboratory data.

Regarding blood samples for serum concentrations of adalimumab (PK and PK/PD analyses), see section 2.3.2.

Sample size

An overall treatment failure rate of 30 - 35% at 6 months was assumed, with an expected treatment effect corresponding to an absolute difference of 15% between the adalimumab and placebo group. For conservative purposes, it was assumed that failures would begin to occur after 2 months of study duration as the prednisone taper reached lower doses. In addition, a pooled dropout rate of 35% over 12 months was assumed. Using these failure rate assumptions for a log-rank test and a 2-sided significance level of 5%, a total of 84 to 107 events (mean of 96) were needed. The assumptions also included power of 80% and an average accrual rate of 3 subjects per month in the first 28 months and 16 subjects per month thereafter. To achieve 96 treatment failure events, it was anticipated that a sample size of approximately 220 subjects was needed.

Randomisation

See study M10-877.

Blinding (masking)

See study M10-877.

Statistical methods

See study M10-877.

2.4.2.2. Results

Participant flow

Both main studies ended upon reaching the predefined number of events of treatment failures, i.e. 138 events for study M10-877 and approximately the 96 (84-107) for study M10-880. A total of 860 Patients were screened; 437 in study M10-877 and 423 in study M10-880.

Table 9 - Participant flow in Studies M10-877 and M10-880 (main studies)

	Study M10-877 (Active Disease)		Study M10-880 (Inactive Disease)	
	Pbo	**Ada**	**Pbo**	**Ada**
Randomised (=mITT[a])	112	111	114	115
Completed Week 80	4	12	17	30
Completed < Week 80[b]	12	20	17	26
Treatment failure	84	60	61	45
Prematurely discontinued study drug	7	18	16	14
Primary reason for discontinuation[c]				
AE	3	10	7	10
Lack of efficacy	2	1	3	0
Withdrew consent	0	2	3	2
Lost to follow-up	0	4	3	0
Other	3	5		

Pbo = Placebo; Ada = Adalimumab; mITT = modified ITT population

a) Six subjects at 2 sites were excluded from the ITT analyses due to incomplete efficacy source data and general GCP compliance issues at the sites
b) Subjects who had to terminate the study because the planned number of treatment failures was reached.
c) Subjects who prematurely discontinued study drug (placebo/adalimumab) 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.

Recruitment

Study M10-877 was conducted between August 10th, 2010 (first subject visit) and August 29th, 2014 (last subject, last visit). A total of 223 subjects with active non-infectious intermediate uveitis, posterior uveitis, or pan-uveitis were randomised and enrolled at 67 study sites located in Australia, Europe, Israel, Latin America, North America and Japan (sub-study).

Study M10-880 was conducted between August 10th, 2010 (first subject visit) and May 14th , 2015 (last subject, last visit). Subjects were randomised and enrolled at 62 study sites located in Europe, US, Canada, Israel, Australia, Latin America, and Japan (sub-study).

Conduct of the study

- Study M10-877

The protocol was amended 10 times. The first 2 amendments were made before any subject had entered the study (Aug 2010). The last amendment was made Nov 2013, i.e. before last subject exited the study (Aug 2014). Amendments included e.g. changes to the overall study design, changes to efficacy endpoints, selection criteria and changes to ensure subject safety. Further, the sample size was increased since the overall treatment failure rate based on the masked study data was higher (60% at 6 months) than assumed for sample size calculation (50% at 6 months).

Incomplete efficacy source data and general GCP compliance issues were found at 2 sites and 6 subjects were excluded from the ITT analyses. One site (USA) was closed due to compliance issues and 4 placebo-treated and 1 adalimumab-treated subjects were excluded from the primary efficacy analysis. Another site (FR) had inadvertently misplaced/lost several subjects' medical charts. The medical charts were partially reconstructed based on multiple sources but 1 placebo-treated subject was excluded from the primary efficacy analysis.

Major protocol deviations were reported for 46 subjects (24 and 28 in the placebo-and in the adalimumab treatment groups, respectively). The main reasons were due to deviations from inclusion/exclusion criteria (16 deviations), use of prohibited concomitant medication (5 placebo, 9 adalimumab), developed withdrawal criteria but were not withdrawn (11) and received wrong treatment or incorrect dose of prednisone (8). In addition, a number of compliance issues (regarded as minor by the Applicant) related to concomitant treatment were recorded, e.g. decreased immunosuppressive therapy during study (3), received CS to treat an AE (1) together with several CS tapering issues.

- Study M10-880

The protocol was amended 11 times. The first amendment was made before any subject had entered the study (Aug 2010). The last amendment was made Feb 2014, i.e. before last subject exited the study (May 2015). Amendments were made for similar reasons as in Study M10-877 and also in this study, the sample size was increased to maintain a statistical power since the failure rate based on the masked study data was higher (35% at 6 months) than originally assumed (30% at 6 months).

Incomplete efficacy source data and general GCP compliance issues were identified at the same sites as for study M10-877) which led to the exclusion of 3 placebo-treated subjects from the ITT analyses.

Major protocol deviations were reported for 54 subjects (23 and 31 in the placebo-and in the adalimumab treatment groups, respectively). The main reasons were due to use of prohibited concomitant medication (11 placebo, 19 adalimumab), deviations from inclusion/exclusion criteria (18) and received wrong treatment or incorrect dose of adalimumab/placebo (7). In addition, a number of compliance issues (regarded as minor by the Applicant) related to concomitant treatment were recorded, e.g. decreased immunosuppressive therapy during study (5), received CS to treat an AE (5) together with several CS tapering issues.

Baseline data

Close to half of the subjects were between 30 and 49 years of age and somewhat more female than male patients were included in the studies. The majority of subjects were white (approximately 80%). Main baseline demographics and disease characteristics are summarised in the below tables. There were no statistically significant differences between treatment arms.

In study M10-877, a total of 96 subjects were from Europe (Western and Eastern). The number of European subjects in study M10-880 was 119.

The mean duration of uveitis was approximately 4 years. A total of 37 % of subjects had idiopathic uveitis and the majority of subjects (91%) had bilateral disease. The majority of the diagnoses listed as 'other' represent one of the categories of idiopathic, Birdshot choroidopathy, multifocal choroiditis and panuveitis, Vogt-Koyanagi-Harada, sarcoid and Behçet's disease, but the investigator chose to report these as 'other'.

Table 10 - Key Baseline Demographics (ITT, Main Study)

	Study M10-877 (Active uveitis)		**Study M10-880 (Inactive uveitis)**	
	Placebo	**Adalimumab**	**Placebo**	**Adalimumab**
	(n = 107)	(n = 110)	(n = 111)	(n = 115)
Age (yr)				
Mean± SD	42.6 ± 14.2	42.7 ± 15.6	42.2 ± 14.0	42.8 ± 12.9
Range	18.0 – 79.0	18.0 – 81.0	20.0 – 79.0	18.0 – 75.0
Sex, n (%)				
Female	65 (60.7)	59 (53.6)	72 (64.9)	66 (57.4)
Male	42 (39.3)	51 (46.4)	39 (35.1)	49 (42.6)
Race, n (%)				
White	86 (80.4)	88 (80.0)	93 (83.8)	96 (83.5)
Black	12 (11.2)	11 (10.0)	93 (83.8)	96 (83.5)
Asian	2 (1.9)	4 (3.6)	3 (2.7)	3 (2.6)
Other	7 (6.5)	7 (6.4)	7 (6.3)	10 (8.7)

Pbo = Placebo; Ada = Adalimumab

Table 11 - Main Diagnostic and Disease Characteristics (ITT, Main Study)

	Study M10-877 (Active uveitis)		**Study M10-880 (Inactive uveitis)**	
	Placebo	**Ada**	**Placebo**	**Ada**
	(n = 107)	(n = 110)	(n=111)	(n=115)
Duration of uveitis (months)				
Mean ± SD	51 ± 72	40 ± 51	63 ± 68	60 ± 64
Median (Range)	24 (1–555)	19 (2–306)	39 (4-394)	35 (2–381)
Time since last flare (months ± SD)	10 ± 15	10 ± 17	5 ± 4	6 ± 4
Duration of current flare (days ±SD)	72 ± 84	69 ± 94	NA	NA
Prednisone dose at last flare (mg)				
Mean ± SD	10 ± 15	12 ± 18	5 ± 4	6 ± 4
Median (range)	0 (0 – 60)	5 (0 – 80)	5 (0 – 60)	5 (0 – 80)
Type of uveitis (n [%])				

	Study M10-877 (Active uveitis)		Study M10-880 (Inactive uveitis)	
	Placebo	Ada	Placebo	Ada
	(n = 107)	(n = 110)	(n=111)	(n=115)
Intermediate	23 (21.5)	24 (21.8)	30 (27.0)	17 (14.8)
Posterior	37 (34.6)	36 (32.7)	34 (30.6)	39 (33.9)
Panuveitis	47 (43.9)	50 (45.5)	46 (41.4)	57 (49.6)
Intermediate/posterior	0	0	1 (0.9)	2 (1.7)
Diagnosis				
Idiopathic	45 (42.1)	36 (32.7)	40 (36.0)	29 (25.2)
Birdshot choroidopathy	20 (18.7)	24 (21.8)	15 (13.5)	15 (13.0)
Multifocal choroiditis and panuveitis	3 (2.8)	8 (7.3)	2 (1.8)	5 (4.3)
Vogt Koyanagi Harada	14 (13.1)	11 (10.0)	25 (22.5)	26 (22.6)
Sarcoidosis	8 (7.5)	10 (9.1)	14 (12.6)	18 (15.7)
Behcet's	4 (3.7)	12 (10.9)	6 (5.4)	10 (8.7)
Other	13 (12.1)	9 (8.2)	9 (8.1)	12 (10.4)
No of flares the past 12 months (n [%])				
1	19 (17.8)	18 (16.4)	46 (41.4)	48 (41.7)
2	46 (43.0)	54 (49.1)	40 (36.0)	43 (37.4)
≥ 3	42 (39.3)	38 (34.5)	25 (22.5)	24 (20.9)
Active chorioretinal lesions [a] (n [%])				
Left eye	44 (41.1)	44 (40.0)	0	0
Right eye	40 (37.4)	46 (41.8)	0	0
Active inflammatory lesions [a] (n [%])				
Left eye	40 (37.4)	45 (40.9)	0	0
Right eye	35 (32.7)	39 (35.5)	0	0
AC cell grade (mean ± SD)				
Left eye	0.61 ± 0.76	0.65 ± 0.88	0.10 ± 0.20	0.10 ± 0.20
Right eye	0.66 ± 0.88	0.65 ± 0.84	0.10 ± 0.20	0.11 ± 0.21
VH grade ± SD				
Left eye	0.95 ± 0.77	1.08 ± 0.92	0.14 ± 0.23	0.16 ± 0.24
Right eye	1.05 ± 0.86	1.00 ± 0.83	0.15 ± 0.23	0.14 ± 0.22
VH grade (n [%])				
BCVA (LogMAR ± SD)				
Left eye	0.23 ± 0.29	0.24 ± 0.36	0.16 ± 0.29	0.14 ± 0.26
Right eye	0.24 ± 0.30	0.22 ± 0.28	0.15 ± 0.27	0.12 ± 0.22
Evidence of OCT macular oedema (n [%])				
Left eye	40 (40.8)	32 (31.4)	8 (7.5)	14 (12.4)
Right eye	40 (39.6)	37 (35.2)	7 (6.5)	16 (14.3)
Missing (left plus right eye) [b]	15	13	7	3

Pbo = Placebo; Ada = Adalimumab
[a] Active, inflammatory, chorioretinal, and/or inflammatory retinal vascular lesions
[b] In Study M10-880, in subjects without macular hole and/or retinal detachment only

Previous and concomitant medication

Previous medication, i.e. any medication taken prior to the first dose of study drug and not necessarily discontinued before first study drug dose, included prednisone, prednisolone, mehtyleprednisolone, triamcinolone, MTX, ciclosporin, MMF, omeprazole, dexamethasone, betamethasone, folic acid, lekovit CA and azathioprine. All subjects used at least 1 previous medication.

Prior uveitis-related medication was defined as any uveitis-related medication discontinued prior to the first dose of study drug as per protocol. Across both studies, over a third of all subjects (37.6% adalimumab and 36.4% placebo) used prior systemic IMM for the treatment of uveitis. Nearly all subjects used at least 1 prior CS for the treatment of uveitis.

Concomitant medication was any medication, excluding the initial topical CS taper, that started prior to the first dose of study drug, and continued to be taken after the first dose of study drug, or any

medication that started after the first dose of the study drug, but not later than 14 days after the last dose of the study drug. The most frequently reported concomitant medication (≥ 20% subjects) in either treatment group was prednisolone and prednisone (see details below including Table 13 for CS use by generic name). Over a third of all subjects reported using at least 1 concomitant systemic IMM at baseline including MMF (or equivalent), MTX, ciclosporin and azathioprine (see details below including Table 14).

- Use of CS and taper

With regards to the steroid taper, in both studies, CS doses were well balanced between treatment arms in both studies over the tapering periods. While in general, treatment compliance to the oral prednisone tapering schedule was greater than 97% for both treatment groups in both studies, the duration of the initial oral prednisone treatment was longer in the adalimumab treatment groups of both studies compared to placebo (see Table 13). The total steroid doses given during the studies were however similar between treatment groups in both studies.

In both studies, subjects received a higher number of doses of topical CS in the adalimumab groups. During taper, the duration of exposure was higher in the adalimumab group compared to placebo in study M10-877. The mean duration of exposure to topical CS was also higher in study M10-880, whereas the median duration of exposure was longer in the placebo group compared to adalimumab. Treatment compliance (total dose received divided with the total dose planned) was >110 % in both groups in both studies, i.e. subjects either did not complete the taper in time or took a higher dose than assigned as per the taper schedule.

Table 12 - Doses of oral and topical CS and Total Exposure and Duration of Treatment (Safety Set, Main Study)

	Study M10-877 (Active uveitis)		Study M10-880 (Inactive uveitis)	
	Placebo	**Ada**	**Placebo**	**Ada**
	(n = 112)	(n = 111)	(n=114)	(n=115)
Oral CS				
Dose (mg/day)				
Week 0 Mean (SD)	58.1 (5.1)	58.2 (3.4)	16.2 (7.3)	15.3 (7.4)
Median (range)	60.0 (17-60)	60 (51-60)	13.9 (0 – 35)	12.5 (0 – 35)
Week 15 Mean (SD)	0.05 (0.1)	0.06 (0.2)	-	-
Median (range)	0 (0 – 0.4)	0 (0 – 2.1)	-	-
Week 19 Mean (SD)	-	-	0.02 (0.12)	0 (0.08)
Median (range)	-	-	0 (0 – 1.0)	0 (0 – 0.1)
Duration(days) of treatment				
Mean (SD)	77 (30.0)	84 (30.4)	86 (30.2)	93 (24.2)
Median (range)	86 (7-108)	105 (7-119)	91 (3 - 147)	91 (13 –134)
Total exposure (mg)[a]				
Mean (SD)	2032 (335)	2048 (357)	621 (284)	630 (299)
Median (range)	2180 (420–2054)	2229 (420-2281)	528 (45-1540)	483 (228-1575)
Topical CS eye drops				
	(n=37)	(n=30)	(n=24)	(n=20)
Total number of doses received[a]				
Mean (SD)	84 (94.6)	94 (113.1)	46 (33.3)	75 (114.6)
Median (range)	50 (7 – 505)	67 (7 – 513)	42 (5 – 147)	33 (7 – 506)
Duration(days) of treatment				
Mean (SD)	27 (17.4)	31 (23.6)	21 (9.6)	28 (27.7)
Median (range)	27 (7 – 92)	28 (7 – 120)	21 (5 – 42)	18 (7 – 113)

[a] The dose of oral prednisone per subject was analysed from date of first study drug to last date or treatment failure date, whichever occurred first.

During study M10-877, prohibited prednisolone was taken by 15 (14.0%) subjects in the placebo group and 20 (18.2%) subjects in the adalimumab group. Six of these were reported as important protocol deviations. Prohibited prednisone (all systemic) was taken by 25 (23.4%) subjects in the placebo group and 15 (13.6%) subjects in the adalimumab group. Two of these were reported as important protocol deviations.

During Study M10-880, prohibited prednisone was taken by 20 subjects (18.0%) in the placebo group and 17 subjects (14.8%) in the adalimumab group. Eight of these were reported as important protocol deviations. Prohibited prednisolone was taken by 15 subjects (13.5%) in the placebo group and 14 subjects (12.2%) in the adalimumab group. Five of these were reported as important protocol deviations.

The overall CS use during the studies is summarised in the below table.

Table 13 - Concomitant CS Use by Generic Name (ITT, Main Studies)

	Study M10-877 (Active uveitis)		Study M10-880 (Inactive uveitis)	
	Placebo (n = 107)	Ada (n = 110)	Placebo (n=111)	Ada (n=115)
	n (%)			
Beclomethasone	0	0	2 (1.8)	2 (1.7)
Betamethasone	1 (0.9)	1 (0.9)	0	3 (2.6)
Clobetasol	1 (0.9)	1 (0.9)	2 (1.8)	0
Cortisone	0	0	7 (6.3)	4 (3.5)
Dexamethasone[a]	4 (3.7)	2 (1.8)	6 (5.4)	6 (5.2)
Difluprednate	4 (3.7)	2 (1.8)	2 (1.8)	1 (0.9)
Fluorometholone	0	0	1 (0.9)	0
Hydrocortisone	2 (1.9)	3 (2.7)	3 (2.7)	2 (1.7)
Loteprednol	0	1 (0.9)	1 (0.9)	0
Methylprednisolone	3 (2.8)	6 (5.5)	7 (6.3)	9 (7.8)
Prednisolone	15 (14.0)	20 (18.2)	15 (13.5)	14 (12.2)
Prednisone	25 (23.4)	15 (13.6)	20 (18.0)	17 (14.8)
Triamcinolone	3 (2.8)	1 (0.9)	3 (2.7)	0
CS unspecified	0	1 (0.9)	1 (0.9)	0
CS and antiinfectives	0	0	1 (0.9)	0
CS unspecified systemic use	1 (0.9)	0	0	1 (0.9)

[a] incl. combinations with antibiotics
CS clearly for inhalation or dermal use not included in table.

- Use of concomitant IMM

Ciclosporin, MMF, MTX and azathioprine was also frequently used with the majority of subjects (>90 %, both studies, all treatment groups) reported use of at least one concomitant medication (excluding the initial topical CS taper).

The concomitant systemic IMM treatment in addition to the baseline CS used at Baseline is summarised in the below table. No subject in any study used tacrolimus.

Table 14 - Concomitant Systemic IMM at Baseline (ITT, main studies)

	Study M10-877 (Active uveitis)		Study M10-880 (Inactive uveitis)	
	Placebo	Ada	Placebo	Ada
	(n = 107)	(n = 110)	(n=111)	(n=115)
Any concomitant IMM (systemic) (n [%])[a]	33 (30.8)	34 (30.9)	53 (47.7)	54 (47.0)
Mycophenolate mofetil or equivalent	15 (14.0)	11 (10.0)	17 (15.3)	17 (14.8)
Ciclosporin	3 (2.8)	11 (10.0)	11 (9.9)	15 (13.0)
MTX	12 (11.2)	9 (8.2)	14 (12.6)	19 (16.5)
Azathioprine	4 (3.7)	4 (3.6)	11 (9.9)	3 (2.6)

Ada = Adalimumab
[a] In Study M10-877, subjects should have active disease despite treatment with ≥10 - ≤ 60 mg/day of prednisone (or equivalent) and all subjects received initial treatment with 60 mg/day of prednisone. In study M10-880, subjects were on 10-35 mg/day of prednisone (or equivalent).

Numbers analysed

In study M10-877, 6 subjects at 2 sites were excluded from the ITT analyses due to incomplete efficacy source data and general GCP compliance issues at the sites; therefore, the ITT set is comprised of 217 subjects. No per protocol set was defined.

For study M10-880, efficacy analyses are provided for the ITT set, which included all randomized subjects recruited outside Japan, and, excluded 3 subjects from 2 sites for which efficacy source data was incomplete and there were general GCP compliance issues.

Table 15 - Studies M10-877 and M10-880 (main studies)

	Study M10-877 (Active Disease)		Study M10-880 (Inactive Disease)	
	Pbo	**Ada**	**Pbo**	**Ada**
ITT	107	110	111	115
mITT[a]	112	111	114	115
Excluded from analysis[a]	5	1	3	0
Safety set*	112	111	114	115

Pbo = Placebo; Ada = Adalimumab

[a] Six subjects from 2 sites (study M10-877) and 3 subjects from 2 sites (study M10-880) were excluded from the ITT analyses due to incomplete efficacy source data and general GCP compliance issues at the sites.

Outcomes and estimation

Extent of exposure

The extent of exposure is summarised below. Further details are given in the clinical safety section 2.5.

Table 16 - Extent of exposure to study treatment (safety set)

	Study M10-877 (Active Disease)		Study M10-880 (Inactive Disease)	
	Placebo	**Ada**	**Placebo**	**Ada**
	(n = 112)	(n = 111)	(n=114)	(n=115)
Total number of doses				
Mean ± SD	11.7 ± 9.9	15.9 ± 12.5	17.6 ± 13.0	22.7 ± 14.1
Median (Range)	8 (2 – 42)	11 (2 – 43)	12 (2 – 42)	19 (2 – 42)
Duration of treatment (days)				
Mean ± SD	144 ± 139	205 ± 176	227.4 ± 184.1	300.2 ± 198.9
Median (Range)	91 (14 – 567)	133 (14 – 570)	155 (14 – 591)	245 (14 – 576)

Pbo = Placebo; Ada = Adalimumab

- **Study M10-877 (VISUAL I)**

Primary efficacy endpoint: Time to treatment failure

The analysis of the primary efficacy endpoint, time to treatment failure at or after week 6 (composite of inflammatory, chorioretinal and/or inflammatory retinal vascular lesions, AC cell grade, VH grade and logMAR BCVA) showed that the risk of treatment failure for subjects in the adalimumab group was reduced by 50% compared to subjects in the placebo group. The median times to treatment failure were 5.6 and 3 months in the adalimumab and placebo groups, respectively.

Sensitivity analyses by IMM use and with the mITT population supported the outcome, see Table and Figure below.

Additional sensitivity analyses censoring subjects who prematurely discontinued due to an adverse event (hazard ratio [HR] 0.50, p<0.001), with major protocol deviations regarding deviations/prohibited use of CS (HR 0.47, p<0.001) and when considering the adverse event of uveitis (HR=0.50, p<0.001) as treatment failures were in line with the primary analysis in the ITT population.

Table 17 - Time to Treatment Failure at or after Week 6 in Study M10-877 (Main Study M10-877 and integrated Japanese Data).

Analysis Treatment	N	Failure N (%)	Median Time to Failure (Months)	HR	95%CI for HR[a]	*P* value[b]
Primary analysis (ITT)						
Placebo	107	84 (78.5)	3.0			
Adalimumab	110	60 (54.5)	5.6	0.50[c]	0.36, 0.70	< 0.001
Adjusted for baseline IMM usage (ITT)						
Placebo	107	84 (78.5)	3.0			
Adalimumab	110	60 (54.5)	5.6	0.50[a]	0.36, 0.70	< 0.001
mITT						
Placebo	112	87 (77.7)	3.0			
Adalimumab	111	61 (55.0)	5.6	0.53[c]	0.38, 0.74	< 0.001

a. HR of adalimumab versus placebo from proportional hazards regression with treatment and baseline IMM usage as factors.
b. 2-sided P value from log rank test.
c. HR of adalimumab versus placebo from proportional hazards regression with treatment as factor.

Note: Treatment failure at or after Week 6 was counted as event. Drop outs due to reasons other than treatment failure were censored at the time of dropping out.

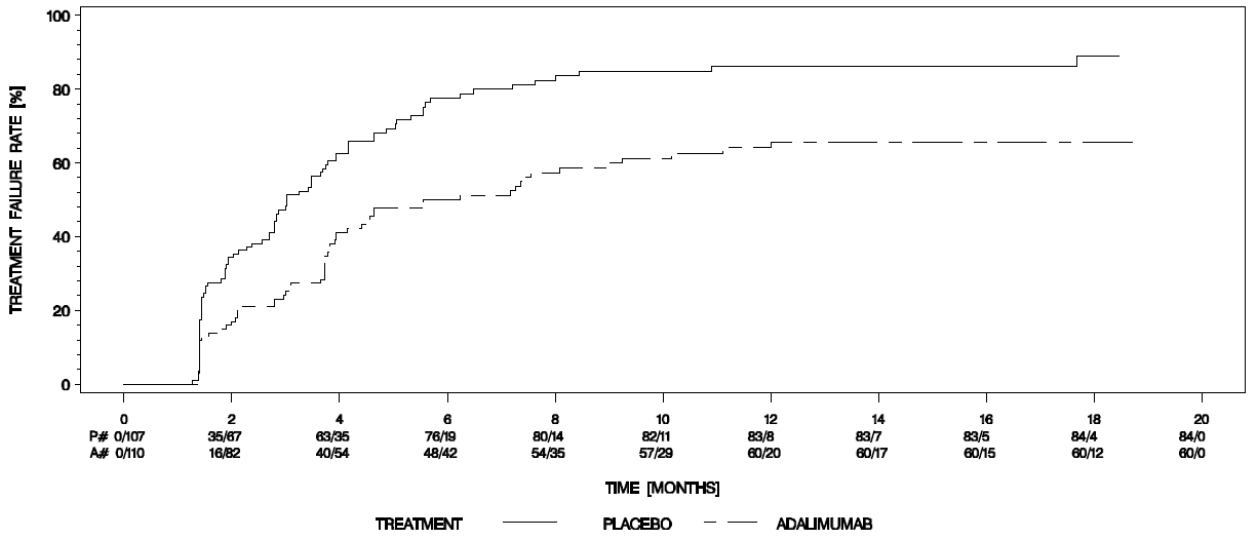


Figure 7 - Kaplan-Meier Curves for the Time to Treatment Failure On or After Week 6 (ITT; Main Study M10-877)

P# - placebo (number of events/number at risk), A# - adalimumab (number of events/number at risk)

Analysis of the time to treatment failure based on the components of the primary endpoint (each analysed separately, with logMAR BCVA analysed post hoc) is summarised in the below table. All

components of the composite endpoint contributed to the treatment failures with the largest difference between active and placebo treatment for VH grade.

Table 18 – Reasons for Treatment Failure by Components of the Primary Endpoint (ITT; Main Study M10-877)

Endpoint Treatment	N	Failure N(%)	Median time to failure (months)	HR[a]	95% CI for HR[b]	P value[c]
Active Inflammatory Lesions						
All ITT subjects (N = 217)						
Placebo	107	29 (27.1)	8			
Adalimumab	110	17 (15.5)	NE[d]	0.38	0.21, 0.69	0.001
Subjects with active inflammatory lesions at baseline (N = 143)						
Placebo	63	25 (39.7)	5.3			
Adalimumab	80	17 (21.3)	NE[d]	0.36	0.19, 0.68	< 0.001
Anterior Chamber Cell Grade						
All ITT subjects (N = 217)						
Placebo	107	34 (31.8)	NE[d]			
Adalimumab	110	24 (21.8)	NE[d]	0.51	0.30, 0.86	0.010
Subjects with AC cell grade ≥ 1 at baseline (N = 86)						
Placebo	42	20 (47.6)	4.2			
Adalimumab	44	19 (43.2)	7.4	0.50	0.26, 0.96	0.032
Vitreous Haze Grade						
All ITT subjects (N = 217)						
Placebo	107	39 (36.4)	6.2			
Adalimumab	110	16 (14.5)	NE[d]	0.32	0.18, 0.58	< 0.001
Subjects with vitreous haze grade ≥ 1 at baseline (N = 149)						
Placebo	72	33 (45.8)	5.7			
Adalimumab	77	15 (19.5)	NE[d]	0.36	0.19, 0.66	< 0.001
Subjects with vitreous haze grade ≥ 2 at baseline (N = 107)						
Placebo	52	26 (50.0)	5.6			
Adalimumab	55	11 (20.0)	NE[d]	0.32	0.15, 0.64	< 0.001
logMAR Best Corrected Visual Acuity[e]						
All ITT subjects (N = 217)						
Placebo	107	27 (25.2)	10.9			
Adalimumab	110	23 (20.9)	NE[d]	0.56	0.32, 0.98	0.040

a. HR of adalimumab versus placebo from proportional hazards regression with treatment as factor.
b. 95% CI for HR.
c. 2-sided P value from log rank test.
d. Not estimable = Less than half of at-risk subjects had an event.
e. *Post hoc* analysis

Secondary efficacy endpoints

Statistically significant differences were observed for the majority of the ranked secondary endpoints. For the endpoints Time to OCT evidence of macular oedema (4) and Change in VFQ-25 subscore distance vision (7), adalimumab was numerically in favour over placebo, but the difference did not reach statistical significance. Sensitivity analysis using the mITT set and analysing better/worse eye separately showed similar results as the primary analysis (ITT).

The outcomes of the 9 ranked efficacy parameters are summarised in the below table.

Table 19 - Summary of Ranked Secondary Efficacy Variables (ITT, Main Study M10-877, LOCF)

Ranked Secondary Variable	Placebo N = 107		Adalimumab N = 110		
	n[a]	Mean	n[a]	Mean	*P* value
1. Change in AC cell grade					

Ranked Secondary Variable	Placebo N = 107		Adalimumab N = 110		
	n[a]	Mean	n[a]	Mean	*P* value
Left eye	102	0.59	101	0.35	
Right eye	102	0.69	101	0.36	
Mean difference of adalimumab minus placebo (95% CI)	–0.29 (–0.51, –0.07)				0.011[b]
2. Change in VH grade					
Left eye	103	0.33	101	0.11	
Right eye	103	0.45	101	0.13	
Mean difference of adalimumab minus placebo (95% CI)	–0.27 (–0.43, –0.11)				<0.001[b]
3. Change in logMAR BCVA					
Left eye	103	0.12	101	0.07	
Right eye	103	0.13	101	0.04	
Mean difference of adalimumab minus placebo (95% CI)	–0.07 (–0.11, –0.02)				0.003[b]
4. Time to OCT evidence of macular oedema (months) in at least 1 eye [c]	45	6.2[d]	55	11.1[d]	
HR (95% CI)	0.70 (0.39, 1.26)				0.231[e]
5. Percent change in CRT					
Left eye	100	20.2	100	9.6	
Right eye	102	22.0	101	8.2	
Mean difference of adalimumab minus placebo (95% CI)	–11.4 (–20.9, –1.8)				0.020[f]
6. Change in VFQ-25 total score	102	–5.50	101	–1.30	
Mean difference of adalimumab minus placebo (95% CI)	4.20 (1.02, 7.38)				0.010[g]
7. Change in VFQ-25 subscore distance vision	102	–5.64	101	–3.77	
Mean difference of adalimumab minus placebo (95% CI)	1.86 (–2.03, 5.75)				0.346[g]
8. Change in VFQ-25 subscore near vision	102	–8.09	101	–2.97	
Mean difference of adalimumab minus placebo (95% CI)	5.12 (0.34, 9.90)				0.036[g]
9. Change in VFQ-25 subscore ocular pain	102	–12.62	101	–2.60	
Mean difference of adalimumab minus placebo (95% CI)	10.02 (4.86, 15.19)				<0.001[g]

[a] For each endpoint, n = number of subjects with non-missing value.
[b] From ANOVA of change from best state achieved prior to Week 6 to Final/Early termination visit with treatment as factor adjusted for clustered observations.
[c] Only in subjects without macular oedema at baseline
[d] Median time to OCT evidence of macular oedema.
[e] 2-sided P value from log rank test.
[f] From ANOVA of change from best state achieved prior to Week 6 to Final/Early termination visit with treatment and OCT machine as factors adjusted for clustered observations.
[g] From ANOVA of change from best state achieved prior to Week 6 to Final/Early termination visit with treatment as factor.
Note: Endpoints 1-3 and 5-9, reflect the change from the best state achieved prior to Week 6 to the Final/Early termination visit in each eye (where applicable). Endpoint 4 reflects the time to event (OCT evidence of macular oedema) on or after week 6 in subjects without macular oedema at baseline.

Other efficacy endpoints

Selected endpoints are summarised below.

Mean AC cell grade, VH grade and logMAR BCVA over time were lower for the adalimumab group compared to the placebo group. The differences of the mean changes from best state achieved to Final/Early Termination visit were statistically significant (see also ranked secondary endpoints). When analysing the mean values (AC cell grade, VH grade and logMAR BCVA) as the areas under the curve (AUCs), at the final visit, values in the adalimumab group were higher compared to the placebo group and the differences between the groups were statistically significant (p=0.008 for AC cell grade, p=0.004 for VH grade, and p=0.008 for logMAR BCVA).

The proportions of subjects in quiescence, i.e. no active inflammatory lesions and AC cell grade ≤ 0.5 and VH grade ≤ 0.5, with and without steroids at each visit between Baseline through Week 52 and between Week 20 through Week 52, respectively were higher in the adalimumab group (see Table 18). At Week 1, 38% and 30% of subjects had controlled disease in the placebo and adalimumab treatment

groups, respectively. At Week 4, the corresponding figures were 59% and 63%. Statistical significance while on CS was achieved from Week 8.

Similar to quiescence, the results for the proportion of subjects with lack of inflammation/steroid-free lack of inflammation, i.e. no active inflammatory lesions and AC cell grade = 0 and VH grade = 0, were overall numerically in favour of adalimumab compared to placebo. Statistical significance was reached at some of the later time points (weeks 36 and 52).

Sensitivity analyses taking into account major protocol deviations/prohibited CS use, the outcomes on proportions of patients in steroid-free quiescence and steroid-free lack of inflammation were similar to that obtained in the primary analysis.

Table 20 - Quiescence and Lack of inflammation (Non-responder imputation, ITT, Main Study M10-877)

Visit	Placebo N = 95[a]	Adalimumab N = 90[a]	*P* value[b]
Number (%) of Subjects in Quiescence			
Week 4*	63 (58.9)	69 (62.7)	0.561
Week 6	59 (62.1)	64 (71.1)	0.195
Week 8	45 (47.4)	59 (65.6)	0.013
Week 16	22 (23.2)	36 (40.0)	0.014
Week 36	7 (7.4)	21 (23.3)	0.002
Week 52	5 (5.3)	13 (14.4)	0.035
Number (%) of Subjects in Steroid-Free Quiescence			
Week 6	--	--	--
Week 16	18 (18.9)	28 (31.1)	0.056
Week 36	6 (6.3)	18 (20.0)	0.006
Week 52	4 (4.2)	12 (13.3)	0.027
Number (%) of Subjects with Steroid-Free Lack of inflammation			
Week 16	10 (10.5)	13 (14.4)	0.420
Week 36	4 (4.2)	13 (14.4)	0.016
Week 52	2 (2.1)	9 (10.0)	0.023

** Post hoc* based on 107 and 100 subjects in placebo and adalimumab groups, respectively.
[a] Subjects who terminated the study because the planned number of treatment failures was reached were excluded.
[b] value to compare adalimumab with placebo was based on chi-square test.
[c] Non-responder imputation

Categorical changes in BCVA from best state achieved prior to Week 6 at selected time points are summarised in the below table.

Table 21 - Summary of Categorical Changes in BCVA from Best State Achieved prior to Week 6 to Selected Visits (ITT, LOCF, Main Study M10-877)

	Placebo (N=103) n (%)	Adalimumab (N=101) n (%)	Placebo (N=103) n (%)	Adalimumab (N=101) n (%)
WEEK 6	**Left eye**		**Right eye**	
Gain ≥ 5 letters	1 (1.0)	2 (2.0)	2 (1.9)	6 (5.9)
Stable [a]	87 (84.5)	83 (82.2)	84 (81.6)	83 (82.2)
Loss of 5-9 letters	9 (8.7)	13 (12.9)	11 (10.7)	9 (8.9)
Loss of 10-14 letters	3 (2.9)	2 (2.0)	3 (2.9)	1 (1.0)
Loss of ≥ 15 letters	3 (2.9)	1 (1.0)	3 (2.9)	2 (2.0)
WEEK 12	**Left eye**		**Right eye**	
Gain ≥ 5 letters	1 (1.0)	6 (5.9)	4 (3.9)	10 (9.9)
Stable [a]	66 (64.1)	74 (73.3)	74 (71.8)	75 (74.3)
Loss of 5-9 letters	24 (23.3)	10 (9.9)	14 (13.6)	10 (9.9)
Loss of 10-14 letters	3 (2.9)	5 (5.0)	4 (3.9)	3 (3.0)
Loss of ≥ 15 letters	9 (8.7)	6 (5.9)	7 (6.8)	3 (3.0)

WEEK 16 [b]				
Gain ≥ 5 letters	1 (1.0)	5 (5.0)	3 (2.9)	8 (7.9)
Stable [a]	63 (61.2)	72 (71.3)	69 (67.0)	72 (71.3)
Loss of 5-9 letters	25 (24.3)	11 (10.9)	15 (14.6)	12 (11.9)
Loss of 10-14 letters	4 (3.9)	2 (2.0)	5 (4.9)	3 (3.0)
Loss of ≥ 15 letters	10 (9.7)	11 (10.9)	11 (10.7)	6 (5.9)
WEEK 24	**Left eye**		**Right eye**	
Gain ≥ 5 letters	1 (1.0)	4 (4.0)	2 (1.9)	12 (11.9)
Stable [a]	59 (57.3)	70 (69.3)	66 (64.1)	62 (61.4)
Loss of 5-9 letters	25 (24.3)	11 (10.9)	13 (12.6)	17 (16.8)
Loss of 10-14 letters	6 (5.8)	4 (4.0)	9 (8.7)	3 (3.0)
Loss of ≥ 15 letters	12 (11.7)	12 (11.9)	13 (12.6)	7 (6.9)
WEEK 48	**Left eye**		**Right eye**	
Gain ≥ 5 letters	0	7 (6.9)	3 (2.9)	11 (10.9)
Stable [a]	62 (60.2)	66 (65.3)	64 (62.1)	65 (64.4)
Loss of 5-9 letters	22 (21.4)	8 (7.9)	12 (11.7)	14 (13.9)
Loss of 10-14 letters	6 (5.8)	4 (4.0)	10 (9.7)	3 (3.0)
Loss of ≥ 15 letters	13 (12.6)	16 (15.8)	14 (13.6)	8 (7.9)
WEEK 80/final value	**Left eye**		**Right eye**	
Gain ≥ 5 letters	0	7 (6.9)	3 (2.9)	11 (10.9)
Stable [a]	60 (58.3)	66 (65.3)	65 (63.1)	65 (64.4)
Loss of 5-9 letters	23 (22.3)	8 (7.9)	11 (10.7)	14 (13.9)
Loss of 10-14 letters	7 (6.8)	4 (4.0)	9 (8.7)	3 (3.0)
Loss of ≥ 15 letters	13 (12.6)	16 (15.8)	15 (14.6)	8 (7.9)

[a] Within ±4 letters

[b] According to the mandatory taper schedule, subjects were to discontinue prednisone no later than Week 15

NOTE: Subjects who do not have values at/after week 6 (e.g. due to premature discontinuation prior to week 6) were excluded. Source TABLE 14.2__2.1.4.3.M

Beginning at Week 4 and through to Week 80/final visit, mean logMAR BCVA was lower and visual acuity was higher in both eyes in the adalimumab treatment group (Week 4: L and R = 0.16) compared to the placebo treatment group (Week 4: L = 0.17 and R = 0.18). The change in BCVA over time is illustrated in Figure 8.

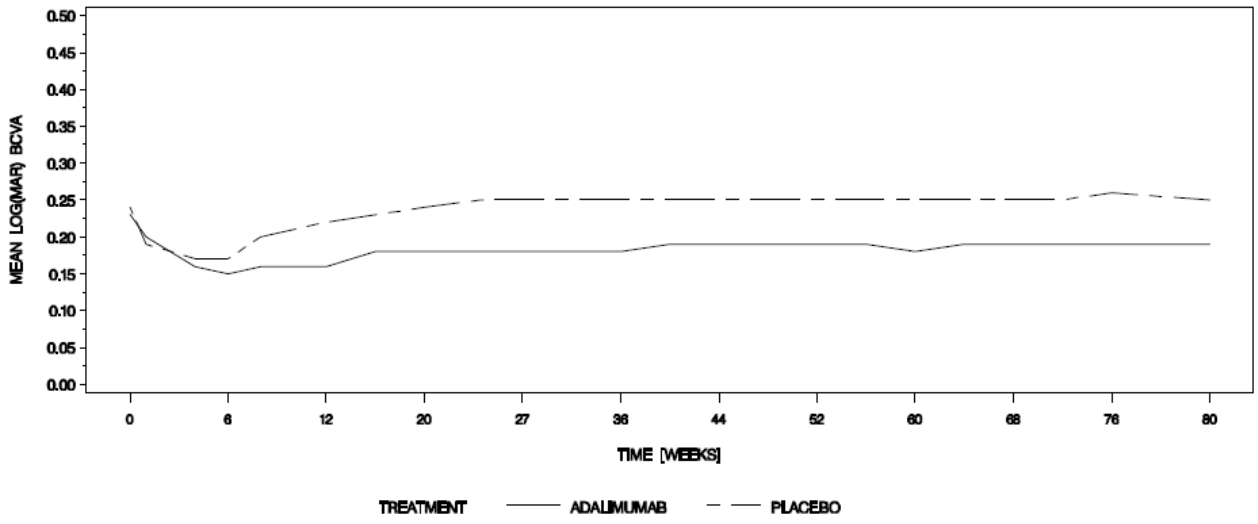


Figure 8 – Mean BCVA over Time (ITT, LOCF, Main Study M10-877)

For the majority of PROs, adalimumab was favoured over placebo:

- In all VFQ-25 subscales, the scores decreased in both treatment groups. However, smaller reductions from best state achieved prior to Week 6 to Final/Early Termination visit were observed in the adalimumab group compared to the placebo group, with the exception of colour vision. Mean reductions that were statistically significantly different between groups in favour of adalimumab included general vision, ocular pain, near vision, mental health, and total score (p values: 0.011, < 0.001, 0.036, 0.033, and 0.010, respectively).
- Similar reductions were observed in the adalimumab and placebo groups for HADS with no statistically significant differences between the groups.
- WPAI-SHP: At Final/Early Termination visit, the percentage of work time missed was similar between the adalimumab and placebo group; however, there was a larger reduction in work time missed in the adalimumab group compared to the placebo group (mean difference: 10.6 %, CIs: -18.75, –2.47; p= 0.011). For percent impairment while working, overall work impairment, and activity impairment, reductions were greater for the adalimumab group compared to placebo without any statistically significant differences.
- At Final/Early Termination visit, values for EQ-5D predicted value and EQ VAS were higher in the adalimumab group compared to the placebo group. A statistically significant difference between groups in favour of adalimumab was observed only for the EQ-5D predicted value.

Post hoc analyses

In subjects with macular oedema and without macular hole/retinal detachment, a *post hoc* analysis was applied to time to OCT evidence of macular oedema and mean percent change in central retinal thickness in each eye from best state achieved prior to Week 6 to the Final/Early Termination visit using different cut-offs for centre point thickness depending on the OCT machine type. Statistically significant differences in favour of adalimumab versus placebo were observed. The risk of macular oedema for subjects in the adalimumab group was reduced by 67% compared to placebo (HR: 0.33, CIs: 0.12, 0.90; p= 0.023, main study data). Less increase in central retinal thickening was observed in subjects who received adalimumab compared to placebo (mean difference: 12 %, CIs: –21.5, –2.5; p= 0.014).

The proportion of subjects in disease control (defined as no new active inflammatory lesions, AC cell grade ≤ 0.5, VH grade ≤ 0.5, and no worsening of logMAR BCVA by ≥ 15 letters to best state achieved) was numerically higher for the placebo group at Week 1 (38%) compared to adalimumab (30%), and numerically higher for the adalimumab group at Week 4 (63%) compared to placebo (59%). There were no statistically significant differences between treatment groups at Week 1 or Week 4.

- **Study M10-880 (VISUAL II)**

Primary efficacy endpoint: Time to treatment failure

The analysis of the primary efficacy endpoint (time to treatment failure at or after Week 2) showed that the risk of treatment failure for subjects in the adalimumab group was reduced by 43% compared to subjects in the placebo group. The median time to treatment failure was 8.3 months for placebo subjects and not estimable (> 18 months) for adalimumab subjects because fewer than half of the subjects experienced treatment failure at the conclusion of the study.

Sensitivity analysis of time to treatment failure using the mITT set showed similar results to the primary analysis. Additional sensitivity analyses censoring subjects with major protocol deviations regarding deviations/prohibited use of CS (HR 0.55, p=0.013) and when considering the adverse

events of uveitis (HR=0.56, p=0.003) as treatment failures were in line with the primary analysis in the ITT population.

Table 22 - Time to Treatment Failure at or after Week 2 (Main Study M10-880)

Analysis Treatment	N	Failure N (%)	Median Time to Failure (Months)	HR	95%CI for HR	*P* value
Primary analysis (ITT)						
Placebo	111	61 (55.0)	8.3			
Adalimumab	115	45 (39.1)	NE	0.57[a]	0.39, 0.84	0.004[b]
Adjusted for baseline IMM usage (ITT)						
Placebo	111	61 (55.0)	8.3			
Adalimumab	115	45 (39.1)	NE	0.58[c]	0.39, 0.85	0.005[d]
mITT						
Placebo	114	63 (55.3)	8.3			
Adalimumab	115	45 (39.1)	NE	0.56[a]	0.38, 0.83	<0.003[b]

NE = not estimable (fewer than half of at-risk subjects had an event)
a. HR of adalimumab versus placebo from proportional hazards regression with treatment as factor.
b. 2-sided P value from log rank test.
c. HR of adalimumab versus placebo from proportional hazards regression with treatment and baseline IMM usage as factors.
d. 2-sided P value from proportional hazards regression with treatment and baseline IMM usage as factors.

Note: Treatment failure at or after Week 2 was counted as event. Drop outs due to reasons other than treatment failure were censored at the time of dropping out.

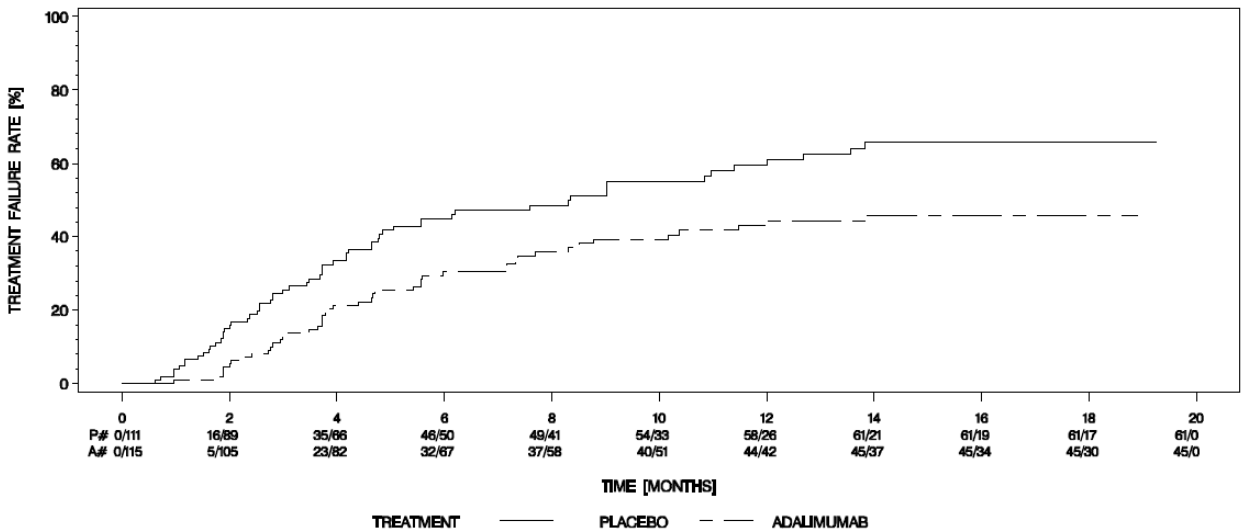


Figure 9 - Kaplan-Meier Curves for the Time to Treatment Failure on or After Week 2 (ITT; Main Study M10-880)
P# - placebo (number of events/number at risk), A# - adalimumab (number of events/number at risk)

To provide an estimate of the difference in time to treatment failure between the 2 treatment groups, given the 50% percentile is not estimable, the 40th percentile was examined and showed the time to treatment failure was 4.8 months and 10.2 months for the placebo and adalimumab groups, respectively.

There were generally fewer triggers leading to treatment failure in subjects receiving adalimumab than in subjects receiving placebo. Numerical differences in favour of adalimumab were shown for active inflammatory lesions, AC cell grade, and VH grade, but the differences were not statistically significant (see Table 23). The risk for treatment failure due to a decrease in the BCVA component was significantly lower in the adalimumab group.

Table 23 – Reasons for Treatment Failure by Components of the Primary Endpoint (ITT; Main Study M10-880)

Endpoint Treatment	N	Failure N(%)	Median time to failure (months)	HR[a]	95% CI for HR	P value[b]
All ITT subjects (N = 226)						
Active Inflammatory Lesions						
Placebo	111	17 (15.3)	NE			
Adalimumab	115	12 (10.4)	NE	0.55	0.26, 1.15	0.105
Anterior Chamber Cell Grade						
Placebo	111	30 (27.0)	NE			
Adalimumab	115	27 (23.5)	NE	0.70	0.42, 1.18	0.180
Vitreous Haze Grade						
Placebo	111	11 (9.9)	NE			
Adalimumab	115	11 (9.6)	NE	0.79	0.34, 1.81	0.569
logMAR Best Corrected Visual Acuity						
Placebo	111	23 (20.7)	NE			
Adalimumab	115	10 (8.7)	NE	0.33	0.16, 0.70	0.002

NE = Not estimable (less than half of at-risk subjects had an event).
a. HR of adalimumab versus placebo from proportional hazards regression with treatment as factor.
b. 2-sided P value from log rank test.

There was a total of 33 patients, who lost ≥15 letter in BCVA. Relevant characteristics of these patients are summarised below:

- The loss of BCVA paralleled increases in one or more of the following inflammation markers, AC cells (≥2 units), VH score (≥2 units) or CRT (≥50 µm) in 13 placebo-treated and in 8 adalimumab-treated subjects. In 8 additional placebo-treated subjects and 2 adalimumab-treated subjects, there were signs of disease activity but below the thresholds set for treatment failure. In 2 placebo-treated and in no adalimumab-treated subjects there was a loss of BCVA without (or essentially without) any other sign of disease activity. In addition, a number of subjects developed cataract changes.
- Sensitivity analyses (AC and VH = 0 and AC or VH < 0.5 at baseline) demonstrated that adalimumab was superior to placebo in both subgroups (HR 0.33, p=0.017 and HR 0.34, p= 0.003, respectively).

Secondary efficacy

No statistically significant differences were observed between the treatment groups for any of the ranked secondary efficacy variables. The outcomes were numerically in favour of adalimumab for all ranked variables except for Change in VFQ-25 subscore near vision (8). Sensitivity analysis using the mITT set and analysis of the better/worse eye separately showed similar results as the primary analysis (ITT).

The outcomes of the 9 ranked efficacy parameters are summarised in the below table.

Table 24 - Summary of Ranked Secondary Efficacy Variables (ITT, Main Study M10-880)

Ranked Secondary Variable	Placebo N = 111		Adalimumab N = 115		*P* value
	n[a]	Mean	n[a]	Mean	
1. Change in AC cell grade					
Left eye	110	0.57	115	0.41	
Right eye	110	0.53	115	0.40	
Mean difference of adalimumab minus placebo (95% CI)	–0.14 (–0.37, –0.08)				0.218[b]
2. Change in VH grade					
Left eye	110	0.33	115	0.16	
Right eye	110	0.27	115	0.18	
Mean difference of adalimumab minus placebo (95% CI)	–0.13 (–0.28, –0.01)				0.070[b]
3. Change in logMAR BCVA					
Left eye	110	0.06	115	0.01	
Right eye	110	0.02	115	–0.01	
Mean difference of adalimumab minus placebo (95% CI)	–0.04 (–0.08, 0.01)				0.096[b]
4. Time to OCT evidence of macular edema based on CRT (months; median)	95	NE	90	NE	
HR (95% CI)	0.75[c] (0.34, 1.69)				0.491[d]
5. Percent change in CRT					
Left eye	107	6.4	114	4.5	
Right eye	108	7.7	113	5.4	
Mean difference of adalimumab minus placebo (95% CI)	–2.3 (–8.5, 3.8)				0.451[e]
6. Change in VFQ-25 total score	109	1.24	115	3.36	
Mean difference of adalimumab minus placebo (95% CI)	2.12 (–0.84, 5.08)				0.160[f]
7. Change in VFQ-25 subscore distance vision	109	0.76	115	2.64	
Mean difference of adalimumab minus placebo (95% CI)	1.88 (–2.53, 6.29)				0.401[f]
8. Change in VFQ-25 subscore near vision	109	3.98	115	3.88	
Mean difference of adalimumab minus placebo (95% CI)	–0.10 (–4.81, 4.61)				0.967[f]
9. Change in VFQ-25 subscore ocular pain	109	2.87	115	3.42	
Mean difference of adalimumab minus placebo (95% CI)	0.56 (–4.56, 5.68)				0.830[f]

[a] For each endpoint, n = number of subjects with non-missing value.
[b] From ANOVA of change from baseline to Final/Early termination visit with treatment as factor adjusted for clustered observations.
[c] HR of adalimumab versus placebo from proportional hazards regression with treatment as factor.
[d] 2-sided P value from log rank test.
[e] From ANOVA of change from baseline to Final/Early termination visit with treatment and OCT machine as factors adjusted for clustered observations.
[f] From ANOVA of change from baseline to Final/Early termination visit with treatment as factor.

Note: Endpoints 1-3 and 5-9 reflect the changes from baseline to the Final/Early termination visit in each eye (where applicable) and missing data have been handled with the LOCF approach. Endpoint 4 reflects the time to event (OCT evidence of macular oedema) on or after week 2 in subjects without macular oedema at baseline.

Other efficacy endpoints

Selected endpoints are summarised below.

Mean AC cell grade, VH grade and logMAR BCVA over time were lower for the adalimumab group compared to the placebo group. Mean AUC of AC cell grade, VH grade and logMAR BCVA at final visit were higher for the adalimumab group compared to the placebo group and the differences between the groups were statistically significant (p=0.010 for AC cell grade, p=0.007 for VH grade and p=0.009 for logMAR BCVA).

Categorical changes in BCVA from best state achieved prior to Week 6 at selected time points are summarised in the below table.

Table 25 - Summary of Change in BCVA from Baseline to Selected Visits (ITT, LOCF, Main Study M10-880)

	Placebo (N=110) n (%)	Adalimumab (N=115) n (%)	Placebo (N=110) n (%)	Adalimumab (N=115) n (%)
WEEK 2	**Left eye**		**Right eye**	
Gain ≥ 5 letters	10 (9.3)	7 (6.1)	11 (10.2)	15 (13.2)
Stable [a]	95 (88.0)	99 (86.8)	88 (81.5)	94 (82.5)
Loss of 5-9 letters	2 (1.9)	8 (7.0)	7 (6.5)	5 (4.4)
Loss of 10-14 letters	1 (0.9)	0	2 (1.9)	0
Loss of ≥ 15 letters	0	0	0	0
WEEK 12	**Left eye**		**Right eye**	
Gain ≥ 5 letters	13 (11.8)	28 (24.3)	19 (17.3)	28 (24.3)
Stable [a]	76 (69.1)	74 (64.3)	70 (63.6)	81 (70.4)
Loss of 5-9 letters	9 (8.2)	9 (7.8)	11 (10.0)	5 (4.3)
Loss of 10-14 letters	3 (2.7)	2 (1.7)	5 (4.5)	0
Loss of ≥ 15 letters	9 (8.2)	2 (1.7)	5 (4.5)	1 (0.9)
WEEK 20[b]	**Left eye**		**Right eye**	
Gain ≥ 5 letters	11 (10.0)	22 (19.1)	23 (20.9)	26 (22.6)
Stable [a]	76 (69.1)	77 (67.0)	65 (59.1)	75 (65.2)
Loss of 5-9 letters	10 (9.1)	8 (7.0)	11 (10.0)	9 (7.8)
Loss of 10-14 letters	2 (1.8)	3 (2.6)	5 (4.5)	3 (2.6)
Loss of ≥ 15 letters	11 (10.0)	5 (4.3)	6 (5.5)	2 (1.7)
WEEK 24	**Left eye**		**Right eye**	
Gain ≥ 5 letters	10 (9.1)	23 (20.0)	23 (20.9)	23 (20.0)
Stable [a]	74 (67.3)	77 (67.0)	63 (57.3)	77 (67.0)
Loss of 5-9 letters	12 (10.9)	6 (5.2)	11 (10.0)	11 (9.6)
Loss of 10-14 letters	2 (1.8)	4 (3.5)	7 (6.4)	2 (1.7)
Loss of ≥ 15 letters	12 (10.9)	5 (4.3)	6 (5.5)	2 (1.7)
WEEK 48	**Left eye**		**Right eye**	
Gain ≥ 5 letters	13 (11.8)	23 (20.0)	21 (19.1)	26 (22.6)
Stable [a]	69 (62.7)	74 (64.3)	63 (57.3)	65 (56.5)
Loss of 5-9 letters	13 (11.8)	7 (6.1)	13 (11.8)	17 (14.8)
Loss of 10-14 letters	2 (1.8)	5 (4.3)	6 (5.5)	3 (2.6)
Loss of ≥ 15 letters	13 (11.8)	6 (5.2)	7 (6.4)	4 (3.5)
WEEK 80 [c]	**Left eye**		**Right eye**	
Gain ≥ 5 letters	13 (11.8)	25 (21.7)	25 (22.7)	28 (24.3)
Stable [a]	67 (60.9)	71 (61.7)	59 (53.6)	64 (55.7)
Loss of 5-9 letters	12 (10.9)	7 (6.1)	13 (11.8)	15 (13.0)
Loss of 10-14 letters	2 (1.8)	5 (4.3)	5 (4.5)	4 (3.5)
Loss of ≥ 15 letters	16 (14.5)	7 (6.1)	8 (7.3)	4 (3.5)

[a] Within ±4 letters
[b] According to the mandatory taper schedule, subjects were to discontinue prednisone no later than Week 19
[c] Final value

The proportions of subjects in quiescence, i.e. no active inflammatory lesions and AC cell grade ≤ 0.5 and VH grade ≤ 0.5) with and without steroids at each visit between baseline through Week 52 and between Week 20 through Week 52, respectively were higher in the adalimumab group as shown in Table 26.

Table 26 - Quiescence and Lack of Inflammation (Non-Responder Imputation, ITT, Main study M10-880)

Number (%) of Subjects in Quiescence			
Visit	Placebo N = 94[a]	Adalimumab N = 89[a]	*P* value[b]
Week 0	94 (100)	89 (100)	-
Week 8	60 (63.8)	75 (84.3)	0.002
Week 16	45 (47.9)	58 (65.2)	0.018
Week 20	35 (37.2)	52 (58.4)	0.004

Week 40	24 (25.5)	37 (41.6)	0.021
Week 52	21 (22.3)	37 (41.6)	0.005
Number (%) of Subjects in Steroid-Free Quiescence			
Week 0	-	-	-
Week 8	-	-	-
Week 16	-	-	-
Week 20	31 (33.0)	48 (53.9)	0.004
Week 40	20 (21.3)	35 (39.3)	0.008
Week 52	18 (19.1)	34 (38.2)	0.004
Number (%) of Subjects with Steroid-Free Lack of Inflammation			
Week 20	21 (22.3)	37 (41.6)	0.005
Week 40	14 (14.9)	26 (29.2)	0.019
Week 52	15 (16.0)	25 (28.1)	0.047

[a] Subjects who terminated the study because the planned number of treatment failures was reached were excluded.
[b] P value to compare adalimumab with placebo was based on chi-square test.

The proportion of subjects with lack of lack of inflammation (defined as no active inflammatory lesions and AC cell grade = 0 and VH grade = 0) at each visit from Baseline through Week 40 was statistically significantly higher in the adalimumab group than in the placebo group beginning at Week 4.

The proportions of subjects with AC cell grade of 0 (absence of flare) in each eye was also consistently higher in the adalimumab group compared to the placebo group starting at Week 2 and continuing to the final value. The same trend was observed for VH grade.

Sensitivity analyses taking into account major protocol deviations/prohibited CS use resulted in similar outcomes for proportions of patients in steroid-free quiescence and steroid-free lack of inflammation as in the primary analyses.

For the majority of PROs, adalimumab was favoured over placebo:

- Smaller mean reductions (worsening) or larger increases (improvements) in VFQ-25 scores from baseline to Final/Early Termination visit were observed in the adalimumab group compared to the placebo group, with the exception of colour vision, peripheral vision, and near vision (ranked secondary endpoint 8). Mean reductions that were statistically significantly different between groups in favour of adalimumab included general vision and mental health (p=0.003, and p=0.022, respectively).
- Similar reductions were observed in the adalimumab and placebo groups for HADS with no statistically significant differences between the groups.
- WPAI-SHP: The percent of work time missed, impairment while working, overall work impairment, and activity impairment showed greater increases from Baseline for the adalimumab group compared to the placebo group without any statistically significant differences between groups.
- At Final/Early Termination visit, values for EQ-5D predicted value and EQ VAS were similar for adalimumab and placebo groups.

2.4.2.3. Ancillary analyses

Anti-adalimumab antibodies (AAA)

See section 2.3.2. for the results of the AAA tests.

In study M10-877, the median (range) time to treatment failure was 15 (6 – 52) weeks for AAA– subjects. All four AAA+ subjects had treatment failure with a median (range) time to treatment failure of 32 (16 – 48) weeks. In study M10-880, the median (range) time to treatment failure was 16 (4 –

60) weeks for AAA– subjects. Six out of eight (6/8) AAA+ subjects had treatment failure with a median (range) time to treatment failure of 16 (10 – 31) weeks.

Subgroup analyses

Analyses of the primary and ranked secondary endpoints were conducted for study M10-877 and study M10-880 for several subgroups. The following is noted for the primary endpoint:

- Age: Results were in favour of adalimumab in 5 out of 6 subgroups, the largest difference in favour of adalimumab was observed at ages ≥ 30 to < 50 years subgroups for both studies.
- Gender: Adalimumab was favoured in males and females with a larger effect in males. In females, the difference between treatment arms with regards the time to failure was one month (both studies).
- Anatomical location: Subgroup analyses were in favour of adalimumab in 5 out of 6 subgroups. The exception was posterior uveitis in Study M10 880, where results for posterior uveitis were not directionally in favour of adalimumab.
- Diagnosis: Statistical analysis was performed only in cases where 20 or more subjects per group were available (i.e., idiopathic [both studies M10-877 and M10-880], birdshot choroidopathy [study M10-877] and VKH [study M10-880]). For idiopathic uveitis, the largest subgroup based on diagnosis, there was a statistically significant difference in time to treatment failure in favour of adalimumab compared to placebo in both studies and there was a numerical advantage in favour of adalimumab compared to placebo for the birdshot choroidopathy subgroup in study M10-877 and for the VKH subgroup in study M10-880. Adalimumab was not favoured in posterior uveitis and sarcoidosis in study M10-880 and seemed less favoured in intermediate uveitis in study M10-877.
- Duration of disease: Compared to subjects with a shorter (<1 year) disease duration, the efficacy of adalimumab was reduced in subjects with a longer duration (≥ 1 year) of the disease in study M10-880, while the opposite was demonstrated in study M10-877.
- Previous uveitis flares: In study M10-880, subjects with 0-1 uveitis flares during the last 12 months and those with ≥ 6 months since the last flare, did not gain any additional benefit of adalimumab.
- Region: Adalimumab was favoured in the US as well as in the EU regions.
- Previous uveitis flares: In study M10-880, subjects with 0-1 uveitis flares during the last 12 months and those with ≥ 6 months since the last flare, did not gain any additional benefit of adalimumab. With regards to treatment failure in the subset of patients with ≥2 flares in the 12 months prior to baseline, the HR was 0.23 (p=0.003). In this subset, the difference between adalimumab and placebo subjects observed in AC cell grade was statistically significant (HR 0.47, p=0.027).
- Weight: Adalimumab was favoured in the analysis by weight (<68 kg, ≥68 to <80 kg, ≥80 to <92 kg and ≥92 kg).
- Immunomodulatory therapy: Results were in favour of adalimumab in all 4 subgroups. (adalimumab yes/no in either of the 2 studies). In subjects with no use of immunomodulators in studies M10-877 and M10-880, the respective outcomes were: HR 0.49, p<0.001, HR 0.64, p=0.068
- Use of prohibited CS (topical and/or systemic and topical): In both studies, censoring subjects with protocol deviations/any prohibited CS use were consistent with that obtained in the

primary analysis with a clearly maintained statistical significance (p <0.001 and 0.013 in studies M10-877 and M10-880, respectively). Furthermore, the outcomes in the ranked secondary analyses were largely consistent with those of the initial analyses, i.e. in most analyses adalimumab was favoured over placebo. Subgroup analyses by prohibited use of topical CS did not change the overall outcomes.

Of the more than 50 subgroups analysed, in study M10-877 adalimumab was disfavoured only in one subgroup: prednisone dose ≥15 to <30 mg/day at last flare (n=22, HR 1.54). In study M10-880, adalimumab was disfavoured in five subgroups: age ≥ 50 years (n=74, HR 1.10), race black (n=14, HR=1.49), posterior uveitis (n=73, HR=1.02), sarcoid including Japanese subjects (n=42, HR 1.09), time since last flare ≥6 months (n=77, HR 1.31). For none of the subgroup analyses was the placebo treatment group favoured in both studies and overall.

Japanese sub-studies

The methodologies for the sub-studies were as for the main studies.

- Study M10-877 – Active uveitis

A total of 16 of the originally planned subjects were enrolled since the main study reached its target number of treatment failures before enrolment of the substudy was completed. No subjects prematurely discontinued study drug.

The majority of subjects were female, all were Japanese, and mean age was 51 years. There were some differences in age (< 40 years), body weight, and tobacco use between the placebo and adalimumab groups, but overall demographic characteristics were similar.

Almost half (7) of the patients were diagnosed with idiopathic uveitis, 6 with sarcoid, 2 with Behçet's and 1 with Vogt Koyanagi Harada. For Baseline characteristics, the treatment groups were numerically similar, but more subjects in the adalimumab treatment group had macular oedema at Baseline.

All subjects used prior uveitis-related CS and 12 subjects used topical CS (5 in the placebo and 7 in the adalimumab group). Overall, 3 subjects (2 placebo and 1 adalimumab) reported concomitant systemic IMM at Baseline. No imbalance between adalimumab and placebo groups in the deviations relating to prohibited steroids or IMM dosage during the study was noted.

The median times to treatment failure (primary efficacy) were 2.8 and 2.4 months in the placebo and adalimumab groups, respectively, with 6/8 (75%) and 8/8 (100%) treatment failures (HR: 1.20, 95% CI: 0.41, 3.54). The integrated analysis of the main study and the Japanese substudy data resulted n a difference between treatment arms of less than 2 months (3.0 vs. 4.8 months, p<0.001).

- Study M10-880 – Inactive uveitis

A total of 32 subjects were enrolled. One subject in each treatment group prematurely discontinued the study. One adalimumab subject discontinued due to an AE and one placebo subject was incorrectly assessed as treatment failure and the subject enrolled in the extension study.

The majority of subjects were female, all were Japanese (one Japanese/Korean), and mean age was 47 years. There were some differences in age (< 40 years), body weight, alcohol and tobacco use between the placebo and adalimumab groups, but overall demographic characteristics were similar.

Four subjects in each treatment arm were diagnosed with idiopathic uveitis, 4 (placebo) and 8 (adalimumab) with Vogt Koyanagi Harada, 6 (placebo) and 4 (adalimumab) with sarcoid, 1 (placebo) with Behçet's and 1 (placebo) with “Other” uveitis. For baseline characteristics, the treatment groups were similar.

All subjects used prior uveitis-related CS and 12 subjects used topical CS (15 in placebo and 12 in the adalimumab group). Overall, 3 subjects (1 placebo and 2 adalimumab) reported concomitant systemic IMM at Baseline. Although prohibited, systemic oral prednisolone was taken by 9/16 subject in the placebo group.

The median times to treatment failure (primary efficacy) were 2.1 and 2.9 months in the placebo and adalimumab treatment groups, respectively, with 14/16 (87.5%) and 12/16 (75.0%) treatment failures (HR: 0.45, 95% CI: 0.20, 1.03).

2.4.2.4. Summary of main study(ies)

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 27 - Summary of Efficacy for Trial M10-877 (VISION I) – Active Uveitis

Title: A Multicenter Study of the Efficacy and Safety of the Human Anti-TNF Monoclonal Antibody Adalimumab as Maintenance Therapy in Subjects Requiring High Dose Corticosteroids for Active Non-infectious Intermediate Uveitis, Posterior Uveitis, or Panuveitis		
Study identifier	M10-877	
Design	A randomised (1:1), double-masked, placebo-controlled multicentre study. Main study & sub-study in Japanese patients Initial combination treatment with 10-60 mg/day of oral prednisone (or oral CS equivalent); standardised taper over 15 weeks.	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	80 weeks duration or ended with the 138th event of treatment failure not applicable Open-label extension ongoing up to March 2018 (Study M11-327)
Hypothesis	Superiority	
Treatment groups	Ada	Adalimumab SC: 80 mg loading dose followed by 40 mg at Week 1 and thereafter eow; No of randomised patients: 111 (main study)
	Placebo	Placebo SC as above; No of randomised patients: 112 (main study)

Endpoints and definitions	Primary endpoint	Time to treatment failure	Time to treatment failure on or after Week 6. Criteria for treatment failure: (i) new active inflammatory (chorio)retinal lesions, (ii) AC cell grade >0.5 at Week 6, and thereafter 2-step increase in VH grade relative best state achieved prior to Week 6, (iii) VH grade >0.5 at Week 6, and thereafter 2-step increase in VH grade relative best state achieved prior to Week 6, 4) worsening of VA (ETDRS) ≥ 15 letters. At least one event present in at least 1 eye.
	Secondary endpoint	Change in AC cell grade	Change in AC cell grade in each eye from best state achieved prior to Week 6 to the final/early termination visit
	Secondary endpoint	Change in VH grade	Change in VH grade according to NEI/SUN criteria in each eye from best state achieved prior to Week 6 to the final/early termination visit
	Secondary endpoint	Change in logMAR BCVA	Change in logarithm of the minimum angle of resolution (logMAR) BCVA in each eye from best state achieved prior to Week 6 to the final/early termination visit
	Other endpoint	Proportion in quiescence	Proportions of patients in quiescence, i.e. no active inflammatory lesions and AC cell grade ≤ 0.5 and VH grade ≤ 0.5
	Other endpoint	Proportion with steroid-free lack of inflammation	Proportion of subjects with steroid-free lack of inflammation, i.e. no active inflammatory lesions and AC cell grade = 0 and VH grade = 0
Database lock	10 September 2014 19 December 2014 (final database lock after the 70-day safety follow-up)		

Results and analysis

Analysis description	**Primary analysis**		
Analysis population and time point description	Intent to treat (excluding sites with GCP violations) Time point for primary analysis: on or after Week 6 until final/early termination visit		
Descriptive statistics	**Treatment group**	**Placebo**	**Ada**
	Number of subjects (ITT)[a]	**107**	**110**
	Time to treatment failure in months (median) Treatment failures n(%)	3.0 84 (78.5%)	5.6 60 (54.5%)
	Change in AC cell grade (mean)	Left eye: 0.59 Right eye: 0.69	Left eye: 0.35 Right eye: 0.36
	Change in VH grade (mean)	Left eye: 0.33 Right eye: 0.45	Left eye: 0.11 Right eye: 0.13

	Change in logMAR BCVA (mean)		Left eye: 0.12 Right eye: 0.13	Left eye: 0.07 Right eye: 0.04
	Proportion in quiescence, n (%)	all	Week 6: 59 (62.1) Week 8: 45 (47.4) Week 16: 22 (23.2) Week 36: 7 (7.4) Week 52: 5 (5.3)	Week 6: 64 (71.1) Week 8: 59 (65.6) Week 16: 36 (40.0) Week 36: 21 (23.3) Week 52: 13 (14.4)
		Without steroids	Week 16: 18 (18.9) Week 36: 6 (6.3) Week 52: 4 (4.2)	Week 16: 28 (31.1) Week 36: 18 (20.0) Week 52: 12 (13.3)
	Proportion with steroid-free lack of inflammation, n (%)		Week 16: 10 (10.5) Week 36: 4 (4.2) Week 52: 2 (2.1)	Week 16: 13 (14.4) Week 36: 13 (14.4) Week 52: 9 (10.0)
Effect estimate per comparison	Primary endpoint: Time to treatment failure		Comparison groups	Placebo vs Ada
			HR	0.50
			95% CI	0.36, 0.70
			P-value	<0.001
	Secondary endpoint: Change in AC cell grade (mean)		Comparison groups	Placebo vs Ada
			Mean difference	-0.29
			95% CI	-0.51, -0.07
			P-value	0.011
	Secondary endpoint: Change in VH grade (mean)		Comparison groups	Placebo vs Ada
			Mean difference	-0.27
			95% CI	-0.43, -0.11
			P-value	<0.001
	Secondary endpoint: Change in logMAR BCVA (mean)		Comparison groups	Placebo vs Ada
			Mean difference	-0.07
			95% CI	0.11, -0.02
			P-value	<0.003
	Other endpoint: Proportion in steroid-free quiescence		Comparison groups	Placebo vs Ada at various time-points
			P-value	<u>All:</u> Week 6: 0.195 Week 8: 0.013 Week 16: 0.014 Week 36: 0.002 Week 52: 0.035 <u>Without steroids:</u> Week 16: 0.056 Week 36: 0.006 Week 52: 0.027
	Other endpoint: Proportion with steroid-free lack of inflammation		Comparison groups	Placebo vs Ada at Week 16, 36 and 52
			P-value	Week 16: 0.420 Week 36: 0.016 Week 52: 0.023

Notes	[a)] The number of patients for the secondary endpoints was the number of subjects with non-missing values; for the other endpoints the number of patients excluded patients who had to terminate the study because the planned number of treatment failures was reached. Difference between treatment arms for time to treatment failure was less than 2 months (3.0 vs. 4.8 months, p<0.001) when including the Japanese subgroup (n=16). No benefit of adalimumab in Japanese patients. Several subgroup analyses were conducted. There appeared to be overall consistency, but the effect in women were less convincing.

Table 28 - Summary of Efficacy for Trial M10-880 (VISION II) – Inactive Uveitis

Title: A Multicenter Study of the Efficacy and Safety of the Human Anti-TNF Monoclonal Antibody Adalimumab in Subjects with Inactive Non-infectious Intermediate Uveitis, Posterior Uveitis, or Panuveitis			
Study identifier	M10-880		
Design	A randomised (1:1), double-masked, placebo-controlled multicentre study. Main study & sub-study in Japanese patients Initial combination treatment with 10-35 mg/day of oral prednisone (or oral CS equivalent); standardised taper over 19 weeks.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		80 weeks duration or ended with the 96th event of treatment failure not applicable Open-label extension ongoing up to March 2018 (Study M11-327)
Hypothesis	Superiority		
Treatment groups	Ada		Adalimumab SC: 80 mg loading dose followed by 40 mg at Week 1 and thereafter eow; No of randomised patients: 115 (main study)
	Placebo		Placebo SC as above; No of randomised patients: 114 (main study)
Endpoints and definitions	Primary endpoint	Time to treatment failure	Time to treatment failure on or after Week 2. Criteria for treatment failure: (i) new active inflammatory (chorio)retinal lesions, (ii) 2-step increase in AC cell grade relative to Baseline, (iii) 2-step increase in VH grade relative to Baseline, 4) worsening of BCVA (ETDRS) ≥ 15 letters. At least one event present in at least 1 eye.
	Secondary endpoint	Change in AC cell grade	Change in AC cell grade in each eye from baseline to the final/early termination visit
	Secondary endpoint	Change in VH grade	Change in VH grade according to NEI/SUN criteria in each eye from baseline to the final/early termination visit

	Secondary endpoint	Change in logMAR BCVA	Change in logarithm of the minimum angle of resolution (logMAR) BCVA in each eye from baseline to the final/early termination visit
	Other endpoint	Proportion in quiescence	Proportions of patients in quiescence, i.e. no active inflammatory lesions and AC cell grade ≤ 0.5 and VH grade ≤ 0.5
	Other endpoint	Proportion with steroid-free lack of inflammation	Proportion of subjects with steroid-free lack of inflammation, i.e. no active inflammatory lesions and AC cell grade = 0 and VH grade = 0
Database lock	10 April 2015 8 June 2015 (final database lock after the 70-day safety follow-up)		

Results and analysis

Analysis description	**Primary analysis**		
Analysis population and time point description	Intent to treat (excluding sites with GCP violations) Time point for primary endpoint analysis: on or after Week 2 until final/early termination visit		
Descriptive statistics	**Treatment group**	**Placebo**	**Ada**
	Number of subjects (ITT)[a]	**111**	**115**
	Time to treatment failure in months (median) Treatment failures n(%)	8.3 61 (55.0%)	NE (>18) 45 (39.1%)
	Change in AC cell grade (mean)	Left eye: 0.57 Right eye: 0.53	Left eye: 0.41 Right eye: 0.40
	Change in VH grade (mean)	Left eye: 0.33 Right eye: 0.27	Left eye: 0.16 Right eye: 0.18
	Change in logMAR BCVA (mean)	Left eye: 0.06 Right eye: 0.02	Left eye: 0.01 Right eye: -0.01
	Proportion in quiescence n (%) – All	Week 8: 60 (63.8) Week 16: 45 (47.9) Week 20: 35 (37.2) Week 40: 24 (25.5) Week 52: 21 (22.3)	Week 8: 75 (84.3) Week 16: 58 (65.2) Week 20: 52 (58.4) Week 40: 37 (41.6) Week 52: 37 (41.6)
	Proportion in quiescence n (%) – Without steroids	Week 20: 31 (33.0) Week 40: 20 (21.3) Week 52: 18 (19.1)	Week 20: 48 (53.9) Week 40: 35 (39.3) Week 52: 34 (38.2)
	Proportion with steroid-free lack of inflammation n (%)	Week 20: 21 (22.3) Week 40: 14 (14.9) Week 52: 15 (16.0)	Week 20: 37 (41.6) Week 40: 26 (29.2) Week 52: 25 (28.1)
Effect estimate per comparison	Primary endpoint: Time to treatment failure	Comparison groups	Placebo vs Ada
		HR	0.57
		95% CI	0.39, 0.84
		P-value	0.004

	Secondary endpoint: Change in AC cell grade	Comparison groups	Placebo vs Ada
		Mean difference	-0.14
		95% CI	-0.37, 0.08
		P-value	0.218
	Secondary endpoint: Change in VH grade	Comparison groups	Placebo vs Ada
		Mean difference	-0.13
		95% CI	-0.28, 0.01
		P-value	0.070
	Secondary endpoint: Change in logMAR BCVA	Comparison groups	Placebo vs Ada
		HR	-0.04
		95% CI	-0.08, 0.01
		P-value	0.096
	Other endpoint: Proportion in quiescence	Comparison groups	Placebo vs Ada at various time points
		P-value	<u>All:</u> Week 8: 0.002 Week 16: 0.018 Week 20: 0.004 Week 40: 0.021 Week 52: 0.005 <u>Without steroids:</u> Week 20: 0.004 Week 40: 0.008 Week 52: 0.004
	Other endpoint: Proportion with steroid-free lack of inflammation	Comparison groups	Placebo vs Ada at Week 20, 40 and 52
		P-value	Week 20: 0.005 Week 40: 0.019 Week 52: 0.047
Notes	[a)] The number of patients for the secondary endpoints was the number of subjects with non-missing values; for the other endpoints the number of patients excluded patients who had to terminate the study because the planned number of treatment failures was reached. Integrating the Japanese subgroup of patients (n=32) did not affect the overall outcome. Although small differences between treatment arms in this subset were observed, there was a trend towards a favour for adalimumab. Several subgroup analyses were conducted. There appeared to be overall consistency, but the effect in women was less convincing.		

2.4.3. Supportive study(ies)

Study M11-327 - A Multicenter Open-Label Study of the Long-term Safety and Efficacy of the Human Anti-TNF Monoclonal Antibody Adalimumab in Subjects with Non-infectious Intermediate-, Posterior-, or Pan-uveitis

Study M11-327 (also referred to as VISUAL III) is an ongoing, open-label extension of studies M10-877 and M10-880. Eligible subjects participated in study M10-877 or study M10-880m, and either

discontinued from the studies for having met the endpoint of Treatment Failure or remained in the studies until completion or until the study was stopped.

Study participants

Main inclusion criteria:

- Subject must have successfully enrolled in either study M10-877 or M10-880 and either met the endpoint of "Treatment Failure" or completed the study.

Main exclusion criteria:

- A subject will be excluded from this study if the patient prematurely discontinued from Study M10-877 or Study M10-880 for any reason other than having a Treatment Failure event.
- Subject with corneal or lens opacity that precludes visualization of the fundus or that likely requires cataract surgery during the duration of the trial.
- Subjects with IOP of ≥ 25 mmHg and on ≥ 2 glaucoma medications or evidence of glaucomatous optic nerve injury.
- Subject with proliferative or severe NPDR or clinically significant DME.
- Subject with neovascular/wet AMD.
- Subject with abnormality of vitreo-retinal interface (i.e., vitreomacular traction, epiretinal membranes, etc.) with the potential for macular structural damage independent of the inflammatory process.
- Subject with a systemic inflammatory disease that requires therapy with a prohibited immunosuppressive agent at the time of study entry.

The primary objective of this study is to evaluate the long-term safety of SC adalimumab 40 mg given eow. Long-term efficacy will also be assessed.

Number of subjects to be enrolled: Estimated 400 subjects who participated in one of the preceding phase 3 studies, Study M10-877 or Study M10-880, and who are eligible for this study based on the inclusion/exclusion criteria.

Treatment

All subjects receive open-label adalimumab 40 mg dose eow SC regardless of treatment assignment in the randomized, double-masked studies.

As subjects who discontinue from study M10-877 or M10-880 due to "Treatment Failure" were considered to have active disease at time of entry into study M11-327, concomitant therapy with CS (oral or topical) and/or any one of the immunosuppressive therapies permitted in study M10-877 and study M10-880 will be allowed as necessary to control intraocular inflammation.

Subjects who successfully completed study M10-877 or M10-880 and have inactive disease at time of entry into study M11-327 may continue, taper and/or discontinue concomitant CS and/or one immunosuppressive therapy based on the Investigator's clinical judgment.

Study visits occur at Week 0, 2, 4, 8, 12, 18 and every 12 weeks thereafter.

Efficacy assessments were performed at every visit. Subjects who enter the study due to Treatment Failure in Study M10-877 or Study M10-880 and fail to achieve adequate control of their disease flare within the first 8 weeks of Study M11-327 may discontinue from the study.

Any other subject experiencing a uveitis flare during the study as determined by the investigator may discontinue the study at any time. Subjects were allowed to continue in the study, if it was determined by the investigator that the flare was triggered by a reduction or discontinuation in concomitant CS or systemic immunosuppressive therapy where further adjustment to the concomitant therapy may be warranted. Any subject continuing to have an active uveitis flare in the opinion of the investigator for 4 weeks or more should be discontinued from the study.

Safety data will be collected in the form of adverse events, physical examination, vital signs and laboratory tests throughout the treatment period and up to 70 days after the last dose of study drug.

All subjects will have a 70-day follow-up phone call or visit to obtain follow-up information on any new or ongoing adverse events. The 70-day follow-up phone call or clinic visit will not be required for any subject that initiates commercial adalimumab.

Efficacy variables include:

- Proportion of subjects at each study time point with no new active, inflammatory chorioretinal or inflammatory retinal vascular lesion in both eyes relative to Baseline for subjects who had inactive uveitis when they entered the study and to Week 8 for subjects who had active uveitis when they entered the study.
- Proportion of subjects at each study time point with a Grade ≤ 0.5+ in AC cells in both eyes on Slit Lamp Exam according to SUN criteria.
- Proportion of subjects at each study time point with a Grade ≤ 0.5+ in VH in both eyes on indirect ophthalmoscopy according to NEI/SUN criteria.
- Proportion of subjects at each study time point without a worsening of BCVA by ≥ 15 letters on the ETDRS in both eyes relative to Baseline for subjects who had inactive uveitis when they entered the study and to Week 8 for subjects who had active uveitis when they entered the study.
- Percent change in central retinal thickness (1 mm subfield) in each eye at each study time point relative to Baseline for subjects who had inactive uveitis when they entered the study and to Week 8 for subjects who had active uveitis when they entered the study.
- Change in NEI VFQ-25 score at each study time point relative to Baseline for subjects who had inactive uveitis when they entered the study and to Week 8 for subjects who had active uveitis when they entered the study.
- Proportion of subjects at each study time point achieving a ≥ 50% reduction in immunosuppression load relative to Baseline for subjects who had inactive uveitis when they entered the study and to Week 8 for subjects who had active uveitis when they entered the study.

Other efficacy variables include: WPAI-SHP, EQ-5D and Health Resource Utilization Questionnaire (HRU).

Safety will be assessed by adverse events, laboratory data, physical examinations and vital signs throughout the study.

Statistical Methods

Efficacy analyses were based on the ITT set which includes all subjects that received at least one dose of study drug in Study M11-327. All statistical analyses were descriptive. Results were stratified between subjects who entered into the study with active versus inactive uveitis. For subjects who had

active uveitis when they entered the study, the efficacy analyses started at Week 8. For subjects who had inactive uveitis when they entered the study, the efficacy analyses started at Week 0. Continuous variables were summarized by the number of non-missing observations, mean, standard deviation, median, quartiles, minimum and maximum. Categorical variables were summarized by counts and percentages.

Outcome – cut-off date 31 August 2015

Extent of exposure

The first subject entered the study in November 2010. A total of 423 subjects received at least 1 dose of adalimumab during the study. Of these, 371 were included in the ITT set. Within the ITT set, a total of 243 subjects had active uveitis at study entry and 128 subjects had inactive uveitis at study entry. Of the 48 Japanese subjects enrolled in the 2 sub-studies of M10-877 and M10-880, 39 subjects (ITT set) rolled over to the open label extension study and at the cut-off date, 28 subjects continued in the study.

Data up to 174 weeks (inactive uveitis at study entry) and 222 weeks (active uveitis at study entry) have been presented. By the cut-off date of 31 August 2015, one subject has finalised the study and 257 subjects (ITT set) remains in the study.

Table 29 - Subject Accountability by Previous Study and Treatment –Study M11-327

Previous Study	Safety N = 423 n (%)	ITT N = 371 n (%)
Study M10-877		
Total	210 (49.5)	182 (49.1)
Double-blind treatment period		
Placebo	110 (25.9)	92 (24.8)
Adalimumab	100 (23.6)	90 (24.3)
Study status		
Completed	0	0
Discontinued	80 (18.9)	69 (18.6)
Ongoing	130 (30.7)	113 (30.5)
Study M10-880		
Total	214 (50.5)	189 (50.9)
Double-blind treatment period		
Placebo	104 (24.5)	91 (24.5)
Adalimumab	110 (25.9)	98 (26.4)
Study status		
Completed	1(0.2)	1 (0.3)
Discontinued	53 (12.5)	44 (11.9)
Ongoing	160 (37.7)	144 (38.8)
All		
Double-blind treatment period		
Placebo	214 (50.5)	183 (49.3)
Adalimumab	210 (49.5)	188 (50.7)
Study status		
Completed	1 (0.2)	1 (0.3)
Discontinued	133 (31.4)	113 (30.5)
Ongoing	290(68.4)	257 (69.3)
Uveitis status at study entry		
Active	283 (66.7)	243 (65.5)
Inactive	141 (33.3)	128 (34.5)

Participant flow

At the cut-of date, one subject had finalised the study and 257 subjects remained in the study. A total of 113 of 371 subjects (ITT) discontinued from the study. The most common reason for premature discontinuation from the study was AE. Amongst the subjects entering the study with controlled uveitis no subject discontinued the study due to lack of efficacy. Among the 243 subjects with active disease at entry, 27 subjects (12.4%) prematurely discontinued due to lack of efficacy (based on investigator's judgement). Amongst the 235 subjects with active uveitis and values at Week 8 or later, 20 (8.5%) had a flare and prematurely discontinued due to lack of efficacy.

The mean (±SD) and median (range) durations of exposure to adalimumab for the all adalimumab analysis set (n=464) were 81.1 (± 57.6) and 68.1 (1.6 – 243.4) weeks, respectively. Three hundred thirty-five (335) subjects were treated with adalimumab for > 48 weeks and 38 subjects for > 192 weeks.

Analysis of efficacy

Evaluations of efficacy started at Week 8 for subjects who entered the study with active uveitis. From those entering the study with inactive uveitis, efficacy was evaluated from Baseline.

The mean dose of systemic CS at study entry was higher in subjects who had active non-infectious uveitis compared to subjects who had inactive non-infectious uveitis. In general, the mean dose of CS for all subjects (those with active or inactive disease at Week 0) decreased over time starting at Week 2. Subjects entering the extension study without active disease generally maintained a low daily dose of CS over time (< 2 mg) while subjects with a flare at study start had a reduction in daily dose of CS over time, from approximately 14 mg at study entry to approximately 4 mg after one year. Overall, the majority of subjects with controlled (inactive) uveitis at entry were not on concomitant CS (systemic and non-systemic) while the majority of subjects that entered the study with active uveitis were on concomitant CS during the first part of the study whereafter this proportion declined. Overall, 40/55 (73%) and 83/171 (48 %) of subjects who entered the study with controlled and active uveitis, respectively, did not receive any concomitant systemic and/or local CS after 1 year.

The time to treatment failure (as defined for the primary endpoint in the main studies) for subjects entering the study with active and inactive uveitis is summarised in the below table.

Table 30 – Time to treatment failure in subjects entering Study M11-327 with inactive and active uveitis up to August 31, 2015 (ITT).

	N	Failure N (%)	Censored N (%)	Median time to failure (months)
Subjects with inactive uveitis	128	16 (12.5)	112 (87.5)	NE
Subjects with active uveitis	243	132 (54.3)	111 (45.7)	12.5

NE= not estimable

Among subjects that entered the study with active uveitis and experienced a treatment failure (54%), for most subjects (30%) this was followed by a period of disease control. Among the subjects with active uveitis at study entry, the previously placebo-treated subjects (n=136) were overall better controlled than those that were treated with adalimumab (n=107) in the core studies. However also the subjects who failed on adalimumab in the core studies seemed to benefit from continued treatment (median time to failure 9.7 months). Furthermore, there were 25 subjects joining the study with active inflammation who did not receive concomitant CS. Of these, 13 (52.0%) reached quiescence at Week 8.

Reasons for treatment failures in subjects that entered the study with inactive uveitis were due to the following: lesions n=5, AC cells n=7, VH n=1, BCVA loss n=6. Most of these patients met 1 (n=13) of

the reasons for failure, a few met 2 (n=3). For those with active uveitis at study entry, the reasons for treatment failures were due to the following: lesions n=26, AC cells n=42, VH n=56, BCVA loss n=36. These patients met 1 (n=111), 2 (n=14) or 3 (n=7) of the reasons for failure.

For patients who experienced a flare at Week 8 or later, no subjects with controlled (inactive) disease at study entry discontinued due to the flare and 20/154 (8.5%) subjects with active disease at study entry discontinued due to the flare.

The proportions of subjects at each study time point who had no new active, inflammatory chorioretinal or inflammatory retinal vascular lesion in both eyes was ≥ 93% at all-time points beyond Week 12 independent on whether the subjects entered the study with active or inactive uveitis .

The proportion of subjects with a AC cell grade ≤ 0.5 in in both eyes, at study entry, was higher for subjects enrolling with inactive disease compared to those enrolling with active disease (96% and 50%, respectively). For subjects with inactive disease, the proportions with an AC cell grade ≤0.5 remained high (92-100 %) over the 174 weeks. For those enrolling in the study with active disease, there was a substantial increase in the proportions of subjects remaining in the study that had an AC cell grade ≤0.5 in both eyes (50 % at Week 0 and > 81% from Week 12 through Week 222).

The proportion of subjects at each study time point with a VH grade ≤ 0.5 in both eyes was higher for subjects enrolling with inactive disease compared to those enrolling with active disease (92.1% and 40.6%, respectively). For subjects with inactive disease, the proportions with an VH grade ≤0.5 remained high (80-100%) over the 174 weeks. For those enrolling in the study with active disease, there was a substantial increase in the proportions of subjects remaining in the study that had a VH grade ≤0.5 in both eyes (41% at Week 0 and > 78% from Week 8 through Week 222).

Mean BCVA in subjects that entered the extension study with controlled (inactive) disease remained essentially unchanged over the duration of the study without any trends of worsening. In the subjects that entered the study with active uveitis, when the flare was controlled, BCVA seemed to improve. During the extension, there were no major differences between males and females with regards to inflammation and CS usage.

2.4.4. Discussion on clinical efficacy

Two global phase 3 studies form the main basis of this application, one in patients with active uveitis not controlled on ≥10 to ≤60 mg prednisolone or oral corticosteroid (CS) equivalent per day (study M10-877, VISION I) and one in patients with inactive uveitis controlled on ≥10 to ≤35 mg prednisone or equivalent (study M10-880, VISION II). In addition, preliminary efficacy data from an ongoing, open label extension study (M11-327, VISION III) that enrolled subjects from the pivotal phase 3 trials have been provided.

No dose-response study has been conducted. In both pivotal phase 3 trials, an adalimumab maintenance regimen of 40 mg eow following an initial loading dose of 80 mg was tested based on experience with this regimen in psoriasis patients. However, steady-state serum adalimumab concentrations were on the lower side of the therapeutic dose range and exposure-response analyses indicated that uveitis patients with treatment failure had lower exposures compared to those without treatment failure (see section 2.3.2.). It could therefore not be excluded that the selected dose might have been too low, or, alternatively a higher dosing frequency may have been needed to achieve maximum efficacy. This view was shared by an expert panel convened by the CHMP (see report from the meeting below). Additional clinical trial simulations indicated an increased benefit in case of weekly 40 mg doses compared to 40 mg eow of approximately 15% less subjects with treatment failures (see section 2.3.2.). However, as this finding was based on simulations, no firm conclusions could be

drawn. However, weekly dosing has been reported/recommended in difficult to control patients in the published literature (Wood, US Pharmacist, 2011; Baughman et al., Sarcoidosis vasculitis and diffuse lung diseases 2012; Reddy and Albini, Retina today, 2015; Dubel, Handbook of Therapeutic Antibodies Vol 2, 2nd edition, 2014). Further, weekly dosing in other indications for Humira has not been associated with any major safety concerns. Therefore, the CHMP recommended that the MAH should study the weekly dosing regimen in the uveitis indication post-approval.

Design and conduct of clinical studies

Together, both pivotal studies randomised more than 450 subjects in the main studies and additional 48 subjects in the Japanese sub-studies, which was recognised by the CHMP as a rather high number of patients in view of the rarity of the disease. The study duration of 80 weeks or until the predefined number of events of treatment failures was reached was considered acceptable.

In both studies, patients received open label oral prednisone at the start of the studies. In study M10-877, all subjects received a prednisone burst of 60 mg/day at randomisation. This approach was considered acceptable, as intense treatment is in line with general uveitis treatment recommendations in order to obtain a rapid control of the inflammation and, considering that the comparison was conducted against placebo, necessary from an ethical perspective. CS were then tapered in a standardised and pre-defined manner during 15 and 19 weeks in the respective studies, which was broadly consistent with recommended schedules in uveitis treatment guidelines. A taper from 60 mg/day over 15 week as performed in study M10-877 was however rather aggressive, but aimed to induce treatment failures, which was considered acceptable by the CHMP in the clinical trial context. Steroid taper was started after 2 weeks and 1 week in patients with active and inactive uveitis, respectively. To ensure that the exposure of adalimumab has reached steady state, it is advised for clinical practice that CS taper can be started 2 week after treatment initiation with Humira (see discussion below on the steroid sparing effect).

Overall, in both studies, CS doses were well balanced between treatment arms during the tapering periods. While the durations of the initial oral prednisone treatment were longer in the adalimumab treatment groups, the total exposure was similar between treatment arms in the respective studies, which was considered reassuring by the CHMP.

Any topical steroids used at Baseline were further to be tapered according to a predefined schedule, which was considered acceptable. Also, in both phase 3 studies, one additional concomitant IMM at stable doses was allowed, which was considered a reasonable approach as such combined treatment is in line with current clinical practice.

The selection criteria were overall adequate to capture the targeted patient population which consisted of subjects with a wide range of uveitis disease aetiologies, e.g. idiopathic, Birdshot choroidopathy, VKH, sarcoid and Behçet's disease. However, there were concerns that the cut-off set for prior intra/peri-ocular CS (6 months in case of dexamethasone intravitreal implants and 30 days for all other CS) may have been too short to exclude a treatment effect. This was addressed in further analyses by the MAH, showing that only 7 adalimumab-treated subjects and 2 placebo-treated subjects in study M10-877 terminated IVT dexamethasone or IVT/periocular triamcinolone within 12 or 6 months, respectively, before start of study M10-877. Due to the fairly low number of subjects, an impact on the overall study outcome was unlikely. Furthermore, the majority of subjects who received topical CS within 30 days prior to baseline were randomized to the placebo treatment group. A bias in favour of adalimumab was thus unlikely. The MAH also provided further reassurance on the prior use of VEGF inhibitors and no impact on the study results was expected in this regard.

The primary endpoints in both studies, time to treatment failure, were defined as composite endpoints that not only included assessment of VH score, but also assessment of inflammatory lesions, AC cell

scores and BCVA. The 4 components were acknowledged by the CHMP as relevant in the assessment of uveitis as per the Standardization of Uveitis Nomenclature (SUN) Working Group. As reported in the CPMP/EWP/908/99 guideline on points to consider on multiplicity issues in clinical trials, a composite endpoint must be *'capable to providing the key evidence of efficacy that it is needed for a licence*". Indeed, eye function (i.e. visual acuity), a hard clinical endpoint, is considered the ideal primary outcome measure for clinical trials in ophthalmology. However, there are several difficulties in selecting visual acuity as outcome measure in uveitis patients. Glaucoma and cataract can reduce vision in these patients even when uveitis is well controlled, and stratifying the patient population for factors affecting vision is not always feasible. Further, patients with a long-standing oedema or even a subclinical inflammation, may not have the potential to re-gain any (or only some) of the lost vision. Further, subjects in the two studies had overall a relatively mild visual impairment at Baseline, thus leaving little room for improvement. As a consequence, most of the trials in uveitis of the posterior eye segment have used as primary efficacy variable VH score only. However, by including all components, it is more likely to detect an inflammation and the primary endpoint will thus be more sensitive. For these reasons and given that the goal in treating non-infectious uveitis is to control acute inflammation, limit recurrences, reduce the dose of systemic steroids and limit the decline in visual acuity, the definition of treatment failures was agreed by the CHMP and the primary endpoints of both studies was considered to be of clinically relevance.

In study M10-877 (active uveitis), treatment failures were counted on or after Week 6 to allow time for subjects to reach a common level of quiescence following the protocol-specified prednisone burst. This implies by definition that no subject could have a shorter time to treatment failure than 6 weeks, which in fact will be the case for many patients in clinical practice. However, it is not believed that this approach caused an overestimation of the time to failure and the methodology for the primary endpoint analysis was considered appropriate. Furthermore, based on interim analyses, the sample sizes in the studies were increased since the overall rate of treatment failures was higher than expected. The interim analyses for sample size re-estimation were not formally planned in the study protocols, but did not cause concerns regarding control of the type I error. In study M10-877 (active uveitis), the primary endpoint also included the proportion of patients that did not achieve quiescence by Week 6. This was considered highly reasonable since it is of critical importance to obtain a rapid control of the inflammation, and it could even have been considered to focus on this aspect in this study.

The secondary and other endpoints that cover aspects of the individual components of the primary endpoint, macular oedema and PROs were generally appropriate, although the rationale behind the order of the ranked secondary endpoints was not clear as they were analysed independently whether or not the previous endpoint reached statistical significance. Further, time to event analyses included treatment failure in any eye, however, since the quality of life of patients with uveitis likely depends on the vision of the best seeing-eye, the assessment of visual acuity of the best seeing-eye may have been more informative to understand the real benefit of the study drug.

In addition, several subgroup and *post-hoc* analyses were conducted. For study M10-877 (but not for study M10-880), the time to failures for the BCVA component of the primary endpoint was evaluated *post hoc.* This is highly reasonable and endorsed, but the usual limitations of *post-hoc* analyses apply. Similarly, as it is of high importance to obtain rapid disease control, the *post hoc* analyses at earlier time-points than 6 weeks were acknowledged by the CHMP to provide information on whether high dose CS in combination with adalimumab could shorten the time to quiescence. However, there were no expectations with regards to the Week 1 analyses when subjects are still on 60mg prednisone per day.

With regards to the overall conduct of the studies, all protocol amendments appear to have been taken place before unmasking the studies. Due to GCP-violations, the ITT analysis excluded a small number of patients, which was considered by the CHMP sufficiently justified. However, no PP set was generated although there were several protocol deviations including prohibited use of CS by several patients during the study. The latter were of concern since prohibited use of CS may well have had an impact on the outcome of the study. The MAH explained that the vast majority of steroid related deviations were related to the taper schedule and doses. They were mainly due to an early (few days) or late step down or other minor nonconformities. In addition, several sensitivity analyses for the primary endpoint and ranked secondary endpoint as well as re-analyses of proportion of patients reaching quiescence/lack of inflammation with and without CS counting major deviations/prohibited medication as failures as well as subgroup analyses by prohibited medication have been provided. Taken together, the analyses showed that CS related deviations were unlikely to have had a major impact on the outcome of the studies.

Protocol deviations regarded as minor in the study reports included a number of subjects that decreased their concomitant immunosuppressive therapy during the study, while they should have been on stable doses. In addition, some subjects received CS to treat an AE. However, due to the overall balanced distribution of these deviations between treatment arms, the CHMP considered that any bias in favour of adalimumab treatment was unlikely.

Baseline demographics were generally well balanced between treatment arms. With regards to disease characteristics, in study M10-877, subjects in the placebo-treatment group had a longer mean and median duration of uveitis. A shorter duration of uveitis, however, does not necessarily translate into a less severe disease. Subgroup analyses by disease duration (<1 and ≥1 year) were inconclusive due to the limitedness of the data. No further action was considered warranted by the CHMP.

With regards to the disease characteristics, the CHMP noted that uveitis distribution according to aetiology in the studies did not fully reflect the known epidemiology of the disease as the vast majority of uveitis types represented in the trials had no or very mild systemic involvement. Patients with Behçet's disease and sarcoidosis were underrepresented, probably because of the difficulties of enrolling patients with such severe diseases in a clinical trial. VKH and Birdshot's disease are rare forms and therefore expected to be poorly represented. Furthermore, in both studies a larger proportion of subjects in the placebo-treatment groups had idiopathic uveitis while more subjects in the adalimumab groups had the difficult to treat Behçet's disease. However, subgroup analyses showed the adalimumab was favoured in most types and diagnoses of uveitis in both studies with the only exceptions of posterior uveitis and sarcoidosis in study M10-880 (see further discussion below).

Efficacy data and additional analyses

- Efficacy outcomes - active uveitis (study M10-877, VISION I)

The overall treatment failure rate was high in both treatment arms with 79% (84/107) and 55% (60/110) in patients receiving placebo and adalimumab, respectively). This may be explained by the choice of a composite endpoint including 4 components representing a sensitive measure of inflammation. Furthermore, the rather aggressive steroid taper may have contributed to the high failure rates. With regards to the primary efficacy variable, median time to treatment failure was longer in the adalimumab arm compared to placebo (5.6 versus 3.0 months). The Kaplan-Meier curve started to separate early and the separation was sustained up to Week 80, supporting maintenance of the treatment effect. Still, the magnitude of the effect was limited with less than a 3 months difference between treatment groups. However, from a statistical point of view, efficacy has been convincingly demonstrated ($p<0.001$) and there is a 50% reduction in the risk (95% CI 0.36, 0.70) of experiencing a treatment failure at or after 6 weeks on treatment with adalimumab.

Overall, the CHMP recognised that the study population was difficult to treat and that the primary endpoint is likely very sensitive. Therefore, the effect size, although modest, was considered to be of clinical relevance. This position of the CHMP took into account the views expressed by an expert panel, which was convened to further discuss the clinical relevance of the observed effect, the duration of treatment and possible place in therapy for Humira (see report from the expert meeting below).

Furthermore, analysis of the time to treatment failure by individual components of the composite primary endpoint showed that all components contributed to the treatment failures with the largest difference between active and placebo treatment being observed for VH grade. A statistically significant difference in favour of adalimumab over placebo was demonstrated for all components ($p < 0.001$ to 0.010).

A numerical favour of adalimumab over placebo was shown in terms of proportion of patients that reached quiescence at Week 6 (i.e. still on 15 mg CS/day) and from Week 8 (10 mg CS/day) statistical significance was achieved (47 vs. 66% in placebo and adalimumab groups, respectively $p=0.013$). Thus, there was a consistently higher proportion of patients in the adalimumab treatment group compared to placebo that remained in quiescence over the course of the study, showing maintenance of treatment effect over the course of the study albeit only for a limited subset of patients (maximum 20% difference between treatment arms).

Of the 9 ranked secondary analyses, adalimumab was numerically favoured in all, and statistical significance was reached in 7 of the analyses, thus supporting robustness of the study results. Some questions were raised in relation to data imputation. Due to the large number of treatment failures the amount of data imputed using LOCF was very large at the later time points. Even though the large amount of missing values at later time-points was mostly due to treatment failure, LOCF is not necessarily equal to worst observation carried forward for all endpoints. However, the imputation strategy was not expected to change the overall interpretation of data, hence no further investigation was considered necessary.

However, the magnitudes of the mean effect sizes of the secondary endpoints, including AC cell and VH grades and visual acuity, are limited. With regards to visual acuity, while it is recognised that some of the patients likely already have an irreversible structural damage and keeping in mind that visual impairment was mild to moderate at Baseline, the ultimate aim of controlling an uveitis flare is to preserve visual function and in this context, the observed mean difference of 3.5 letters (0.07 logMAR, $p=0.003$) between treatment arms in favour of adalimumab was not convincing. The MAH explained this finding with the inclusion of both eyes in the endpoint even if only one eye failed as well as with the dilution of the effect since a large proportion of the study subjects (63.6% to 85%) did not experience a treatment failure (i.e., were responders) with regards to a particular component of the primary endpoint. This was acknowledged by the CHMP.

With regards to BCVA, the proportion of patients who gained ≥ 5 letters or had no relevant changes in BCVA (within $\pm$4 letters) was numerically higher in the adalimumab group at each time-point beyond Week 6. While the differences between treatment arms were rather small and overall few subjects gained visual acuity, it is recognised that many subjects had only mild vision loss at Baseline (approximately 20/32) leaving not much room for improvement. With regards to patients experiencing a significant loss of BCVA (≥15 letters), inconsistently, at the later time points, adalimumab seemed not to be favoured over placebo for the left eye, while the opposite was observed for the right eye. However, at Week 80 a total of 3 and 14 eyes gained ≥ 5 letters in BCVA in the placebo and adalimumab groups, respectively, while 38 and 24 eyes in the respective groups lost ≥ 15 letters. There was furthermore a small, but consistent numerical trend in favour of adalimumab over placebo in terms of proportion of patients that gained 10-14, or ≥15 letters in BCVA throughout the study. Thus, adalimumab seemed overall favoured.

With regards to the VFQ-25 total score as well as near vision and ocular pain, the magnitude of the difference between treatment arms was in line with, or beyond what is generally regarded as clinically relevant (4-5 units). However, vision-related quality of life seemed to decrease during the study (general health was markedly reduced with 8.4 units in the adalimumab group, and even more so in the placebo group). This may be explained by the fact that quality of life is evaluated from the best state achieved and subjects had not much potential for improvement since the average change in VFQ-25 score included both deterioration (treatment failures) and no or minimal change in those who did not fail. *Post hoc* analyses indicated that declines in the VFQ-25 total score increased with the number of failure components, while in subjects who did not experience treatment failures, the score remained at the same level as best state achieved (+0.2). Overall, the PROs (except for HADS) tended to favour adalimumab.

For the other endpoints, adalimumab was generally superior to placebo although the differences between treatment arms were generally limited in size.

- Efficacy outcomes - controlled (inactive) uveitis (study M10-880, VISION II).

Similar to study M10-877, the rate of treatment failures was high in both treatment arms of study M10-880 with 55% (61/110) and 39% (45/115) in the adalimumab and placebo groups, respectively. The risk of treatment failure for subjects in the adalimumab group was reduced by 43% (95% CI 0.39, 0.84) compared to subjects in the placebo group. As these were subjects with controlled disease, it was expected that the time to treatment failure would be longer than in subjects with active disease. This was confirmed with a median time to treatment failure of 8.3 months in the placebo group (compared to 3.0 months in the active uveitis study). Time to treatment failure was not estimable (i.e. >18 months) for adalimumab subjects because fewer than half of the patients experienced treatment failure at the time of conclusion of the study. The outcome was statistically significant (p=0.004).

No statistically significant differences were observed for the 3 components of the primary endpoint directly related to inflammation (active inflammatory lesions, AC cell grade and VH cell grade) which is also reflected in some of the ranked secondary variables, as discussed below. The treatment effect of the primary endpoint was mainly driven by the visual acuity component. However, while statistically in favour of the adalimumab group (p=0.002, HR 0.33), only a small proportion of patients actually lost 15 letters; 23 (20.7%) patients in the placebo arm versus 10 (8.7%) patients in the adalimumab arm, and this loss occurred mostly early on in the study (by Week 20). Changes in retinal lesions and/or visual acuity in the study population, i.e. patients with uveitis controlled with CS and free of flare for a mean of 5 months at Baseline, would however normally be expected to occur gradually and be preceded by episodes of active inflammation. Furthermore, even though the risk for treatment failure due to worsening of visual acuity by at least 15 letters was clearly reduced in the adalimumab group, there was only a 2 letter (logMAR 0.04, p=0.096) mean difference in BCVA change from Baseline between treatment arms, further supporting the notion that only a small proportion of patients seemed to have benefited from adalimumab treatment. The MAH provided further characteristics of the 33 subjects with a ≥15 letter loss demonstrating that the vision loss paralleled increases in AC cells, VH scores and/or central retinal thickness in all but 2 placebo-treated subjects, although the criteria for failure were not reached in all patients. Similarly, in all but one placebo-treated subject with an early loss of BCVA (around Week 12 or earlier), this was associated with increases in other inflammatory parameters. Some patients also developed cataract, but these few cases were considered unlikely to have had an impact on the study outcome. Overall, these data supported an association of the vision loss with disease manifestations. As for the small mean difference in BCVA (logMAR 0.04) between treatment arms, the MAH explained that this difference was mainly driven by patients/eyes reaching treatment failure (23 and 10 subjects for placebo and adalimumab, respectively) and therefore a large

difference may not be expected. This was acknowledged by the CHMP. Still, the results only support a modest treatment effect.

Further support with regards to long-term maintenance treatment could be deducted from the preliminary results of the ongoing long-term extension study in which some subjects with controlled disease at study entry have been treated for up to 174 weeks (see discussion below). Notably, in the subset of patients that entered the extension with controlled (inactive) uveitis, overall only 12.5% experienced a flare during the treatment period and, so far, no one discontinued the study due to lack of efficacy. Further, in this subset of patients, the mean dose of CS was <2 mg/day (compared to approximately 4 mg/day for those entering the study with active uveitis) and the majority of these patients were controlled without CS. Thus, there are clear indications of a treatment benefit with long-term continuous therapy and a potential for a relevant steroid-sparing effect.

With regards to the ranked secondary endpoint, no statistically significant differences were observed between the treatment groups for any of the 9 variables. The results were numerically in favour of adalimumab for all ranked variables except for the change in VFQ-25 sub-score near vision where essentially no difference was observed between treatment arms. Similar to study M10-877, the effect sizes were modest, but some were likely diluted including AC and VH outcomes as few treatment failures were due to these components. Overall, it was recognised by the CHMP that the mean AC cell scores, VH scores and BCVA were consistently better in the adalimumab group compared to placebo over the course of the study although the differences were smaller than in study M10-877. There was also a consistently higher number of adalimumab-treated subjects that gained ≥5 letters in BCVA and similarly, a consistently lower number of subjects in this treatment group that lost <15 letters. At Week 80, a total of 38 and 53 eyes gained ≥5 letters in BCVA in the placebo and adalimumab groups, respectively, while 24 and 11 eyes in the respective groups lost ≥ 15 letters. Furthermore, the proportion of patients in quiescence without steroids was consistently higher during the course of the study, providing further support for adalimumab as a steroid-sparing option. Altogether, and taking into account the view expressed by experts in the treatment of uveitis (see summary of ad-hoc expert group meeting below), these results were considered by the CHMP to be reassuring and supporting a beneficial effect of Humira in maintaining disease control.

Among the PROs, adalimumab was overall favoured in the VFQ-25 and also in the WPAI-SHP. However, with regards to VFQ-25 near vision, in contrast to study M10-877, in study M10-880 adalimumab was not favoured over placebo. In study M10-880, Baseline scores were markedly higher than in M10-877 (score of 75 versus 62), which can be explained as patients in M10-877 represent a population with controlled disease and there may not be room for a significant treatment effect in this respect. For HADS and EQ-5D, outcomes were similar in the treatment groups. As in study M10-877, overall vision-related quality of life decreased during the study, including in the adalimumab-treatment arm.

- Subgroup analyses including Japanese sub-studies

Analyses of the primary and ranked secondary endpoints were conducted for both pivotal trials for numerous subgroups. Of the more than 50 subgroups analysed, adalimumab was favoured in the vast majority of analyses conducted with either study data sets, demonstrating a reasonably consistency of the results. Furthermore, none of the subgroup analyses favoured placebo in both studies, which provides further reassurance.

Since the population PK exercise indicated that body weight influenced clearance and exposure, additional subgroup analyses by weight have been conducted by the MAH. In these analyses, adalimumab was consistently favoured over placebo without any trends towards an inferior effect in heavier patients.

Adalimumab was also favoured in most types and diagnoses of uveitis in both studies. In study M10 877, adalimumab appeared less effective in intermediate uveitis which may be of concern in view of the potentially increased risk of demyelinating disorders in these patients (see also section 2.5.). However, the limited effect was only observed in one of the studies and due to the small sample size, no firm conclusions could be drawn from the data. The CHMP agreed to expand SmPC section 4.4 with information on the association of immediate uveitis and demyelinating disorders together with a recommendation to conduct a neurological evaluation (see section 2.5.4. for details).

With regards to gender, a limited effect in females was observed in both studies with only 1 month difference in the median time to treatment failure between treatment arms. Although the duration of uveitis was longer in female patients compared to males, there was no significant interaction between treatment and gender when adjusting for the duration of the disease. In study M10-880, there were some imbalances between genders with regards to location of the inflammation (intermediate and panuveitis) and diagnosis (VKH and Behçet's disease). Substantially more women than men (46 vs. 5) were affected with VKH, while the opposite was observed for Behçet's disease (13 males and 3 females). The separation of the Kaplan-Meier curves for patients with VKH was clearly less prominent compared to the subset with Behçet's disease. It could be speculated if the efficacy of Humira is lower in subjects with VKC, but the number of subjects concerned was too low to draw firm conclusions. The MAH also presented data from the extension study separated by gender. The available data indicated that there were no major differences between men and women with regards to inflammation and CS usage, thereby providing support of a relevant effect of Humira in both genders and thus some reassurance. It was also acknowledged by the CHMP that the studies were not powered to assess effects in subgroups.

With regards to antibody formation, the number of anti-adalimumab antibody positive (AAA+) subjects was too small with 4 patients in study M10-877 and 8 patients in study M10-880 to conclude on any impact on efficacy. Further data presented by the MAH showed that AAA development remained low regardless of concomitant IMM therapy (2.2%, 2/91) or not (6.3%, 10/158). However, the data were too limited to draw any conclusions whether the absence of a protective umbrella of prednisolone and immunosuppressive therapy would affect antibody formation. Overall, the CHMP was of the view that the current information in the SmPC about immunogenicity was sufficient.

With regards to the Japanese sub-studies, notably, adalimumab was not favoured in patients with active uveitis with median times to treatment failures of 2.8 and 2.4 months in the placebo and adalimumab group, respectively (HR=1.2). However, the number of study subjects was very limited (16 and 32 subjects enrolled in the sub-studies of M10-877 and M10-880, respectively), and the number of patients with active uveitis may have been too small to determine the true effect size. No further information in this regards was considered necessary by the CHMP. In inactive uveitis, the risk for failure was reduced (HR=0.55) for the adalimumab group, but there was less than a month difference between treatment arms with regards to time to treatment failure. However, even though the effect size was limited, there was at least a trend towards a benefit of adalimumab, which is consistent with the main study results.

- Long-term data (open label extension study M11-327, VISION III)

The overall duration of study drug exposure was rather short in the two pivotal phase 3 trials, in particular in study M10-877 in which subjects were treated for a mean of 5 and 7 months in the placebo and adalimumab treatment groups, respectively. In the extension study (M11-327), the mean and median durations of exposure to adalimumab for the All Adalimumab Analysis Set (n=464) was 81 and 68 weeks, respectively. The study is ongoing and preliminary data have been provided. At the cut-off date, 335 subjects had been treated with adalimumab for >48 weeks and 38 subjects for >192 weeks.

Although acknowledged that a large proportion of patients from the main studies entered the extension study (423/452), there are limitations resulting from the uncontrolled, open-label design of the study and the fact that a fairly large proportion discontinued the study. Despite these caveats, the preliminary efficacy data seem promising with low proportions of patients with increases in AC cells or VH grades and thus apparently being well controlled.

Of the 243 subjects with active disease entering the extension, 132 (54.3%) experienced treatment failures, which was a relatively high proportion of patients. However, for the majority, the flare was followed by a period of disease control and the median time to treatment failure was 12.5 months and notably longer than in the core studies. Also, the subjects who failed on adalimumab in the core studies, i.e. a potentially even more difficult to treat population, seemed to benefit from continued treatment with a median time to treatment failure of 9.7 months. Few patients with controlled uveitis at study entry experienced treatment failures (12.5%) and the time to treatment failure could not be estimated. Although these results were promising, due to the uncontrolled nature of the study, it was not possible to conclude to what extent adalimumab contributed to the large proportion of patients in quiescence. To further explore this issue, the MAH provided additional analyses for the 83 patients entering the extension from study M10-880. Amongst these patients, 39 and 44 subjects had experienced <2 and ≥2 flares, respectively, in the 12 months prior to enrolling in M10-880. The rate of treatment failures was higher in the subgroup with ≥2 flares (13.6% vs 5.1%), but was still fairly low. While recognizing the limited number of subjects and that concomitant treatment may well have influenced these outcomes, use of CS was low and the analyses provided reassurance of a relevant effect of Humira.

Overall, vision remained essentially the same in patients with controlled disease at study entry. For patients with active disease, there were trends towards an improvement in BCVA with improved disease control. These results were independent of concomitant use of IMM or when stratified for previous treatment (placebo/adalimumab). There was no indication of deterioration of BCVA with time.

Based on these results, patients seemed better controlled than in the main studies, but this may have been due to the option to receive concomitant CS at the Investigator's discretion. It was however reassuring that the subjects entering the extension study with controlled disease generally maintained a low daily CS dose over time (< 2 mg) while subjects with a flare at study start had a reduction in daily dose of CS from approximately 14 mg at study entry to approximately 4 mg after 1 year. Overall, the majority of subjects with controlled uveitis at study entry did not receive concomitant CSs.

Taken together, the extension study supports a benefit of Humira in the long-term, in subjects with active and controlled disease as well as a relevant steroid sparing effect.

Indication and posology recommendations

In the EU, CS and ciclosporin are the only compounds formally approved for the treatment of uveitis. With regards to ciclosporin, in clinical practice, other IMMs, for example, MTX, MMF or azathioprine are often the preferred standard of care. TNF-inhibitors are generally used as later line options.

Subjects included in study M10-877 were representative of a target population insufficiently responsive to steroids and 31% of subjects were on one additional IMM. In study M10-880, all subjects received steroids and half were controlled with IMMs. Thus, Humira was studied in patients already receiving conventional therapy and consequently, the initially proposed first line indication was not agreed by the CHMP. Instead, use in patients with inadequate response to CS, in need for CS-sparing or in whom CS are inappropriate, was considered adequate. Use in patients with inadequate response to CS was in line with the study population of the pivotal trials which demonstrated a clinically relevant treatment effect of Humira as well as a CS sparing effect, which was further supported by the ongoing extension study. While patients in which CS are inappropriate were not recruited in the clinical development

program, there was no reason to believe that the efficacy or safety profile should be significantly different in such population. It was thus considered appropriate to include this subset of the population as part of the indication. The decision to limit use of Humira to second-line therapy also took into account its safety profile as use of Humira is not without risks (see section 2.5.).

With regards to IMM use, subgroup analyses for patients without concomitant use of IMM were consistently in favour of adalimumab (HR 0.49, p<0.001 for study M10-877 and HR 0.64, p=0.068 for study M10-880). Therefore, and taking into account the relatively large proportion of patients without concomitant IMMs (about 70% and 50 % in studies M10-877 and M10-880, respectively), and the fact that other than ciclosporin, IMMs were not approved for the treatment of uveitis at the time of this report, the CHMP agreed that limitation to last line treatment option was not needed. This position and the proposed indication was supported by the expert panel (see below).

The CHMP furthermore noted that the protocol pre-specified use of CS at the start of study M10-877 did not fully treatment initiation of Humira as monotherapy in active uveitis. In fact, the available limited data indicated a lower response rate if treatment was initiated with Humira alone; in the extension study, amongst the 25 patients with active uveitis at study entry and receiving adalimumab as monotherapy, only 13 (52%) patients achieved quiescence at Week 8. It is thus not known whether disease control with Humira alone would be obtained as rapidly as in combination with CS. Therefore, the CHMP was of the view that treatment with Humira should be initiated in combination with CS and/or with other non-biologic immunomodulatory agents. Once disease control has been achieved, Humira could continue in monotherapy. The CHMP agreed that the physician should determine the CS tapering schedule whereby the risk of CS-associated AEs should be balanced against the risk of flare-up. To ensure that the exposure of adalimumab has reached steady state, it was recommended that CS taper be started no earlier than 2 week after treatment initiation with Humira.

As previously discussed, the CHMP considered that there was sufficient support for a beneficial effect of Humira in the maintenance treatment of uveitis patients. Nevertheless, the CHMP considered that continuation of treatment should be re-evaluated by physicians on an annual basis taking into account the benefits and risks of long-term treatment.

Additional expert consultation

During the course of the procedure, the CHMP identified the need for expert input and thus an ad-hoc expert meeting was convened to address the following questions:

Question 1.

In the study including patients with non-infectious active uveitis (patients insufficiently controlled on ≥10 but ≤60 mg prednisolone/day), there was a statistically significant difference in time to treatment failure between Humira and placebo (5.6 versus 3 months). All components of the primary endpoint contributed to the results.

Please discuss the clinical relevance of this effect, as well as a possible corticosteroid sparing effect.

There was a general view amongst the experts that, based on the totality of the available data, a clinically relevant beneficial effect of Humira had been shown in the treatment of non-infectious uveitis. The observed effect size was considered modest. However at the same time, the composite primary endpoint, comprising new active lesions, anterior chamber cells, vitreous haze and visual acuity as criteria for treatment failure, was rather stringent and hard to meet, in particular considering the study population including difficult to treat patients. In that sense, the observed effect was considered more relevant. Other study outcomes, including the steroid sparing effect, were considered relevant, although it was noted that the corticosteroid tapering regimen in the study was rather aggressive. Further data may become available from the open-label extension study VISUAL III, in which the

conditions are closer to actual clinical practice. Finally, the experts highlighted the importance of the short time until onset of action of Humira, as rapid control of the inflammation is key in the treatment of active uveitis.

Questions were however raised if the proposed dosing regimen (80mg loading dose followed by 40mg every other week) was suboptimal and if better result could be achieved with a higher dose and/or dosing frequency. It was not considered self-evident that TNF-α inhibitors could be used for treatment of uveitis in the same way as for rheumatic disorders.

During the discussion, the occurrence of demyelinating events in patients receiving Humira was considered of concern and some experts stated that they would not use Humira in patients with demyelinating disease or signs of development of such disease including multiple sclerosis. Furthermore, it was stated that in clinical practice Humira is used together with immunosuppressants such as methotrexate. Concomitant use of immunosuppressants may be required to reduce the risk of development of anti-adalimumab antibodies.

Finally, while an obvious aim in uveitis therapy is the prevention/reduction of recurrences, the experts also highlighted that a reduction of the severity of the disease and of any recurrence was of relevance. In this context it would be interesting to explore if in the clinical studies, uveitis flares were milder in patients treated with Humira compared to placebo.

Question 2.

In the study examining patients with inactive uveitis, there was also a statistically significant effect favouring Humira over placebo with respect to time to treatment failure. However, in this study the effect was driven only by a difference in visual acuity while no statistical significant difference was observed for other components of the primary endpoint or for the ranked secondary endpoints.

a. *Please discuss the clinical relevance and plausibility of these results based on current knowledge with respect to the extent and temporal pattern of loss of visual acuity in patients with non-infectious inactive uveitis.*

b. *Taking the results into account as well as current clinical praxis, please discuss adequate duration of treatment in patients with inactive uveitis.*

With regards to the demonstration of a treatment effect for Humira, the experts considered the totality of the available data from the clinical development program and their experience with Humira in clinical practice. Based on this, the experts considered that a clinically relevant effect for Humira had been robustly demonstrated. With regards to the study in patients with inactive uveitis (VISUAL II), analyses of the course of the disease for individual patients, who experienced treatment failure because of loss of vision (loss of best corrected visual acuity ≥ 15 letters) showed a correlation with the worsening of the other components of the composite primary endpoint in the majority of cases. The secondary study endpoints furthermore did not account for time and the delay in disease progression/vision loss observed with Humira compared to placebo. One expert suggested that occurrence of cystoid macular oedema could theoretically explain the observed loss in vision as main driver of treatment failure, but this was not supported by the data.

It was also pointed out that the study population was representative of patients with less severe disease, reflecting broader clinical practice. The clinical relevance of a treatment option with rapid onset of action to prevent visual threatening sequelae was reiterated and one expert stated that in his experience, Humira also improves quality of life of patients seeing that subcutaneous injections can be self-administered, i.e. at home rather than requiring presentation in a ward.

With regards to treatment duration, the experts agreed that there was a need for regular check-ups of the patients and that re-evaluation of treatment continuation on a yearly basis was reasonable. As uveitis is a chronic disease, long-term treatment may be needed, possibly life-long. In this context, the experience with Humira in the treatment of arthritis and other rheumatic and inflammatory diseases was considered reassuring with regards to the safety of its long-term use.

Question 3.

The proposed indication for Humira (treatment of non-infectious intermediate, posterior and panuveitis in adult patients) could be interpreted as including treatment both as monotherapy and combination therapy as well as all patients with all types of uveitis (e.g. acute, recurrent, chronic). Please discuss the potential, adequate place in therapy for Humira, taking into consideration current standard of care, the characteristics of patients included in the pivotal clinical trials as well as the results of these trials.

The experts agreed with the revised proposal for the indication by the company as further amended by the Rapporteurs limiting the use of Humira to uveitis patients who have had an inadequate response to corticosteroids, in need of corticosteroid-sparing, or in whom corticosteroid treatment is inappropriate. The majority of the experts saw Humira as a second or third line treatment option after use of corticosteroids and immunosuppressants.

At the same time a trend was noticed, whereby biologics are increasingly used earlier in therapy as more experience is gained in their use and safety profiles. In clinical practice, there is a need to tailor treatment to individual patients and some experts would even considered Humira for very severe diseases (e.g. Behçet disease) as first line treatment option.

Finally, as previously discussed, it was noted that Humira should not be used in patients with developing or pre-existing demyelinating disease and that concomitant use of immunosuppressants is preferred to reduce the risk of development of anti-adalimumab antibodies.

2.4.5. Conclusions on the clinical efficacy

Based on the data presented in support of this application, the CHMP was of the view that a modest, but clinical relevant effect of Humira in the treatment of adult patients with non-infectious intermediate, posterior and pan-uveitis had been robustly demonstrated. Taking into account the conditions under which Humira has been studied, as well as current clinical practice and the views expressed by an ad-hoc expert group, the CHMP was however of the view that use of Humira should be restricted to patients with inadequate response to corticosteroids, in need of corticosteroid-sparing, or in whom corticosteroid treatment is inappropriate.

Taken together, the CHMP concluded that the available clinical efficacy data were adequate to support this application subject to s limitations in use as discussed above. As the proposed dose regimen might not be sufficient to achieve maximum efficacy, the CHMP recommended that a weekly 40 mg dosing regimen should be further explored post-approval by the MAH.

2.5. Clinical safety

2.5.1. Introduction

The adalimumab clinical development program in uveitis includes 2 pivotal, randomized, double-masked, placebo-controlled studies (studies M10-877 and M10-880) and 1 open-label extension study (study M11-327). In addition, separate sub-studies in Japanese patients were conducted for studies M10-877 and M10-880. For a more detailed description of the study design and methods, see section 2.4.2. and 2.4.3.

Safety analyses were performed within each study and integrated across studies. Safety was assessed by adverse events (AEs) including AEs of special interest (AESIs), physical examination, vital signs, and laboratory data.

The following analysis sets were used for the safety analysis:

- The Placebo-Controlled Analysis Set: All subjects who received at least 1 dose of randomized double-masked adalimumab (N = 250) or placebo (N = 250) in study M10-877 or study M10-880. This set was meant to allow for an assessment of the short- term safety profile for adalimumab, with focus on the comparison between the adalimumab versus placebo group.
- The All Adalimumab Analysis Set: All subjects who received at least 1 dose of adalimumab (double masked or open label) in studies M10-877, M10-880 or M11-327. This set was meant to allow for an assessment of long-term safety profile for adalimumab, from first dose through last available observation.

All AE summaries/analyses include treatment-emergent AEs (TEAEs) only. A TEAE was defined as:

- Placebo-Controlled Analysis Set: Any event with onset or worsening at or after the first dosing date, and
    - before first application of open-label study drug in the extension study or up to 70 days after the last double-masked study drug injection (whatever is the earliest) for subjects who rolled over into the open-label extension study, or
    - up to 70 days after the last double-masked study drug injection for subjects who did not roll over in the open label extension study.
- All Adalimumab Analysis Set: Any event with onset or worsening at or after the first dose of adalimumab treatment and up to 70 days (equivalent to 5 half-lives of adalimumab) after the last study drug injection or until the data cut-off date in Study M11-327, whatever is the earliest.

For each AE category presented, a comparison between treatment groups of the percentage of subjects experiencing at least one such AE was performed using Fisher's exact test. Only p values ≤ 0.100 when rounded to three digits were presented.

The safety assessment also took into account that the AE profile of Humira has already been extensively characterised in previous development programmes and post-marketing: The most commonly reported adverse reactions of Humira are infections (such as nasopharyngitis, upper respiratory tract infection and sinusitis), injection site reactions (erythema, itching, haemorrhage, pain or swelling), headache and musculoskeletal pain. Serious infections, including sepsis, due to bacterial, mycobacterial, invasive fungal, parasitic, viral, or other opportunistic infections such as listeriosis,

legionellosis and pneumocystis have also been reported in patients receiving Humira. In addition, serious haematological, neurological and autoimmune reactions have been reported. These include rare reports of pancytopenia, aplastic anaemia, central and peripheral demyelinating events and reports of lupus, lupus-related conditions and Stevens-Johnson syndrome. Finally, in the controlled portions of clinical trials of TNF-antagonists, more cases of malignancies including lymphoma have been observed among patients receiving a TNF-antagonist compared with control patients. However, the occurrence was rare. In the post marketing setting, cases of leukaemia have been reported in patients treated with a TNF-antagonist.

2.5.2. Patient exposure

Patient exposure is summarised by analysis set in the below two tables.

Table 31 - Extent of Exposure (Placebo-Controlled Analysis Set)

Exposure	Placebo N = 250	Adalimumab N = 250	Total N = 500
Total number of doses received			
Mean ± SD	14.1 ± 11.72	18.7 ± 13.54	16.4 ± 12.86
Median (min – max)	10.0 (2.0 – 42.0)	13.5 (2.0 – 43.0)	11.0 (2.0 – 43.0)
Treatment compliance (%)			
Mean ± SD	92.2 ± 7.44	92.8 ± 9.41	92.5 ± 8.48
Median (min – max)	93.8 (56.9 – 116.7)	95.2 (20.1 – 102.9)	94.2 (20.1 – 116.7)
Duration of treatment (days)			
Mean ± SD	175.0 ± 165.57	241.6 ± 191.07	208.3 ± 181.68
Median (min – max)	105.0 (6 – 585)	166.5 (14 – 576)	132.5 (6 – 585)

Mean duration of study drug exposure was longer for subjects in the adalimumab group versus the placebo group in the Placebo-Controlled Analysis Set. The majority of the subjects were treated up to 32 weeks (147 subjects, 58.8%). More subjects in the adalimumab group were treated longer than 561 days (33 patients) than those in the placebo group (13 patients). The shorter duration of exposure in the placebo group can be attributed to the fact that more subjects in the placebo group experienced treatment failures earlier during the studies, leading to earlier treatment discontinuation. Treatment compliance was higher than 90% in the adalimumab and placebo groups.

Table 32 - Extent of Exposure (All Adalimumab Analysis set)

Exposure	Adalimumab (N = 464)
Total number of doses received	
Mean ± SD	41.1 ± 28.63
Median (min – max)	34.5 (1.0 – 122.0)
Treatment compliance (%)	
Mean ± SD	93.4 ± 11.69
Median (min – max)	97.5 (16.5 – 106.1)
Duration of treatment (weeks)	
Mean ± SD	81.1 ± 57.58
Median (min – max)	68.1 (1.6 – 243.4)

In the All Adalimumab Analysis Set, mean duration of exposure to adalimumab was 81.1 weeks. A total of 384 subjects were treated with adalimumab for > 24 weeks, 302 subjects for > 48 weeks, and 24 subjects (5.2%) for > 192 weeks. Cumulative treatment exposure in the All Adalimumab Analysis Set was 721.4 patient-years (PY). In the All Adalimumab Analysis Set, median treatment compliance was approximately 97%.

As of 30 April 2015, 299 patients who completed the initial studies (M10-877 and M10-880) are ongoing in Study M11-327. The proportion of subjects in the placebo-controlled studies that rolled over to the open-label study was 84.5%.

Subject disposition in the Placebo-Controlled and All Adalimumab Analysis Sets are shown in Table 33.

Table 33 - Subject Disposition

	Placebo-Controlled Analysis Set			All ADA Set
Subjects Who:	Placebo N = 250	Adalimumab N = 250	Total N = 500	Adalimumab (N = 464)
Premature discontinuation of study				
Yes	26 (10.4)	33 (13.2)	59 (11.8)	156 (33.6)
No	224 (89.6)	217 (86.8)	441 (88.2)	9 (1.9)
Ongoing				299 (64.4)
Premature discontinuation due to (any reason)[a]				
TEAE	10 (4.0)	21 (8.4)	31 (6.2)	71 (15.3)
Lack of efficacy	6 (2.4)	1 (0.4)	7 (1.4)	31 (6.7)
Withdrew consent	3 (1.2)	4 (1.6)	7 (1.4)	19 (4.1)
Lost to follow-up	3 (1.2)	4 (1.6)	7 (1.4)	9 (1.9)
Other	8 (3.2)	7 (2.8)	15 (3.0)	47 (10.1)

TEAE = Treatment-emergent adverse event
Four subjects who discontinued due to treatment failure also had an AE leading to discontinuation. These 4 subjects (2 adalimumab and 2 placebo) were considered completers and were not counted under premature discontinuation due to the TEAE category presented in this table.
Notes: Subjects who discontinued 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. Subjects who did not prematurely discontinue include: 1) subjects who discontinued due to treatment failure, 2) subjects who completed Week 80 without treatment failure, and 3) subjects who had to terminate the study because the planned number of treatment failures was reached.

- Demographic Characteristics

The baseline demographics and main diagnostic and disease characteristics for the two pivotal phase 3 trials are summarised in Table 10 and Table 11. The majority of subjects treated with adalimumab were female (59.4%) and white, with a mean age of 43 years.

Approximately half of all subjects in the Placebo-Controlled Analysis Set were diagnosed with panuveitis, while approximately 30% were diagnosed with posterior uveitis and approximately 20% with intermediate uveitis. No statistically significant differences were observed between adalimumab and placebo treatment groups with regards to Baseline demographics or disease characteristics. The study population included 52.8% subjects with isolated uveitis (idiopathic, Birdshot choriodopathy, and multifocal choroiditis and panuveitis) and 38.2% of patients with uveitis associated with systemic manifestations (VKH, Behçet's disease and sarcoidosis).

In the All Adalimumab Analysis Set, eye disease/disorder (50.2%), hypertension (25.6%) and hyperlipidemia (12.5%) were the most commonly reported conditions/diagnoses during medical history data collection. A small percentage of All Adalimumab Analysis Set had a medical history of diabetes mellitus (5.2%), osteoarthritis (6.0%) and osteoporosis (5.4%).

Previous and concomitant medication is summarised in section 2.4.2.2.

2.5.3. Adverse events (AEs)

An overview of treatment-emergent adverse events (TEAEs) reported in the uveitis clinical development program is provided in Table below. A TEAE was defined as any adverse event with onset or worsening at or after the first dosing date.

Table 34 - Overview of Subjects with TEAEs (Placebo-Controlled and All Adalimumab Analysis Sets)

	Placebo-Controlled Analysis Set					All Adalimumab Analysis Set	
	Placebo (N = 250) (PYs = 119.76)		Adalimumab (N = 250) (PYs = 165.39)			Adalimumab (N = 464) (PYs = 721.43)	
Category	n (%)	E (E/100 PYs)	n (%)	E (E/100 PYs)	*P* value[a]	n (%)	E (E/100 PYs)
Any TEAE	201 (80.4)	1148 (958.6)	218 (87.2)	1581 (955.9)	0.052	423 (91.2)	4290 (594.6)
Any TEAE at least possibly related to placebo/adalimumab[b]	88 (35.2)	194 (162.0)	113 (45.2)	359 (217.1)	0.028	241 (51.9)	921 (127.7)
Any TEAE at least possibly related to prednisone[b]	105 (42.0)	239 (199.6)	116 (46.4)	326 (197.1)		119 (25.6)	330 (45.7)
Any severe TEAE	19 (7.6)	31 (25.9)	26 (10.4)	39 (23.6)		80 (17.2)	155 (21.5)
Any SAE	16 (6.4)	18 (15.0)	25 (10.0)	34 (20.6)		85 (18.3)	143 (19.8)
Any SAE at least possibly related to placebo/adalimumab[b]	4 (1.6)	5 (4.2)	9 (3.6)	9 (5.4)		30 (6.5)	38 (5.3)
Any SAE at least possibly related to prednisone[b]	6 (2.4)	7 (5.8)	3 (1.2)	3 (1.8)		3 (0.6)	3 (0.4)
Any TEAE leading to discontinuation of placebo/adalimumab	12 (4.8)	13 (10.9)	23 (9.2)	26 (15.7)	0.078	73 (15.7)	86 (11.9)
Any AE leading to death	0	0	2 (0.8)	3 (1.8)		3 (0.6)	4 (0.6)
Death[c]	0	0	2 (0.8)	2 (1.2)		3 (0.6)	3 (0.4)

[a.] P value for comparisons between placebo and adalimumab using Fisher's exact test. Only P values ≤ 0.100 are presented.
[b.] As assessed by the investigator.
[c.] Two subjects died during the placebo-controlled double-masked studies due to TEAEs. One additional subject included in the Placebo-Controlled Analysis Set died due to a TEAE experienced in Study M11-327. For clarity, this additional death was not presented for the Placebo-Controlled Analysis Set in the table above.

In the Placebo-Controlled Analysis Set, 80% and 87% of subjects in the Placebo-Controlled Analysis Set receiving placebo and adalimumab, respectively, experienced ≥1 TEAE. In the All Adalimumab Analysis Set, approximately 90% experienced ≥1 TEAE. There was an increase in the reporting of any TEAE possibly related drug, any SAE and any TEAE leading to discontinuation in adalimumab treated subjects in the Placebo-Controlled Analysis Set with exposure time.

Common AEs

An overview of the most common TEAEs reported by at least 2% of the subjects in either treatment group is provided in Table 34.

The most common TEAEs with an incidence >10% were nasopharyngitis, arthralgia, headache and fatigue in the Placebo-Controlled Analysis Set. There was a higher incidence of nasopharyngitis (17.6% versus 12.4%), arthralgia (15.2% versus 10.0%) and fatigue (10.4% versus 6.8%) in the adalimumab group compared to placebo. There was a statistically significant ($p<0.05$) higher frequency for adalimumab-treated patients compared to placebo for anxiety (4.4% vs 0.8%), paraesthesia (4.0% vs 0.4%), and rash pustular (2.4% vs 0%). Pustular rash was reported by 6 subjects (2.4%) in the adalimumab group compared to none in the placebo group in the Placebo-Controlled Analysis Set.

Table 35 - TEAEs Reported in ≥ 2% of Subjects in Either Treatment Group in the Placebo-Controlled Analysis Set by MedDRA PT by Adalimumab Exposure-Adjusted Incidence Rate (Placebo-Controlled and All Adalimumab

	Placebo-Controlled Analysis Set					All Adalimumab Analysis Set	
	Placebo (N = 250) (PYs = 119.76)		Adalimumab (N = 250) (PYs = 165.39)			Adalimumab (N = 464) (PYs = 721.43)	
MedDRA PT	n (%)	E (E/100 PYs)	n (%)	E (E/100 PYs)	*P* value[a]	n (%)	E (E/100 PYs)
Subjects with any TEAE	201 (80.4)	1148 (958.6)	218 (87.2)	1581 (955.9)		423 (91.2)	4290 (594.6)
Nasopharyngitis	31 (12.4)	42 (35.1)	44 (17.6)	61 (36.9)		114 (24.6)	191 (26.5)
Arthralgia	25 (10.0)	34 (28.4)	38 (15.2)	46 (27.8)		81 (17.5)	110 (15.2)
Headache	33 (13.2)	39 (32.6)	30 (12.0)	44 (26.6)		73 (15.7)	104 (14.4)
Fatigue	17 (6.8)	19 (15.9)	26 (10.4)	29 (17.5)		53 (11.4)	58 (8.0)
Urinary tract infection	11 (4.4)	15 (12.5)	21 (8.4)	27 (16.3)	0.099	50 (10.8)	63 (8.7)
Back pain	10 (4.0)	11 (9.2)	19 (7.6)	21 (12.7)		31 (6.7)	36 (5.0)
Injection site pain	13 (5.2)	13 (10.9)	10 (4.0)	21 (12.7)		19 (4.1)	36 (5.0)
Insomnia	11 (4.4)	11 (9.2)	18 (7.2)	21 (12.7)		24 (5.2)	32 (4.4)
Uveitis	17 (6.8)	19 (15.9)	20 (8.0)	21 (12.7)		93 (20.0)	153 (21.2)
Cough	10 (4.0)	11 (9.2)	18 (7.2)	20 (12.1)		42 (9.1)	45 (6.2)
Eye pain	8 (3.2)	11 (9.2)	18 (7.2)	20 (12.1)	0.068	36 (7.8)	42 (5.8)
Sinusitis	6 (2.4)	12 (10.0)	12 (4.8)	16 (9.7)		29 (6.3)	38 (5.3)
Upper respiratory tract infection	7 (2.8)	8 (6.7)	15 (6.0)	16 (9.7)		45 (9.7)	57 (7.9)
ALT increased	3 (1.2)	4 (3.3)	10 (4.0)	15 (9.1)	0.088	22 (4.7)	29 (4.0)
Visual acuity reduced	12 (4.8)	13 (10.9)	10 (4.0)	15 (9.1)		30 (6.5)	43 (6.0)
Anxiety	2 (0.8)	2 (1.7)	11 (4.4)	14 (8.5)	0.021	18 (3.9)	23 (3.2)
Pain in extremity	5 (2.0)	8 (6.7)	12 (4.8)	14 (8.5)		26 (5.6)	29 (4.0)
Vision blurred	8 (3.2)	8 (6.7)	12 (4.8)	14 (8.5)		28 (6.0)	32 (4.4)
Nausea	16 (6.4)	20 (16.7)	10 (4.0)	13 (7.9)		33 (7.1)	45 (6.2)
AST increased	2 (0.8)	3 (2.5)	9 (3.6)	12 (7.3)	0.063	23 (5.0)	29 (4.0)
Cystoid macular oedema	13 (5.2)	24 (20.0)	10 (4.0)	12 (7.3)		37 (8.0)	58 (8.0)
Injection site erythema	1 (0.4)	1 (0.8)	5 (2.0)	12 (7.3)		11 (2.4)	28 (3.9)
Muscle spasms	5 (2.0)	6 (5.0)	9 (3.6)	12 (7.3)		22 (4.7)	26 (3.6)
Myalgia	4 (1.6)	4 (3.3)	11 (4.4)	12 (7.3)		25 (5.4)	30 (4.2)
Bronchitis	10 (4.0)	11 (9.2)	10 (4.0)	11 (6.7)		33 (7.1)	38 (5.3)
Hypertension	6 (2.4)	7 (5.8)	11 (4.4)	11 (6.7)		26 (5.6)	27 (3.7)
Paraesthesia	1 (0.4)	1 (0.8)	10 (4.0)	11 (6.7)	0.011	18 (3.9)	26 (3.6)
Pruritus	6 (2.4)	6 (5.0)	10 (4.0)	11 (6.7)		21 (4.5)	23 (3.2)
Pyrexia	8 (3.2)	8 (6.7)	10 (4.0)	11 (6.7)		27 (5.8)	30 (4.2)
Hyperhidrosis	3 (1.2)	3 (2.5)	9 (3.6)	10 (6.0)		11 (2.4)	13 (1.8)
Oropharyngeal pain	8 (3.2)	8 (6.7)	10 (4.0)	10 (6.0)		27 (5.8)	32 (4.4)
Pharyngitis	3 (1.2)	6 (5.0)	8 (3.2)	10 (6.0)		19 (4.1)	22 (3.0)
Rash	9 (3.6)	10 (8.3)	9 (3.6)	10 (6.0)		23 (5.0)	25 (3.5)
Vitreous floaters	10 (4.0)	12 (10.0)	10 (4.0)	10 (6.0)		27 (5.8)	30 (4.2)
Dry eye	12 (4.8)	13 (10.9)	9 (3.6)	9 (5.4)		20 (4.3)	24 (3.3)
Dyspnoea	7 (2.8)	7 (5.8)	8 (3.2)	9 (5.4)		11 (2.4)	13 (1.8)
Intraocular pressure increased	4 (1.6)	4 (3.3)	9 (3.6)	9 (5.4)		22 (4.7)	30 (4.2)
Oedema peripheral	3 (1.2)	3 (2.5)	9 (3.6)	9 (5.4)		15 (3.2)	18 (2.5)
Palpitations	2 (0.8)	2 (1.7)	8 (3.2)	9 (5.4)		11 (2.4)	15 (2.1)
Abdominal pain	5 (2.0)	5 (4.2)	6 (2.4)	8 (4.8)		11 (2.4)	14 (1.9)
Epistaxis	1 (0.4)	1 (0.8)	7 (2.8)	8 (4.8)	0.068	11 (2.4)	13 (1.8)
Joint swelling	3 (1.2)	3 (2.5)	6 (2.4)	8 (4.8)		11 (2.4)	13 (1.8)

	Placebo-Controlled Analysis Set					All Adalimumab Analysis Set	
	Placebo (N = 250) (PYs = 119.76)		Adalimumab (N = 250) (PYs = 165.39)			Adalimumab (N = 464) (PYs = 721.43)	
MedDRA PT	n (%)	E (E/100 PYs)	n (%)	E (E/100 PYs)	*P* value[a]	n (%)	E (E/100 PYs)
Arthritis	4 (1.6)	4 (3.3)	5 (2.0)	7 (4.2)		9 (1.9)	11 (1.5)
Erythema	6 (2.4)	6 (5.0)	7 (2.8)	7 (4.2)		18 (3.9)	18 (2.5)
Injection site rash	1 (0.4)	1 (0.8)	7 (2.8)	7 (4.2)	0.068	15 (3.2)	17 (2.4)
Peripheral swelling	3 (1.2)	3 (2.5)	5 (2.0)	7 (4.2)		11 (2.4)	13 (1.8)
Posterior capsule opacification	2 (0.8)	2 (1.7)	5 (2.0)	7 (4.2)		13 (2.8)	15 (2.1)
Abdominal pain upper	6 (2.4)	6 (5.0)	6 (2.4)	6 (3.6)		15 (3.2)	17 (2.4)
Alopecia	9 (3.6)	9 (7.5)	6 (2.4)	6 (3.6)		21 (4.5)	21 (2.9)
Blood creatinine increased	5 (2.0)	5 (4.2)	6 (2.4)	6 (3.6)		8 (1.7)	9 (1.2)
Blood pressure increased	1 (0.4)	1 (0.8)	5 (2.0)	6 (3.6)		6 (1.3)	7 (1.0)
Conjunctivitis	4 (1.6)	4 (3.3)	6 (2.4)	6 (3.6)		16 (3.4)	16 (2.2)
Conjunctivitis allergic	4 (1.6)	5 (4.2)	6 (2.4)	6 (3.6)		20 (4.3)	24 (3.3)
Dizziness	7 (2.8)	11 (9.2)	5 (2.0)	6 (3.6)		12 (2.6)	14 (1.9)
Dry mouth	3 (1.2)	3 (2.5)	6 (2.4)	6 (3.6)		7 (1.5)	8 (1.1)
Gastroenteritis	2 (0.8)	3 (2.5)	6 (2.4)	6 (3.6)		15 (3.2)	17 (2.4)
Malaise	4 (1.6)	4 (3.3)	6 (2.4)	6 (3.6)		9 (1.9)	9 (1.2)
Musculoskeletal stiffness	5 (2.0)	5 (4.2)	6 (2.4)	6 (3.6)		10 (2.2)	11 (1.5)
Neck pain	4 (1.6)	4 (3.3)	5 (2.0)	6 (3.6)		8 (1.7)	10 (1.4)
Oral herpes	1 (0.4)	1 (0.8)	5 (2.0)	6 (3.6)		12 (2.6)	14 (1.9)
Rash pustular	0	0	6 (2.4)	6 (3.6)	0.030	10 (2.2)	10 (1.4)
Tinnitus	5 (2.0)	5 (4.2)	5 (2.0)	6 (3.6)		6 (1.3)	8 (1.1)
Tremor	1 (0.4)	1 (0.8)	6 (2.4)	6 (3.6)		6 (1.3)	7 (1.0)
Vomiting	8 (3.2)	11 (9.2)	6 (2.4)	6 (3.6)		11 (2.4)	19 (2.6)
Acne	9 (3.6)	9 (7.5)	5 (2.0)	5 (3.0)		9 (1.9)	10 (1.4)
Cataract	6 (2.4)	9 (7.5)	4 (1.6)	5 (3.0)		25 (5.4)	32 (4.4)
Contusion	8 (3.2)	9 (7.5)	5 (2.0)	5 (3.0)		7 (1.5)	7 (1.0)
Diabetes mellitus	0	0	5 (2.0)	5 (3.0)	0.061	9 (1.9)	11 (1.5)
Diarrhoea	12 (4.8)	15 (12.5)	5 (2.0)	5 (3.0)		23 (5.0)	26 (3.6)
Ligament sprain	0	0	5 (2.0)	5 (3.0)	0.061	9 (1.9)	9 (1.2)
Muscular weakness	0	0	5 (2.0)	5 (3.0)	0.061	7 (1.5)	10 (1.4)
Nasal congestion	3 (1.2)	4 (3.3)	5 (2.0)	5 (3.0)		10 (2.2)	10 (1.4)
Weight increased	2 (0.8)	2 (1.7)	5 (2.0)	5 (3.0)		8 (1.7)	8 (1.1)
Conjunctival haemorrhage	5 (2.0)	5 (4.2)	3 (1.2)	4 (2.4)		14 (3.0)	17 (2.4)
Dyspepsia	7 (2.8)	9 (7.5)	4 (1.6)	4 (2.4)		12 (2.6)	13 (1.8)
Influenza	13 (5.2)	14 (11.7)	4 (1.6)	4 (2.4)	0.045	23 (5.0)	30 (4.2)
Injection site bruising	5 (2.0)	5 (4.2)	4 (1.6)	4 (2.4)		8 (1.7)	9 (1.2)
Migraine	5 (2.0)	6 (5.0)	4 (1.6)	4 (2.4)		10 (2.2)	10 (1.4)
Eye pruritus	5 (2.0)	5 (4.2)	2 (0.8)	3 (1.8)		4 (0.9)	5 (0.7)
Photophobia	6 (2.4)	6 (5.0)	1 (0.4)	1 (0.6)		6 (1.3)	6 (0.8)

[a)] P value for comparisons between placebo and adalimumab using Fisher's exact test. Only P values ≤ 0.100 are presented.

Serious adverse event / deaths / other significant events

- Serious adverse events

There were only few serious TEAE and the majority were reported in single subjects in the Placebo-Controlled Analysis Set. In the Placebo-Controlled Analysis Set, more subjects in the adalimumab group reported serious TEAEs (25/250, 10%) compared to placebo (16/250, 6.4%). In the All Adalimumab Analysis Set, serious TEAEs reported by 2 or more subjects included: uveitis (6 subjects, 1.3%), pneumonia (5 subjects, 1.1%), cataract (4 subjects, 0.9%), and urinary tract infection and obesity (3 subjects each, 0.6%). Furthermore, demyelination, tuberculosis, basal cell carcinoma,

retinal detachment, visual acuity reduced, and vitreous haemorrhage were each reported by 2 subjects (0.4%) in the All Adalimumab Analysis Set.

- Deaths

Three subjects died in the uveitis clinical development program. None of the events were considered related to adalimumab by the investigator.

- Other significant events

Other significant TEAEs include those leading to discontinuation of study drug (see dedicated section below) and those of special interest.

The TEAS of special interest for the uveitis clinical development program defined by the Applicant were

- Non-ocular events: infections, malignancies, immunological reactions, demyelinating disorders, haematological events including pancytopenia, hepatological events, and injection site reactions;
- Ocular events: uveitis related events, intraocular pressure (IOP) increased, and lens opacity.

Non ocular events

Infections

In the Placebo-Controlled Analysis Set, significantly more subjects in the adalimumab group reported infection TEAEs versus placebo (p = 0.004) for a total of 48.8% and 35.6% of subjects in the adalimumab and placebo groups, respectively. Exposure-adjusted incidence rates of subjects with any infection TEAE were similar for the adalimumab and placebo groups (146.9 and 143.6 events (E)/100 patient years [PYs], respectively, see Table 35).

The most frequently reported TEAE (>10%) were nasopharyngitis (24.6%), and urinary tract infection (10.8%) in the All Adalimumab Analysis Set.

Serious infections were reported in 7 subjects (2.8% and 4.8 E/100 PYs) in the adalimumab group and in 4 subjects (1.6% and 4.2 E/100 PYs) in the placebo group in the Placebo-Controlled Analysis Set. In the All Adalimumab Analysis Set 27 subjects reported serious infections (5.8% and 4.6 E/100PY).

There were no cases of opportunistic infections (excluding tuberculosis) reported in the Placebo-Controlled Analysis Set. In the All Adalimumab Set, 2 cases (0.4%, 0.3 E/100PYs) were reported.

In the Placebo-Controlled Analysis Set, there were 5 cases of treatment-emergent tuberculosis in the adalimumab group (2.0%, 3.0E/100PYs) including 1 case of active tuberculosis and 4 cases of latent tuberculosis. In the placebo group, there was 1 case of latent tuberculosis. In the All Adalimumab Analysis Set, 2 subjects treated with adalimumab reported treatment-emergent active tuberculosis (0.3 E/100 PYs) and 17 subjects reported treatment-emergent latent tuberculosis. Of the 17 subjects with latent tuberculosis, 12 subjects reported mycobacterium tuberculosis complex test positive and 4 subjects reported tuberculin test positive.

In the uveitis clinical development program, initially, subjects with latent tuberculosis were allowed to enrol. Subsequently the protocols were amended to exclude subjects with previous and latent tuberculosis (as well as active tuberculosis) to avoid potential confounding effects of tuberculosis prophylactic medications. Thus, the number of tuberculosis conversions reported was higher compared to previous clinical studies for other indications.

Table 36 – Treatment-Emergent Infections Reported in ≥ 2 Subjects in Either Treatment Group in the Placebo-Controlled Analysis Set by MedDRA PT (Placebo-Controlled and All Adalimumab Analysis Sets)

	Placebo-Controlled Analysis Set				All ADA Analysis Set	
	Placebo (N = 250) (PYs = 119.76)		Adalimumab (N = 250) (PYs = 165.39)		Adalimumab (N = 464) (PYs = 721.43)	
MedDRA PT	n (%)	E (E/100 PYs)	n (%)	E (E/100 PYs)	n (%)	E (E/100 PYs)
Subjects with any infection TEAE	89 (35.6)	172 (143.6)	122 (48.8)	243 (146.9)	275 (59.3)	763 (105.8)
Nasopharyngitis	31 (12.4)	42 (35.1)	44 (17.6)	61 (36.9)	114 (24.6)	191 (26.5)
Urinary tract infection[a]	11 (4.4)	15 (12.5)	21 (8.4)	27 (16.3)	50 (10.8)	63 (8.7)
Upper respiratory tract infection	7 (2.8)	8 (6.7)	15 (6.0)	16 (9.7)	45 (9.7)	57 (7.9)
Sinusitis	6 (2.4)	12 (10.0)	12 (4.8)	16 (9.7)	29 (6.3)	38 (5.3)
Bronchitis	10 (4.0)	11 (9.2)	10 (4.0)	11 (6.7)	33 (7.1)	38 (5.3)
Pharyngitis	3 (1.2)	6 (5.0)	8 (3.2)	10 (6.0)	19 (4.1)	22 (3.0)
Rash pustular[b]	0	0	6 (2.4)	6 (3.6)	10 (2.2)	10 (1.4)
Gastroenteritis	2 (0.8)	3 (2.5)	5 (2.0)	6 (3.6)	14 (3.0)	17 (2.4)
Oral herpes	1 (0.4)	1 (0.8)	5 (2.0)	6 (3.6)	12 (2.6)	14 (1.9)
Influenza[c]	13 (5.2)	14 (11.7)	4 (1.6)	4 (2.4)	23 (5.0)	30 (4.2)
Vulvovaginal candidiasis	1 (0.4)	2 (1.7)	4 (1.6)	4 (2.4)	5 (1.1)	5 (0.7)
Hordeolum	2 (0.8)	3 (2.5)	3 (1.2)	3 (1.8)	9 (1.9)	11 (1.5)
Rhinitis	0	0	3 (1.2)	3 (1.8)	8 (1.7)	9 (1.2)
Tinea versicolour	0	0	3 (1.2)	3 (1.8)	4 (0.9)	4 (0.6)
Fungal infection	0	0	2 (0.8)	2 (1.2)	3 (0.6)	3 (0.4)
Fungal skin infection	0	0	2 (0.8)	2 (1.2)	4 (0.9)	4 (0.6)
Gingivitis	1 (0.4)	1 (0.8)	2 (0.8)	3 (1.8)	4 (0.9)	6 (0.8)
Helicobacter infection	0	0	2 (0.8)	4 (2.4)	2 (0.4)	4 (0.6)
Iridocyclitis	2 (0.8)	2 (1.7)	2 (0.8)	4 (2.4)	14 (3.0)	21 (2.9)
Ophthalmic herpes simplex	0	0	2 (0.8)	3 (1.8)	3 (0.6)	5 (0.7)
Otitis externa	1 (0.4)	1 (0.8)	2 (0.8)	2 (1.2)	5 (1.1)	5 (0.7)
Periodontitis	0	0	2 (0.8)	2 (1.2)	2 (0.4)	2 (0.3)
Pharyngitis streptococcal	2 (0.8)	3 (2.5)	2 (0.8)	2 (1.2)	5 (1.1)	5 (0.7)
Pneumonia	0	0	2 (0.8)	2 (1.2)	8 (1.7)	9 (1.2)
Tinea pedis	0	0	2 (0.8)	2 (1.2)	2 (0.4)	2 (0.3)
Tonsillitis	1 (0.4)	1 (0.8)	2 (0.8)	4 (2.4)	9 (1.9)	13 (1.8)
Viral infection	1 (0.4)	1 (0.8)	2 (0.8)	2 (1.2)	5 (1.1)	5 (0.7)
Gastroenteritis viral	3 (1.2)	3 (2.5)	1 (0.4)	1 (0.6)	7 (1.5)	9 (1.2)
Laryngitis	3 (1.2)	3 (2.5)	1 (0.4)	1 (0.6)	5 (1.1)	6 (0.8)
Lower respiratory tract infection	3 (1.2)	3 (2.5)	1 (0.4)	1 (0.6)	3 (0.6)	3 (0.4)
Respiratory tract infection	3 (1.2)	3 (2.5)	0	0	9 (1.9)	9 (1.2)
Tinea infection	2 (0.8)	2 (1.7)	0	0	2 (0.4)	2 (0.3)
Tooth infection	2 (0.8)	2 (1.7)	0	0	5 (1.1)	5 (0.7)
Vaginal infection	2 (0.8)	2 (1.7)	0	0	0	0

[a.] P = 0.099.
[b.] P = 0.030.
[c.] P = 0.045.
Note: P value for comparisons between placebo and active using Fisher's exact test. Only P values ≤ 0.100 are presented.

Malignancies

In the All Adalimumab Analysis Set, 12 subjects reported malignancies in the uveitis clinical development program. Four events were reported in 4 adalimumab subjects during the double-masked studies. The remaining 8 events were reported during the open-label extension study, whereby 5 of those subjects were initially assigned to receive placebo during the double-masked studies. In the All Adalimumab Analysis Set, the rates of all malignancies, lymphoma, and non-melanoma skin cancer (NMSC) were 1.7, 0.1 and 0.7 events/100 PYs.

Table 37 - Treatment-Emergent Malignancies by MedDRA PT (Placebo-Controlled and All Adalimumab Analysis Set)

	Placebo-Controlled Analysis Set				All ADA Analysis Set	
	Placebo (N = 250) (PYs = 119.76)		Adalimumab (N = 250) (PYs = 165.39)		Adalimumab (N = 464) (PYs = 721.43)	
MedDRA PT	n (%)	E (E/100 PYs)	n (%)	E (E/100 PYs)	n (%)	E (E/100 PYs)
Any malignancy TEAE	0	0	4 (1.6)	4 (2.4)	12 (2.6)	12 (1.7)
Carcinoid tumour of the gastrointestinal tract	0	0	1 (0.4)	1 (0.6)	1 (0.2)	1 (0.1)
Glioblastoma multiforme	0	0	1 (0.4)	1 (0.6)	1 (0.2)	1 (0.1)
Lung adenocarcinoma stage IV	0	0	1 (0.4)	1 (0.6)	1 (0.2)	1 (0.1)
Squamous cell carcinoma of skin	0	0	1 (0.4)	1 (0.6)	1 (0.2)	1 (0.1)
Adenocarcinoma of colon	0	0	0	0	1 (0.2)	1 (0.1)
B-cell lymphoma	0	0	0	0	1 (0.2)	1 (0.1)
Basal cell carcinoma	0	0	0	0	3 (0.6)	3 (0.4)
Basosquamous carcinoma	0	0	0	0	1 (0.2)	1 (0.1)
Lobular breast carcinoma in situ	0	0	0	0	1 (0.2)	1 (0.1)
Rectal adenocarcinoma	0	0	0	0	1 (0.2)	1 (0.1)

Immunological reactions

A summary of the TEAEs immunological reactions reported by at least 2 subjects in either treatment group is provided in Table 37.

Table 38 - Treatment-Emergent Allergic Reactions Reported in ≥ 2 Subjects in Either Treatment Group in the Placebo-Controlled Analysis Set by MedDRA PT (Placebo-Controlled and All Adalimumab Analysis Sets)

	Placebo-Controlled Analysis Set				All ADA Analysis Set	
	Placebo (N = 250) (PYs = 119.76)		Adalimumab (N = 250) (PYs = 165.39)		Adalimumab (N = 464) (PYs = 721.43)	
MedDRA PT	n (%)	E (E/100 PYs)	n (%)	E (E/100 PYs)	n (%)	E (E/100 PYs)
Subjects with any immune reaction TEAE	13 (5.2)	17 (14.2)	15 (6.0)	21 (12.7)	32 (7.0)	38 (5.5)
Eye pruritus	4 (1.6)	5 (4.2)	2 (0.8)	3 (1.8)	2 (0.4)	5 (0.7)
Hypersensitivity	4 (1.6)	4 (3.3)	2 (0.8)	2 (1.2)	7 (1.5)	8 (1.1)
Pruritus allergic	2 (0.8)	3 (2.5)	2 (0.8)	2 (1.2)	3 (0.6)	3 (0.4)
Drug hypersensitivity	1 (0.4)	5 (4.2)	2 (0.8)	3 (1.8)	2 (0.4)	3 (0.4)
Urticaria	1 (0.4)	1 (0.8)	2 (0.8)	4 (2.4)	4 (0.9)	6 (0.8)
Pruritus generalised	0	0	2 (0.8)	2 (1.2)	4 (0.9)	4 (0.6)
Rash generalized	0	0	2 (0.8)	2 (1.2)	2 (0.4)	2 (0.3)
Asthma	2 (0.8)	3 (2.5)	0	0	3 (0.6)	3 (0.4)

Demyelinating disorders

A total of 6 subjects who received adalimumab reported events of demyelinating disorders or optic neuritis (ON) in the uveitis clinical development program. Among the 6 cases, 4 cases were reported as events of demyelination or multiple sclerosis (MS) and 2 events were reported as ON.

Table 39 - Treatment-Emergent Demyelinating Disorders by MedDRA PT (Placebo-Controlled and All Adalimumab Analysis Sets)

	Placebo-Controlled Analysis Set				All ADA Analysis Set	
	Placebo (N = 250) (PYs = 119.76)		Adalimumab (N = 250) (PYs = 165.39)		Adalimumab (N = 464) (PYs = 721.43)	
MedDRA PT	n (%)	E (E/100 PYs)	n (%)	E (E/100 PYs)	n (%)	E (E/100 PYs)
Subjects with any demyelinating disorder TEAE	0	0	1 (0.4)	1 (0.6)	6 (1.3)[a]	6 (0.8)
Demyelination	0	0	1 (0.4)	1 (0.6)	3 (0.6)	3 (0.4)
Multiple sclerosis	0	0	0	0	1 (0.2)	1 (0.1)
Optic neuritis	0	0	0	0	2 (0.4)	2 (0.3)

In the 2 cases of ON, the MRI did not show any lesions in the brain suggestive of central demyelinating disorders. Furthermore, in 1 of the 2 cases of ON, the TEAE occurred in a subject with Behçet-associated uveitis at Baseline and was reported as papillitis, which codes to the preferred term of ON. The MRI was normal and ruled out lesions suggestive of a demyelinating disease. Thus, the ON in this case likely was inflammation in the optic nerve associated with Behçet's disease. In the second ON case, no MRI or clinical findings of brain demyelination were noted with >2 years of follow-up.

The total exposure of the All Adalimumab Analysis Set was notably higher than the placebo group of the Placebo-Controlled Analysis Set (721.43 versus 119.76 PYs). The exposure adjusted incidence rates and the 95% CI for the placebo group of the Placebo-Controlled Analysis Set and the All Adalimumab Analysis Set were 0 (0.00 – 3.08) E/100 PYs and 0.83 (0.31 – 1.81) E/100 PYs, respectively, indicating widely overlapping confidence intervals (CIs).

The association between demyelinating disorders and uveitis, particularly in cohorts of patients with intermediate uveitis, has been described in the scientific literature. In patients with intermediate uveitis, estimated incidence of multiple sclerosis ranges from 1.5 – 3.4 E/100 PYs and estimated incidence of optic neuritis ranges from 0.5 – 1.0 E/100 PYs in the published literature (Malinowski et al., 1993; Raja et al., 1999; Prieto et al., 2001). Furthermore, an epidemiological study (study P150002) was conducted by the applicant using Truven Health MarketScan® claims database. The study utilized data from 2000 to 2014 with a total of 103,877 subjects enrolled. The data from the MarketScan® claims database study are consistent with the published literature in showing the highest incidence rate of demyelination/multiple sclerosis in the intermediate uveitis subtype. The results from the data analysis are presented in Table 39 below. For comparison, incidence rates based on the data from the uveitis clinical trial program are provided in Table 40.

Table 40 - Incidence Rates of Demyelinating Disorders and Optic Neuritis in Patients with Uveitis Based on Truven Health MarketScan® Data

	Incidence Rate (Cases/100 PYs)		
Patient Population	Demyelination/ Multiple Sclerosis	Optic Neuritis	Total
All uveitis[a]	0.40	0.33	0.71
Intermediate uveitis	0.81	0.28	1.00
Posterior uveitis	0.21	0.28	0.44
Panuveitis	0.34	0.38	0.75

[a] Incidence rates for all uveitis, including intermediate, posterior and panuveitis were standardized to the uveitis clinical trial patients on the type of uveitis.

Table 41 - Incidence Rates of Demyelinating Disorders and Optic Neuritis in Patients with Uveitis Reported in the Uveitis Clinical Development Program (All Adalimumab Analysis Set)

Disease Type	Exposure 100 PYs	Incidence Rate (E/100 PYs) (95% CI)		
		Demyelination / Multiple Sclerosis	Optic Neuritis	Total
All Uveitis	721.43	0.55 (0.15 – 1.42)	0.28 (0.03 – 1.00)	0.83 (0.31 – 1.81)
Intermediate uveitis	140.26	2.14 (0.44 – 6.25)	-	2.14 (0.44 – 6.25)
Posterior uveitis	200.45	-	1.00 (0.12 – 3.60)	1.00 (0.12 – 3.60)
Panuveitis	377.35	0.27 (0.01 – 1.48)	-	0.27 (0.01 – 1.48)

Haematological Events, including Pancytopenia

In the Placebo-Controlled Analysis Set, 4 adalimumab subjects and 1 placebo subject reported treatment-emergent haematologic events. In the All Adalimumab Analysis Set, 12 subjects reported hematologic events. None of the events were severe.

Hepatological Events

In the Placebo-Controlled Analysis Set, 2 adalimumab subjects and 1 placebo subject reported treatment-emergent hepatologic events. In the All Adalimumab Analysis Set, 5 subjects treated with adalimumab reported hepatologic events. All events were considered non serious.

Injection Site Reactions

A total of 12.4% and 8.8% of subjects in the adalimumab and placebo groups, respectively (representing 39.3 and 19.2 events/100 PYs, respectively), reported treatment-emergent injection site reactions (see Table 41).

Table 42 - Treatment-Emergent Injection Site Reactions Reported in ≥ 2 Subjects in Either Treatment Group in the Placebo-Controlled Analysis Set by MedDRA PT (Placebo-Controlled and All Adalimumab Analysis Sets)

	Placebo-Controlled Analysis Set				All ADA Set	
	Placebo (N = 250) (PYs = 119.76)		Adalimumab (N = 250) (PYs = 165.39)		Adalimumab (N = 464) (PYs = 721.43)	
MedDRA PT	n (%)	E (E/100 PYs)	n (%)	E (E/100 PYs)	n (%)	E (E/100 PYs)
Subjects with any injection site reaction TEAE	22 (8.8)	23 (19.2)	31 (12.4)	65 (39.3)	64 (13.8)	135 (18.7)
Injection site pain	13 (5.2)	13 (10.9)	10 (4.0)	21 (12.7)	19 (4.1)	36 (5.0)
Injection site rash[a]	1 (0.4)	1 (0.8)	7 (2.8)	7 (4.2)	15 (3.2)	17 (2.4)
Injection site erythema	1 (0.4)	1 (0.8)	5 (2.0)	12 (7.3)	11 (2.4)	28 (3.9)
Injection site bruising	5 (2.0)	5 (4.2)	4 (1.6)	4 (2.4)	8 (1.7)	9 (1.2)
Injection site swelling	0	0	4 (1.6)	5 (3.0)	7 (1.5)	9 (1.2)
Injection site reaction	1 (0.4)	1 (0.8)	2 (0.8)	4 (2.4)	4 (0.9)	9 (1.2)

a. $P = 0.068$.
Note: P value for comparisons between placebo and active using Fisher's exact test. Only P values ≤ 0.100 are presented.

a. P = 0.068.
Note: P value for comparisons between placebo and active using Fisher's exact test. Only P values ≤ 0.100 are presented.

Sarcoidosis

In the Placebo-Controlled Analysis Set, 6 adalimumab subjects (2.4%) and 2 placebo subjects (0.8%) reported an event of sarcoidosis. In the All Adalimumab Analysis Set, 8 subjects reported events of

sarcoidosis. Studies have shown that uveitis in patients with systemic sarcoidosis is common and the development of uveitis may precede the systemic symptoms and diagnosis of sarcoidosis for many years (Baughman et al., 2010 and Rizzato et al., 1996). Five of the events were considered to be worsening or aggravation of pre-existing underlying sarcoidosis.

Ocular events

Uveitis Related Adverse Events

In order to identify uveitis related AEs, the study results were adjudicated by a masked study designated physician to be either related or not related to uveitis before unmasking the study. An overview of the results is presented in Table 42.

Table 43 - Treatment-Emergent Uveitis-Related Adverse Events by AbbVie Adjudication Reported in ≥ 2 Subjects in Either Treatment Group in the Placebo-Controlled Analysis Set by MedDRA PT (Placebo-Controlled and All Adalimumab Analysis Sets)

	Placebo-Controlled Analysis Set				All ADA Set	
	Placebo (N = 250) (PYs = 119.76)		Adalimumab (N = 250) (PYs = 165.39)		Adalimumab (N = 464) (PYs = 721.43)	
MedDRA PT	n (%)	E (E/100 PYs)	n (%)	E (E/100 PYs)	n (%)	E (E/100 PYs)
Any uveitis-related TEAE (per investigator)	65 (26.0)	128 (106.9)	77 (30.8)	127 (76.8)	219 (47.2)	580 (80.4)
Any uveitis-related TEAE (per adjudication)	52 (20.8)	78 (65.1)	60 (24.0)	82 (49.6)	193 (41.6)	407 (56.4)
Uveitis	17 (6.8)	19 (15.9)	20 (8.0)	21 (12.7)	93 (20.0)	153 (21.2)
Eye pain[a]	8 (3.2)	11 (9.2)	17 (6.8)	20 (12.1)	35 (7.5)	42 (5.8)
Cystoid macular oedema	13 (5.2)	24 (20.0)	10 (4.0)	12 (7.3)	37 (8.0)	58 (8.0)
Vitreous floaters	6 (2.4)	12 (10.0)	6 (2.4)	10 (6.0)	18 (3.9)	30 (4.2)
Macular oedema	3 (1.2)	3 (2.5)	4 (1.6)	4 (2.4)	21 (4.5)	23 (3.2)
Iridocyclitis	2 (0.8)	2 (1.7)	4 (1.6)	4 (2.4)	17 (3.7)	21 (2.9)
Iris adhesions	2 (0.8)	2 (1.7)	2 (0.8)	2 (1.2)	2 (0.4)	2 (0.3)
Iritis	0	0	2 (0.8)	2 (1.2)	6 (1.3)	6 (0.8)
Macular fibrosis	0	1 (0.8)	2 (0.8)	2 (1.2)	4 (0.9)	5 (0.7)
Retinal detachment	2 (0.8)	2 (1.7)	1 (0.4)	1 (0.6)	5 (1.1)	7 (1.0)

[a.] P = 0.099.

Note: P value for comparisons between placebo and active using Fisher's exact test. Only P values ≤ 0.100 are presented.

In the Placebo-Controlled Analysis Set, 24.0% and 20.8% of subjects (representing 49.6 and 65.1 events/100 PYs) in the adalimumab and placebo groups, respectively, reported uveitis-related TEAEs per adjudication. A significantly higher proportion of subjects in the adalimumab group experienced eye pain compared to those in the placebo group (p = 0.099).

Intraocular pressure (IOP) increased

AEs associated with increased IOP were observed in 9 subjects (3.6%) in the adalimumab group and 4 subjects (1.6%) in the placebo group. All of these events were mild or moderate in severity. None of the events were considered to be related to adalimumab or placebo; the majority (5/9 in the adalimumab group and 3/4 in the placebo group) were possibly or probably related to prednisone. One subject reported a SAE of IOP increased. In the All Adalimumab Analysis Set, AEs of increased IOP were reported by 22 subjects (4.7%).

In the Placebo-Controlled Analysis Set, shifts towards increased IOP were observed generally with a similar incidence in both treatment groups. Increases in IOP in the worse eye from Baseline (0 - ≤ 30 mmHg) to > 30 mmHg were observed in 5 subjects in the adalimumab group and 3 subjects

in the placebo group. Increases in IOP in the better eye from Baseline (0 – ≤ 30 mmHg) to > 30 mmHg were observed in 1 subject in the adalimumab group and 2 subjects in the placebo group.

Lens opacity

In the Placebo-Controlled Analysis Set, 3 subjects in the adalimumab treatment group experienced a 2-step increase from Baseline to maximum in lens opacity in at least 1 eye in at least 1 of the 3 opacity variables (nuclear lens opacity grade, cortical lens opacity grade, posterior subcapsular lens opacity grade; no placebo subjects experienced a 2-step increase in lens opacity.

Laboratory findings

A greater percentage of adalimumab subjects experienced shifts in neutrophils from normal or high at Baseline to low at final visit (4.0% versus 0.4%).

There were small shifts from Baseline to maximum values observed in the Placebo-Controlled Analysis Set as well as in the All Adalimumab Analysis set in serum glutamic pyruvic transaminase/alanine aminotransferase and serum glutamic oxaloacetic transaminase/aspartate aminotransferase. Alanine aminotransferase elevations ≥ 3 x upper normal limit occurred in 2.4% of Humira-treated patients and 2.4% of control-treated patients.

Safety in special populations

- Intrinsic factors

The number and percentage of TEAEs, overall, by primary MedDRA System Organ Class (SOC), and by Preferred Term (PT) were assessed by the subgroups of sex, age, race, type of uveitis, and evidence of macular oedema. Relevant findings are summarised below.

Sub-group analyses were performed based on the age categories < 30 years of age; ≥30 to <50 years; and subjects ≥ 50 years. No clinically meaningful differences were observed when comparing subgroups in the Placebo-Controlled Analysis Set. The results in elderly are summarised below.

Among all race categories, a greater proportion of white subjects versus Asian and black subjects reported TEAEs of eye pain (8.1% versus 0 and 0), fatigue (13.0% versus 3.2% and 0), headache (11.9% versus 3.2% and 5.9%).

When analysing TEAEs by uveitis category, in the Placebo-Controlled Analysis Set, the adalimimab group showed a greater percentage of subjects with posterior uveitis and intermediate uveitis versus subjects with panuveitis who reported overall TEAEs (92.4% and 90.5% versus 82.7%) and any TEAE at least possibly related to adalimumab (55.7% and 52.4% versus 35.4%). There was also a statistically significant interaction observed for uveitis-related TEAEs by investigator (p = 0.024). In the All Adalimumab Analysis Set, a total of 6 subjects were reported with events of demyelinating disease including 3 patients with MS (n = 1) or ON (n = 2). The relation to the underlying type of uveitis has been previously discussed. See also Table 39 and Table 40.

In the Placebo-Controlled Analysis Set, a greater percentage of subjects without evidence of macular oedema versus subjects with evidence of macular oedema in the adalimumab group reported severe TEAEs (12.4% versus 5.9%), SAEs (12.4% versus 4.4%), SAEs possibly related to study drug (5.1% versus 0), and TEAEs leading to discontinuation of study drug (11.2% versus 4.4%). Furthermore, a higher proportion of subjects without evidence of macular oedema versus subjects with evidence of macular oedema in the adalimumab group reported infection TEAEs (53.9% versus 35.3%) and serious infection TEAEs (3.9% versus 0). Among subjects in the All Adalimumab Analysis Set, a greater percentage of subjects without evidence of macular oedema versus subjects with evidence of macular

oedema reported TEAEs possibly related to study drug (54.8% versus 45.8%). A smaller percentage of subjects without evidence of macular oedema versus subjects with evidence of macular oedema reported uveitis-related TEAEs by adjudication (38.9% versus 51.7%).

- Extrinsic factors

The number and percentage of TEAEs, overall, by primary SOC, and by PT were assessed by the subgroups of region, Baseline concomitant medications (IMMs, azathioprine, ciclosporin, MTX, MMF or equivalent, tacrolimus, Baseline oral prednisone use, prednisone dose at last flare, and systemic CS use once the mandatory prednisone taper was completed).

Although there were a few statistically significant differences, no clinically meaningful differences were observed when comparing subgroups in the Placebo-Controlled Analysis Set. Statistically significant interactions were observed for the following subgroups:

- Baseline MMF (or equivalent drug) use: prednisone-related TEAEs ($p = 0.019$)
- Baseline oral prednisone use: allergic reactions ($p = 0.048$)
- Prednisone dose at last flare: uveitis-related TEAEs by adjudication ($p = 0.003$) and infection TEAEs ($p = 0.006$)

Safety parameters were further compared by dose of concomitant CS (dosing intervals of 0 mg, 0≤15 mg, and >15 mg/day prednisone or equivalent). Generally the reporting rate was comparable, however an increased reporting of infections was found in subjects treated with 0 mg or <15 mg CS compared to >15 mg CS. When taking exposure into consideration, a general increase in reporting of TEAEs was observed in the group >15 mg CS. With regards to IMMs, a breakdown in the individual IMMs was not meaningful, but the incidence of AEs was compared for patients with and without concomitant IMMs. Generally the reporting rate was comparable, however the patient years of exposure was low.

- Pregnancy and Lactation

Three positive pregnancy test results or events of pregnancy were reported in the uveitis clinical development program. The outcome of the 3 pregnancy reports included 1 subject each with pregnancy termination, ectopic pregnancy, or continuation of study drug due to false positive test results.

- Elderly

An overview of TEAEs by age groups is provided in Table 44 and Table 45.

Table 44 – Overview of No and % of TEAEs by Age (Placebo-Controlled Analysis Set)

	< 65 years		65 – 74 years		75 – 84 years	
	PBO (N = 231) n (%)	ADA (N = 228) n (%)	PBO (N = 16) n (%)	ADA (N = 17) n (%)	PBO (N = 3) n (%)	ADA (N = 5) n (%)
Total	184 (79.7)	198 (86.8)	14 (87.5)	16 (94.1)	3 (100)	4 (80.0)
Fatal	0	1 (0.4)	0	0	0	1 (20.0)
Serious	13 (5.6)	21 (9.2)	3 (18.8)	3 (17.6)	0	1 (20.0)
Withdrawal	11 (4.8)	19 (8.3)	1 (6.3)	2 (11.8)	0	2 (40.0)
CNS (confusion/ extrapyramidal)	43 (18.6)	58 (25.4)	3 (18.8)	2 (11.8)	0	1 (20.0)
AE related to falling	0	1 (0.4)	1 (6.3)	0	0	0
CV events	0	0	0	0	0	0
Cerebrovascular events	0	0	0	0	0	0
Infections	82 (35.5)	116 (50.9)	7 (43.8)	5 (29.4)	0	1 (20.0)

Table 45 - Overview of No and % of TEAEs by Age (All Adalimumab Analysis Set)

	< 65 years (N = 427) n (%)	65 – 74 years (N = 29) n (%)	75 – 84 years (N = 8) n (%)
Total	387 (90.6)	28 (96.6)	8 (100)
Fatal	1 (0.2)	1 (3.4)	1 (12.5)
Serious	70 (16.4)	13 (44.8)	2 (25.0)
Withdrawal	63 (14.8)	7 (24.1)	3 (37.5)
CNS (confusion/extrapyramidal)	129 (30.2)	3 (10.3)	3 (37.5)
AE related to falling	3 (0.7)	1 (3.4)	0
CV events	1 (0.2)	1 (3.4)	0
Cerebrovascular events	0	0	0
Infections	260 (60.9)	13 (44.8)	2 (25.0)

In the Placebo-Controlled Analysis Set, a lower percentage of subjects who were ≥65 years versus <40 years and 40 – <65 years reported infections (27.3% versus 54.5% and 48.1%). Furthermore, a greater proportion of subjects in the adalimumab group who were <40 years versus 40 – <65 years and ≥65 years reported TEAEs of uveitis (11.1% versus 6.2% and 4.5%) and nasopharyngitis (27.3% versus 13.2% and 0). A greater proportion of subjects in the adalimumab group who were 40 – <65 years versus <40 years and ≥65 years reported TEAEs of fatigue (14.7% versus 7.1% and 0) and arthralgia (19.4% versus 12.1% and 4.5%).

Immunological events

Immunogenicity of adalimumab was evaluated in subjects with non-infectious uveitis in the two pivotal Phase 3 studies (Studies M10-877 and M10-880). In these studies, the percentage of subjects who received adalimumab 40 mg eow and testing positive for AAA was 4.8% (12/249) including both subjects from the main and the Japanese sub-studies.

The results and effects on the PK of adalimumab in the uveitis population are further discussed in the PK section 2.3.2.1. of this report. With regards to the safety analysis, the rate of any AEs was comparable between AAA+ and AAA– subjects. One death (AAA– subject) occurred in each study, but as previously described, the investigators considered the events not related to study drug.

Safety related to drug-drug interactions and other interactions

Specific drug-drug interactions were not evaluated in the uveitis clinical development program. However, in both studies M10-877 and M10-880, subjects were allowed to continue on 1 ongoing non-biologic IMM at study entry provided the dose had not been increased within 28 days prior to Baseline; the dose was to remain unchanged throughout the study and be within the acceptable limits as defined in the study protocols.

In the Placebo-Controlled Analysis Set, the most frequently reported concomitant medication (≥20%) in either treatment group was prednisolone and prednisone. In the All Adalimumab Set, prednisolone and prednisone use was >30% and was accompanied by omeprazole, paracetamol and ibuprofen reported by >20% subjects. In the Placebo-Controlled Analysis Set and in the All Adalimumab Set, over a third of all subjects reported using at least 1 concomitant systemic IMM at Baseline. Concomitant systemic IMMs reported at Baseline were MMF (or an equivalent drug), MTX, ciclosporin, and azathioprine.

Discontinuation due to adverse events

In the Placebo-Controlled Analysis Set, more TEAEs leading to discontinuation were reported in the adalimumab group than in the placebo group (9.2% vs 4.8%).

In the All Adalimumab Analysis Set, the TEAEs leading to discontinuation reported by 2 or more subjects included: mycobacterium tuberculosis complex test positive (12 subjects); cystoid macular oedema (5 subjects); tuberculin test positive (4 subjects); demyelination and uveitis (3 subjects each); and vision blurred, visual acuity reduced, vitreous haemorrhage, and bronchitis, pneumonia, tuberculosis, and ON (2 subjects each). The events of tuberculosis and positive tuberculosis test, uveitis-related events, and ON have already been discussed (see above).

Post marketing experience

There is no post marketing experience for the use of Humira in patients with uveitis.

The estimated cumulative post-marketing patient exposure since the international birth date through 31 December 2014 was 3.5 million patient years. The currently ongoing adalimumab safety registries (including JIA, CD, UC, psoriasis, and pregnancy) comprise approximately 32,000 adult and paediatric patients. One MAH-sponsored registry of 3,435 patients (12,193.3 PYs of adalimumab exposure) with moderate to severe rheumatoid arthritis (ReAlise) has been completed.

2.5.4. Discussion on clinical safety

The safety database presented in support of this application includes data from 2 pivotal placebo-controlled studies (studies M10-877 and M10-880), and an ongoing open-label extension study (study M11-327), which recruited 84% of the subjects from the 2 pivotal studies. Furthermore, the CHMP took into account the known safety profile of Humira across the range of approved indications, which has been well characterised with more than 9000 patients exposed in controlled and open clinical trials. In this context, the CHMP noted that the proposed dosing regimen for Humira in uveitis therapy was in line with the posology for psoriasis.

Two analysis sets were defined for the integrated safety analyses for this application. The Placebo-Controlled Analysis Set including study drug exposure (mean ± SD) of 241.6±191.07 days in the adalimumab group and 175.0±165.57 in the placebo group was intended for the assessment of the short- term safety profile for adalimumab. The All Adalimumab Analysis Set for the assessment of

long-term safety included data for subjects with a mean duration of exposure to adalimumab of 81.1 weeks.

The individual studies were generally balanced between placebo and adalimumab arms with regards to Baseline demographics, concomitant medication and disease history/characteristics (with few exceptions, see also more detailed discussion in section 2.4.4.). Idiopathic and Birdshot choroidopathy dominated the diagnoses compared to the systemic diagnoses.

Overall in the uveitis trials, in the Placebo-Controlled Analysis Set, 80.4% versus 87.2% of subjects reported any TEAE in the placebo and the adalimumab group, respectively, and 91.2% in the All Adalimumab Analysis Set. SAEs were reported by 10.0% versus 6.4% of the patients in the adalimumab and placebo group, respectively, in the Placebo-Controlled Analysis Set. In the All Adalimumab Analysis Set, 18.3% of the patients reported any SAE. Almost 5% in the placebo group discontinued due to any TEAE compared to almost twice as many in the adalimumab group.

The previously identified most commonly reported adverse drug reactions (ADRs) of Humira for the approved indications were infections, injection site reactions, headache and musculoskeletal pain. Serious infections as well as serious haematological, neurological, autoimmune reactions as well as malignancies had also been reported. The most frequently reported neoplasms were non-melanoma skin cancer and benign neoplasms (common). Solid organ neoplasms, melanoma and lymphoma are uncommon.

The most common TEAEs in the clinical development program for uveitis with an incidence >10% were nasopharyngitis, arthralgia, headache and fatigue in the Placebo-Controlled Analysis Set. There was a higher incidence of nasopharyngitis (17.6% versus 12.4%), arthralgia (15.2% versus 10.0%) and fatigue (10.4% versus 6.8%) in the adalimumab group compared to placebo. Serious TEAEs were generally few and consistent with the known safety profile of Humira, as described above, with the addition of ocular events that were likely to be related to the disease. Three deaths were reported in the trials but were considered unlikely to be related to Humira.

Adalimumab affects the immune system and patients taking adalimumab are more susceptible to infections. The increased reporting of infections, mainly nasopharyngitis, following adalimumab administration in the uveitis studies is thus expected and consistent with the known safety profile of Humira. There was also an increased reporting of serious infections following adalimumab treatment, both for short (2.8% vs 1.6% placebo) and long term use (5.8%), which again was considered by the CHMP to be consistent with the known safety profile of Humira. Furthermore it is known that multiple immunosuppressants used in combination therapy have an additive effect, and an increased reporting of infections in this situation was thus not surprising (see also discussion on concomitant medication for uveitis treatment below).

Generally, common adverse events in uveitis patients occurring with a frequency of ≥2% in the adalimumab group and >1.5 times compared to placebo, were consistent with the known safety profile of Humira. However, although small, there was an increased reporting rate in the adalimumab group compared to placebo of ocular events like uveitis, eye pain, vision blurred, IOP increased, and posterior capsular opacification. The difference in percentage may be explained by the longer exposure of the patients in the adalimumab group compared to those on placebo. Overall, ocular adverse events were considered likely due to the underlying uveitis. Reporting rates for uveitis in the adalimumab (8.0%) and placebo (6.8%) groups in the Placebo-Controlled Analysis Set increased with duration of exposure up to 20% in the All Adalimumab Analysis Set. Reporting of uveitis may have been due to lack of efficacy as well as worsening of the underlying disease. Further review of the study results by the MAH indeed suggested that lack of meeting the primary efficacy endpoint criteria (treatment failure) may have led to reporting of uveitis as an AE.

Pustular rash was reported by 6 subjects (2.4%) in the adalimumab group compared to none in the placebo group in the Placebo-Controlled Analysis Set. Despite including very limited information, all cases were non-serious, the study drug was not interrupted and the event resolved despite continued Humira treatment. All but one case was assessed as not related to study drug and no further action was considered necessary by the CHMP given that rash and related events, including more severe skin reactions, are known ADRs of Humira and other anti-TNF inhibitors as reflected in the PI.

Hyperglycaemia is also a known side effect of Humira and therefore the reports on diabetes mellitus in the uveitis trials including 5 (2.0%) subjects in the adalimumab group versus none in the placebo group in the Placebo-Controlled Analysis Set, and 9 (1.9%) subjects in the All Adalimumab Analysis Set, did not raise concerns. In any event, considering the short study period, at least in the controlled studies, it was considered unlikely that diabetes mellitus occurred as a result of the treatment with adalimumab.

Although the proposed dosing regimen for Humira in uveitis therapy is in line with the approved regimen for psoriasis, the CHMP noted the limited experience in the uveitis population, which is heterogeneous including uveitis as an isolated ocular disorder and also as part of a systemic disease. In particular, the choice of concomitant medication for treatment of uveitis patients is different compared to other previously approved indications for Humira. Almost all subjects in the pivotal uveitis studies used CS and/or IMMs. Their use was balanced between the treatment groups in the pivotal (short term) studies.

Concomitant use of prednisolone was almost 40% in the All Adalimumab Analysis Set. Humira combined with CS in low doses (7.5 mg prednisone equivalent or less) is widely used in clinical praxis in the long-term treatment of RA, and the safety profile is well known. The safety profile of Humira in combination with CS up to 15 mg/day (prednisone equivalent) short-term (≤3 month) is also well known from clinical trials and post-marketing data. In contrast, the experience is limited for use of Humira in combination with high CS doses >15 mg/day (prednisone equivalent), both short and long-term. When comparing safety data by CS dose intervals (0 mg, 0≤15 mg, and >15 mg), an increased reporting of TEAEs (including infections) can be seen in the >15 mg subgroup compared to the other groups, although the number of patient years was low. The rates of infections including serious infections were however broadly in line with previous clinical data as already described in the SmPC. While this was considered reassuring, still, the CHMP was of the view that the limited knowledge of the safety of Humira in combination with high doses of CS and medium doses in long-term use in the uveitis population was of concern and should be further addressed in future PSURs as well as in the RMP (see section 2.6. for details on the RMP). Further data were expected to be obtained from the open label extension study.

More than a third (35.3%) of the study subjects used IMMs as concomitant medication, predominantly MTX and MMF, followed by azathioprine and ciclosporin. Humira in combination with MTX is approved for treatment of RA and the safety profile is well known. Likewise, there is wide experience of use of Humira together with azathioprine in inflammatory bowel disease. In contrast, the combination of Humira with ciclosporin, MMF and tacrolimus is less well known. Further, combination of Humira with one or several IMMs can be expected in the uveitis population, with potentially new or increased risks for adverse effects. In addition, despite the long experience of Humira with MTX and azathioprine, it cannot be excluded that the uveitis population may react differently, depending on disease characteristics, possible other systemic inflammatory diseases associated with uveitis, as well as the choice of doses of the concomitant medications. Immunosuppressed patients with inflammatory bowel disease treated with triple medication of IMMs (such as azathioprine or MTX), TNF-α antagonist and high dose CS have been shown to have an increased risk of opportunistic infections including pneumocystitis jiroveci. Fatal outcomes of pneumocystitis jiroveci infections have been reported. It is

therefore recommended in the European clinical guideline (Second European evidence-based consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease) to consider prophylactic anti-infective therapy in this patient group. The CHMP therefore considered that the risk of fatal opportunistic infections (e.g. pneumocystis, legionellosis) following Humira and IMM triple medication should be followed in future PSURs in the uveitis indication and other indications. Otherwise, data on AEs of special interest with the respective IMMs and Humira is limited preventing any firm conclusions.

Diagnosis of sarcoidosis at Baseline in the uveitis trials was balanced with about 13% of subjects in either study arm, with more case reports in study M10-880 than in M10-877. There was a three times higher incidence of reports of sarcoidosis as an AE in adalimumab treated subjects compared to placebo, but the numbers were overall low. Further information provided by the MAH showed that all AEs of sarcoidosis occurred in subjects that enrolled in the study with sarcoidosis-associated uveitis and/or had sarcoidosis in their medical history. Depending on the disease characteristics of these patients, the reporting of AEs of sarcoidosis may be an expression of worsening of the disease. There is an apparent contradictory effect of TNF-alpha antagonists, as they are used off-label in treatment of sarcoidosis but are also reported to be a trigger of the same disease. Sarcoidosis was already included in the product information (PI) as an uncommon ADR and in the RMP as important identified risk. The CHMP considered that sarcoidosis should continue to be reviewed in future PSURs.

Occasional malignancies were reported in the adalimumab group (4 subjects, 1.6%) compared to no cases in the placebo group in the Placebo-Controlled Analysis Set of the uveitis trials. Considering the limited duration of treatment, an association with adalimumab was considered unlikely. The reported malignancies during the open-label extension study (n=12, 2.6%), including basal cell carcinoma (n=3) which is a common but clearly manageable adverse reaction of Humira, were difficult to interpret in terms of causality. The overall rate of malignancies decreased over time, as reflected in patient years (PY) with 2.4 compared to 1.7/100PYs for adalimumab treatment in the short and long term studies, respectively.

Development of demyelinating disorders (including MS) is an important identified risk of Humira and is described in the RMP. Based on clinical trials and post-marketing experience with Humira, demyelinating disorders including ON and MS are rare events with a frequency of ≥1/10,000 to <1/1,000. At the same time, in the scientific literature, an association between demyelinating disorders and uveitis has been estimated at an incidence of MS ranging from 1.5–3.4 E/100 PYs and an incidence of ON ranging from 0.5–1.0 E/100 PYs. The incidence rates of demyelinating disorders and ON in patients with uveitis from MarketScan® data presented by the MAH were based on a total of 103 877 patients, with a total incidence rate of 0.71 E/100 PYs in a population including all uveitis. This rate was similar to that found in the uveitis studies with Humira (0.83 E/100 PYs). However, when incidence rates were analysed by location of the inflammation, a higher rate was found for patients with posterior and intermediate uveitis in the uveitis trials compared to the MarketScan® data. A direct comparison between the two data sources was however considered difficult by the CHMP. Nevertheless, given that an association between demyelinating disorders and in particular intermediate uveitis has been described in the scientific literature, the CHMP was of the view that SmPC section 4.4. should be updated to inform prescribers accordingly. Furthermore, neurologic evaluation should be performed in patients with non-infectious intermediate uveitis prior and during Humira therapy to assess for pre-existing or developing central demyelinating disorders. Ophthalmologists are advised to consult specialists experienced in the use of Humira before initiation of Humira treatment. Prescribers are furthermore advised to consider discontinuation of Humira if any of these disorders develop. Demyelinating events should furthermore be followed in future PSURs.

Haematological events including pancytopenia, and hepatic events reported in the studies did not raise any concerns. Injection site disorders are listed as very common adverse reactions associated with subcutaneous injection of adalimumab. There were no serious or severe injection site reactions in the uveitis clinical development program. Finally, immune reactions reported in the uveitis studies were in line with previous experience with Humira. Development of AAA is discussed in section 2.3.2.1. Hypersensitivity is listed as a common adverse reaction in the SmPC of Humira.

2.5.5. Conclusions on clinical safety

Overall, the safety profile of Humira in the treatment of adult patients with non-infectious intermediate, posterior and pan-uveitis seemed to be broadly in line with that reported for other, previously approved indications. However, the safety analysis for use of Humira in uveitis is based on a relatively limited patient population and there are limited long-term data. Besides having different disease characteristics compared to the already approved target populations for Humira, uveitis patients are commonly co-treated with other immunosuppressive therapies to control the inflammation, thus leading to some uncertainties, including risks associated with immunosuppression. In addition, uveitis patients, in particular those with intermediate disease location, have been described in the scientific literature to be at risk of developing demyelinating disorders, which is also an important identified risk of Humira. To address these concerns, the RMP and SmPC were updated, including an extended warning on neurological events with further advice on demyelinating disorders.

2.5.6. PSUR cycle

The PSUR cycle remains unchanged.

The annex II related to the PSUR, refers to the EURD list which remains unchanged.

2.6. Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 12.0.1 is acceptable. The PRAC endorsed PRAC Rapporteur assessment report is attached.

The CHMP endorsed the Risk Management Plan version 12.0.1 with the following content:

Safety concerns

Summary of Safety Concerns	
Important identified risks	• Serious infections including diverticulitis and opportunistic infection, e.g., invasive fungal infections, parasitic infections, legionellosis and TB; • Reactivation of hepatitis B; • Pancreatitis; • Lymphoma; • HSTCL; • Leukaemia; • NMSC; • Melanoma;

Summary of Safety Concerns	
	• Merkel Cell Carcinoma (Neuroendocrine carcinoma of the skin); • Demyelinating disorders (including MS, GBS and optic neuritis); • Immune reactions (including lupus-like reactions and allergic reactions); • Sarcoidosis; • CHF; • MI; • CVA; • ILD; • Pulmonary embolism; • Cutaneous vasculitis; • SJS and erythema multiforme; • Worsening and new onset of Ps; • Haematologic disorders;
	• Intestinal perforation; • Intestinal stricture in CD; • Liver failure and Other Liver Events; • Elevated ALT levels; • Autoimmune Hepatitis; and • Medication errors and maladministration.
Important potential risks	• Other malignancies (except lymphoma, HSTCL, leukaemia, NMSC, and melanoma); • Vasculitis (non-cutaneous); • PML; • RPLS; • ALS; • Adenocarcinoma of colon in UC patients; • Infections in infants exposed to adalimumab in utero; • Medication errors with paediatric vial; and • Off-label use.
Missing information	• Subjects with immune-compromised conditions either due to underlying conditions (i.e., diabetes, renal or liver failure, HIV infection, alcohol or illicit drug abuse) or due to medications (post cancer chemotherapy, anti-rejection drugs for organ transplant) may have increased known risks of infection or other unknown risks related to the condition or to the concomitant medications; • Long-term safety information in the treatment of children aged from 6 years to less than 18 years with CD and pedERA; • Pregnant and lactating women; • Remission-withdrawal-retreatment nr-axSpA data and

Summary of Safety Concerns	
	episodic treatment in Ps, CD, UC, and JIA. • Long-term safety data in the treatment of adults with HS. • Long-term safety data in the treatment of adults with uveitis.

Pharmacovigilance plan

Actions	Milestone / Exposure	Milestones / Calendar Time	Study Status
Ongoing Pharmacovigilance Actions			
Long-Term PedERA Data (OL Extension Period of Study M11-328)	Up to 204 weeks	July 2016	Ongoing
Annual interim data from Registry for CD patients (Study P06-134)	--	Reporting February through 2015	Ongoing
Registry for CD patients (Study P06-134)	6 years	Final report August 2016	Ongoing
Annual interim data from Registry for pedCD patients (Study P11-292)	--	Reporting August through 2023	Ongoing
Registry for pedCD patients (Study P11-292)	10 years	TBD	Ongoing
Annual interim data from Registry for Ps patients (Study P10-023)	--	Reporting February through 2022	Ongoing
Registry for Ps patients (Study P10-023)	10 years	Final Report February 2023	Ongoing
Evaluation of treatment interruptions with the Ps registry (Study P10-023)	10 years	February 2023	Ongoing
Annual interim data from Registry for pJIA patients (Study P10-262)	--	Reporting August through 2024	Ongoing
Registry for pJIA patients (Study P10-262)	10 years	Final Report September 2024	Ongoing
Evaluation of treatment interruptions with the pJIA registry (Study P10-262)	10 years	September 2024	Ongoing
Support Rheumatoid Arthritis National Registry in Germany (RABBIT) until the end of 2017 (Biannual summary report)	NA	Reporting February through 2017 (Biannually)	Ongoing
Support Rheumatoid Arthritis National Registry in United Kingdom (BSRBR) until 2017	NA	TBD	Ongoing
Support Rheumatoid Arthritis National Registry in Sweden (ARTIS) until 2015	NA	TBD	Ongoing
Progress report for Registry for UC (Study P11-282)	--	TBD	Ongoing
Long-term HS data (Study M12-555)	--	4Q 2016	Ongoing
Long-term uveitis data (Study M11-327)	--	4Q 2018	Ongoing

Actions	Milestone / Exposure	Milestones / Calendar Time	Study Status
Planned Pharmacovigilance Actions			
Annual Interim data from Registry for UC (Study P11-282)	--	Reporting August through 2019	Planned
Biannual Interim data from Registry for UC (Study P11-282)	--	Reporting August from 2019 through 2023	Planned
Registry for UC patients (Study P11-282)	10 years	TBD	Planned

Risk minimisation measures

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Important Identified Risk		
Serious infections including diverticulitis and opportunistic infections, e.g., invasive fungal infections, parasitic infections, legionellosis, and TB	Labelling.	To educate prescribers and patients about the risk of serious infections associated with the use of Humira: • Patient Alert Card • HCP Educational Material.
Reactivation of hepatitis B	Labelling.	None proposed.
Pancreatitis	Labelling.	None proposed.
Lymphoma	Labelling.	To educate prescribers and patients about the risk of malignancies associated with the use of Humira: • Patient Alert Card • HCP Educational Material.
HSTCL	Labelling.	To educate prescribers and patients about the risk of malignancies associated with the use of Humira: • Patient Alert Card • HCP Educational Material.
Leukaemia	Labelling.	To educate prescribers and patients about the risk of malignancies associated with the use of Humira: • Patient Alert Card • HCP Educational Material.
NMSC	Labelling.	To educate prescribers and patients about the risk of malignancies associated with the use of Humira: • Patient Alert Card • HCP Educational Material.
Melanoma	Labelling.	To educate prescribers and patients about the risk of malignancies associated with the use of Humira: • Patient Alert Card • HCP Educational Material.

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Merkel cell carcinoma (Neuroendocrine carcinoma of the skin)	Labelling.	To educate prescribers and patients about the risk of malignancies associated with the use of Humira: • Patient Alert Card • HCP Educational Material.
Demyelinating disorders	Labelling.	To educate prescribers and patients about the risk of demyelinating disorders associated with the use of Humira: • Patient Alert Card • HCP Educational Material.
Immune reactions (including lupus-like reactions and allergic reactions)	Labelling.	None proposed.
Sarcoidosis	Labelling.	None proposed.
CHF	Labelling.	To educate prescribers and patients about the risk of CHF associated with the use of Humira: • Patient Alert Card • HCP Educational Material.
MI	Labelling.	None proposed.
Cerebrovascular accident	Labelling.	None proposed.
Interstitial lung disease	Labelling.	None proposed.
Pulmonary embolism	Labelling.	None proposed.
Cutaneous vasculitis	Labelling.	None proposed.
SJS	Labelling.	None proposed.
Erythema multiforme	Labelling.	None proposed.
Worsening and new onset of Ps	Labelling.	None proposed.
Haematologic disorders	Labelling.	None proposed.
Intestinal perforation	Labelling.	None proposed.
Intestinal stricture in CD	Labelling.	None proposed.
Liver failure and other liver events	Labelling.	None proposed.
Elevated ALT levels	Labelling.	None proposed.
Autoimmune hepatitis	Labelling.	None proposed.
Medication errors and maladministration	Labelling	None proposed.
Important Potential Risks		
Other malignancies (except lymphoma, HSTCL, leukaemia, NMSC, and melanoma)	Labelling.	To educate prescribers and patients about the risk of malignancies associated with the use of Humira: • Patient Alert Card • HCP Educational Material.

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Vasculitis (non-cutaneous)	The SmPC currently contains no text regarding vasculitis (non-cutaneous).	None proposed.
Progressive multifocal leukoencephalopathy (PML)	The SmPC currently contains no text regarding PML.	None proposed.
Reversible posterior leukoencephalopathy syndrome (RPLS)	The SmPC currently contains no text regarding RPLS.	None proposed.
Amyotrophic lateral sclerosis (ALS)	The SmPC currently contains no text regarding reversible ALS.	None proposed.
Adenocarcinoma of colon in UC patients	Labelling.	None proposed.
Infections in infants exposed to adalimumab in utero	Labelling.	None proposed.
Medication errors with paediatric vial	Labelling.	None proposed.
Off-label use	The SmPC currently contains no text regarding off-label use.	None proposed.
Missing Information		
Subjects with immune-compromised conditions either due to underlying conditions (i.e., diabetes, renal or liver failure, HIV infection, alcohol or illicit drug abuse) or due to medications (post cancer chemotherapy, anti-rejection drugs for organ transplant) may have increased known risks of infection or other unknown risks related to the condition or to the concomitant medications	Labelling.	None proposed.
Long-term safety information in the treatment of children aged from 6 years to less than 18 years with CD and pedERA	Labelling.	None proposed.
Pregnant and lactating women	Labelling.	None proposed.
Remission-withdrawal-retreatment nr-axSpA data and episodic treatment in Ps, CD, UC, and JIA	The SmPC currently contains no text regarding remission-withdrawal-retreatment in nr-axSpA or episodic treatment in Ps, CD, UC, and JIA.	None proposed.
Long-term safety information in the treatment of adults with HS	Labelling.	None proposed.
Long-term safety information in the treatment of adults with uveitis	Labelling.	None proposed.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated for all presentations of Humira except the vial (Humira 40 mg/0.8 ml solution for injection), which is for paediatric use only. For the vial, relevant safety information was updated in SmPC sections 4.4 and 4.8. Particularly, an update to the warning on neurological events with regard to demyelinating disorders has been added to the product information for all presentations. The Package Leaflet has been updated accordingly.

Changes to SmPC sections 4.1, 4.2 and 4.4 are shown below (additions are shown in **bold**, deletions as ~~strike-through~~):

- SmPC section 4.1

Uveitis

Humira is indicated for the treatment of non-infectious intermediate, posterior and panuveitis in adult patients who have had an inadequate response to corticosteroids, in patients in need of corticosteroid-sparing, or in whom corticosteroid treatment is inappropriate.

- SmPC section 4.2

Humira treatment should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of conditions for which Humira is indicated. **Ophthalmologists are advised to consult with an appropriate specialist before initiation of treatment with Humira (see section 4.4).** Patients treated with Humira should be given the special alert card.

(…)

Uveitis

The recommended dose of Humira for adult patients with uveitis is an initial dose of 80 mg, followed by 40 mg given every other week starting one week after the initial dose. There is limited experience in the initiation of treatment with Humira alone. Treatment with Humira can be initiated in combination with corticosteroids and/or with other non-biologic immunomodulatory agents. Concomitant corticosteroids may be tapered in accordance with clinical practice starting two weeks after initiating treatment with Humira.

It is recommended that the benefit and risk of continued long-term treatment should be evaluated on a yearly basis (see section 5.1).

(…)

Paediatric uveitis

The safety and efficacy of Humira in children aged 2-17 years have not yet been established. No data are available.

- SmPC section 4.4

Neurological events

TNF-antagonists including Humira have been associated in rare instances with new onset or exacerbation of clinical symptoms and/or radiographic evidence of central nervous system

demyelinating disease including multiple sclerosis and optic neuritis, and peripheral demyelinating disease, including Guillain-Barré syndrome. Prescribers should exercise caution in considering the use of Humira in patients with pre-existing or recent-onset central or peripheral nervous system demyelinating disorders**; discontinuation of Humira should be considered if any of these disorders develop. There is a known association between intermediate uveitis and central demyelinating disorders. Neurologic evaluation should be performed in patients with non-infectious intermediate uveitis prior to the initiation of Humira therapy and regularly during treatment to assess for pre-existing or developing central demyelinating disorders.**

(...)

Elderly

The frequency of serious infections among Humira treated subjects over 65 years of age (**3.7**~~3.6~~%) was higher than for those under 65 years of age (**1.5**~~1.4~~%). Some of those had a fatal outcome. Particular attention regarding the risk for infection should be paid when treating the elderly.

Changes were also made to the PI to bring it in line with the current Agency/QRD template, which were reviewed and accepted by the CHMP.

The CHMP furthermore noted that SmPC section 5.1 was rather lengthy. The MAH should consider to shorten this section in a future procedure.

3. Benefit-Risk Balance

Benefits

Beneficial effects

The established treatment of non-infectious uveitis consists of corticosteroids (CS), whereby inflammation involving the posterior segment of the eye usually requires systemic or intra-/periocular CS administration over prolonged periods of time. Long-term use of systemic or intra-/periocular CS is however associated with serious adverse reactions. IMMs and TNF-α inhibitors are also used in clinical practice but only ciclosporin is approved in this indication and its use is limited due to safety concerns. Thus, new effective therapies are needed, including agents allowing reduction in CS use.

This extension of the indication of Humira for treatment of adult patients with non-infectious intermediate, posterior and pan-uveitis, was supported by two clinical trials, one in active uveitis, i.e. patients insufficiently controlled on 10-60 mg/day prednisone or equivalent (M10-877), and one in inactive uveitis, i.e. in maintenance therapy of CS dependent patients (10-35 mg/day prednisone equivalent, M10-880). The main studies recruited 452 adult subjects with various uveitis diagnoses, including both isolated disease (e.g. idiopathic, Birdshot choroidopathy) and uveitis as part of systemic disease (e.g. Behçet's disease, sarcoidosis and VKH), thus covering a wide range of patients with different disease aetiologies and reflecting the heterogeneous target population.

From a statistical point of view, an effect of adalimumab with regards to the primary composite endpoint, time to treatment failure, has been convincingly demonstrated in both studies, although the size of the effect was limited. The median times to failure in active uveitis was 3 and 5.6 months for placebo and adalimumab, respectively, translating in a moderate difference of less than 3 months between treatment arms. In inactive uveitis, the corresponding median times to failure were 8.3 months for placebo and >18 months for adalimumab (i.e. not estimable since fewer than 50% of patients had an event during the study). The risk of experiencing treatment failures was significantly reduced in patients receiving adalimumab compared to placebo with risk reductions of 50% ($p<0.001$) and 43 % ($p=0.004$) in active and inactive uveitis, respectively. The absolute difference in failure rates between treatment arms was 24% (78.5% for placebo versus 54.5% for adalimumab) and 15.8% (55.0% for placebo versus 39.1% for adalimumab) in active and inactive uveitis patients, respectively.

Overall, the CHMP recognised that the patients enrolled in the clinical development program were representative of a population that is difficult to treat, with all subjects receiving concomitant systemic CS at study start and many also taking IMMs. Furthermore, the composite primary endpoint – time to treatment failure – was regarded to be highly sensitive to detect an intraocular inflammation since it captured both measurements of inflammation as well as a functional outcomes. The sensitivity of the composite endpoint was likely also the reason for the high failure rates observed in both studies.

Taken together, based on the selected study population, the stringent primary endpoint and the rather aggressive CS tapering schedule, the observed beneficial effect, albeit modest in size, was considered by the CHMP to be of clinical relevance. Furthermore, in both studies, the Kaplan-Meier curves separated early and remained separated during the studies, supporting maintenance of the effect.

For active uveitis, all components of the composite endpoint contributed to the difference in treatment failures (statistical significance for the components ranged from $p <0.001$ to 0.010) with the largest difference between active and placebo treatment observed for VH grade. There was also a numerical favour shown for adalimumab in terms of proportion of patients that reached quiescence (defined as no active inflammatory lesions and AC cell grade ≤ 0.5 and VH grade ≤ 0.5) from Week 6 onwards while tapering CS (still on 15 mg/day). As of Week 8 (10 mg/day CS), statistical significance was

reached (47 vs. 66% in the placebo and adalimumab groups, respectively, p=0.013). Furthermore, while overall few subjects had a relevant gain in best corrected visual acuity (BCVA), generally and across all analyses conducted, there was a consistent trend in favour of adalimumab over placebo in terms of gaining, maintaining and losing vision during the study. With regards to other endpoints, including vision-related quality of life, adalimumab was generally favoured and statistically significant outcomes were achieved for the majority of variables.

In inactive uveitis, the majority of treatment failures were due to loss in vision, i.e. the VA component of the composite endpoint (p=0.002, HR 0.33). For the other components of the primary endpoint as well as for the vast majority of secondary efficacy endpoints, adalimumab was numerically favoured, but statistical significance was not reached. As in study M10-877, adalimumab was consistently numerically favoured with regards to BCVA outcomes.

Support for adalimumab as a steroid-sparing option was derived from analyses of the proportions of patients in quiescence without steroids, although the numbers were small. For both patients with active and inactive uveitis, greater proportions of patients receiving adalimumab remained in quiescence after tapering of steroids compared to placebo (Weeks 16, 36 and 52 for active uveitis, p-values 0.027 to 0.056; Weeks 20, 40 and 52 for inactive uveitis, p-values 0.004 to 0.008). Similar results were obtained for steroid-free lack of inflammation (i.e. no active inflammatory lesions and both VH and AC cells = 0), whereby larger differences were observed between treatment arms for patients with inactive uveitis compared to those with active uveitis.

Additional support for a steroid-sparing effect as well as for maintenance of the effect in the long-term was provided by the interim results of the ongoing, open-label extension study. While a relatively high proportion of patients who entered the study with active uveitis experienced a treatment failure/flare (54 %), for the majority of these patients the flare was followed by a long period of disease control with a median time to treatment failure of 12.5 months. In the subset of patients who failed while on adalimumab in the core studies, median time to failure was 9.7 months. Few patients with controlled uveitis at study entry experienced treatment failures (12.5%) and the time to treatment failure could not be estimated. Subjects entering the study without active disease generally maintained a low daily dose of CS over time (< 2 mg) while subjects entering the study with a flare were able to reduce the daily dose of CS from approximately 14 mg at study entry to approximately 4 mg after 1 year. At that time, 40/55 (73%) and 83/171 (48%) of subjects who entered the study with controlled and active uveitis, respectively, did not receive any concomitant systemic and/or local CS.

Uncertainty in the knowledge about the beneficial effects

No dose-response studies have been conducted. The dose regimen selected for clinical development and proposed for commercial use, i.e. an initial loading dose of 80 mg adalimumab, followed by 40 mg every other week, was based on the regimen previously studied and approved for use in psoriasis. Based on the available data, the CHMP considered the dose regimen acceptable. However, analyses of systemic exposure levels in relation to the effect (prevention of treatment failure) indicated that steady-state serum adalimumab concentrations were on the lower side of the therapeutic range. Clinical trial simulations furthermore suggested a potentially greater benefit of a weekly maintenance dose of 40 mg adalimumab (approximately 15% additional decrease in failure rate compared to 40 mg eow). There is experience with this regimen in other indications for Humira seemingly without major safety concern and weekly dosing is sometimes also reported and recommended in the scientific literature. Therefore, the CHMP recommended for the MAH to study the weekly dose regimen in uveitis patients post approval as it may provide an increased benefit.

With regards to the target population, the CHMP noted that during clinical development, Humira was used in patients already receiving conventional therapy (i.e. all patients initially received CS and some

also IMMs). Consequently, the CHMP did not agree to a first line indication, but rather that Humira should be used only in patients with an inadequate response to CS, in need of CS-sparing, or when CS treatment is inappropriate. Furthermore, the proposal to initiate treatment with Humira without CS in patients with active uveitis was not considered to be sufficiently supported by the data from the clinical development program. There was only very limited data from the extension study and uncertainties remained if disease control with Humira alone could be obtained as quickly and to the same extend as in combination therapy. Consequently, the CHMP recommended initiating treatment only in combination with CS and/or IMMs.

Anti-adalimumab antibody generation remained low regardless of concomitant IMM therapy (2.2% with and 6.3% without IMMs). The data were too limited to conclude whether an absence of a protective umbrella of prednisolone and immunosuppressive therapy would impact antibody formation. The PI already informs about the formation of anti-adalimumab antibodies and the finding of increased antibodies formation when Humira is used without concomitant methotrexate. No change to this information was considered necessary based on the data from the uveitis development program.

The CHMP furthermore noted that in active uveitis, while all individual components of the primary endpoint contributed to the overall effect of adalimumab, the magnitudes of the mean changes in AC cell grade, VH grade and VA (that tended to decrease after an initial gain) were limited. This, however, could likely, at least in part, be explained by a “dilution” effect as the difference would be mainly driven by the cases of treatment failures and one individual disease manifestation (endpoint component) may or may not be associated with the other 3 components occurring both individually or in combination and in one or both eyes. The effect sizes for the individual components of the primary endpoint in patients with inactive uveitis were also rather small. However, in contrast to the study in active uveitis, the 4 parameters did not equally contribute to the overall treatment effect in patients with inactive uveitis even if adalimumab was numerically favoured for all components. Few subjects appeared to have failed due to other causes than worsening of BCVA (loss of ≥15 letters) and this vision loss occurred early in many cases. Such sudden decrease in vision was unexpected given the usual clinical course of the disease, whereby changes in retinal lesions and vision would be expected to occur gradually in patients with inactive uveitis and be preceded by episodes of active inflammation. Further analyses for the 33 patients with treatment failure due to a low of BCVA (23 in the placebo arm versus 10 in the adalimumab arm) showed that in all but 2 placebo-treated subjects, the loss of BCVA paralleled increases in one or more inflammation markers including AC cells, VH scores and/or central retinal thickness, however the cut-off for actual failures as defined in the primary endpoint was not always reached. Likewise, in all but one placebo-treated subject with an early loss of BCVA (around week 12 or earlier), this was associated with signs of low grade inflammation, but again, the threshold for failure was not always reached. Overall, these data supported an association of the observed early vision loss with disease manifestations.

Even though the risk for treatment failure due to the worsening of VA was clearly reduced in the adalimumab group in patients with inactive uveitis, only a 2 letter (logMAR 0.04) mean difference in BCVA was observed compared to placebo. A plausible explanation for this small difference may be the limited difference in the rate of treatment failures due to BCVA loss as the main driver for this endpoint. On the other hand this finding only supports a modest treatment effect. The low number of treatment failures due to other causes than vision loss may also explain, at least in part, why for the vast majority of the key secondary efficacy variables in study M10-880 no statistically significant differences between the treatment groups were reached.

Similarly, while data on quiescence and freedom of inflammation with and without steroids overall support a beneficial effect of adalimumab, they only showed an advantage in a small number of patients at various time points (less than 10% and 20% absolute difference between adalimumab and

placebo arm, in active and non-active uveitis, respectively). Again, this supports only a moderate beneficial effect.

The interim results from the ongoing extension study were considered supportive, both in terms of maintenance of the treatment effect in the long-term as well as with regards to a steroid-sparing effect. However, although it is acknowledged that a large proportion of patients from the main studies entered the extension (82%), there were some limitations due to the uncontrolled nature of the study, the high drop-out rate (30%) and the fact that the study only represents a part of the initially randomised patient populations. For these reasons, the study results should be interpreted with caution.

Finally, although adalimumab was favoured in the vast majority of subgroups, a limited effect size was observed in women where there was only 1 month difference in the median time to treatment failure between treatment arms. It is acknowledged that the studies were not powered to assess the effect in subgroups, but this finding was observed in both studies. It was suggested that the results were due to an imbalance in diagnosis, whereby substantially more women than men had a diagnosis of VKH while the opposite was observed for Behçet's disease. At the same time, a less prominent treatment effect was observed for VKH compared to Behçet's disease. Overall, the number of subjects concerned was too low to draw firm conclusions and the issue was not further pursued given that some additional support for an effect of Humira in both genders was available from the extension study, in which no major differences between men and women were observed. The CHMP also noted that in the subgroup analyses by location of the inflammation in study M10 877, adalimumab appeared less effective in intermediate uveitis. However, this observation was limited to only one of the two pivotal trials and due to the small sample size, no firm conclusions could be drawn.

Risks

Unfavourable effects

The most commonly reported short-term TEAEs with an incidence of >10% for adalimumab in the placebo-controlled studies, were nasopharyngitis (17.6% vs 12.4% for adalimumab vs placebo), arthralgia (15.2% vs 10.0%) and fatigue (10.4% vs 6.8%). In addition, in the extension study, urinary tract infection (10.8%) and uveitis (20%) were reported frequently. The latter, i.e. reports of uveitis may be due to lack of efficacy as well as worsening of the underlying disease. Further review of the study results by the MAH indeed suggested that lack of meeting the primary efficacy endpoint criteria (treatment failure) was the primary reason underlying the reporting of uveitis as an adverse event.

Overall the safety profile as observed in the uveitis studies was broadly consistent with the known safety profile of Humira with respect to adverse events as well as reporting frequencies, apart from the ocular events which were likely related to the underlying disease. Furthermore, reports of sarcoidosis were three times more frequent in adalimumab treated subjects compared to placebo (2.4% vs 0.8%). All adverse events of sarcoidosis occurred in subjects who entered the study with a history of sarcoidosis or diagnosis or sarcoidosis-associated uveitis. There is an apparent contradictory effect of TNF-alpha antagonists, as they are used off-label in treatment of sarcoidosis but are also reported to be a trigger of the same disorder. Sarcoidosis was already included in the PI as an uncommon ADR and in the RMP as important identified risk. No further conclusions could be drawn based on the data from the uveitis program. The CHMP requested that cases of sarcoidosis should be monitored and reviewed in future PSURs.

There was furthermore an increased reporting rate of demyelinating disorders in the uveitis trials, which was not surprising given that demyelinating events are an important identified risk of Humira. However, since an association between demyelinating disorders and uveitis has been reported in the scientific literature, in particular for intermediate uveitis, the CHMP recommended that neurologic

evaluation should be performed in patients with non-infectious intermediate uveitis prior and during Humira therapy to assess for pre-existing and developing central demyelinating disorders. Ophthalmologists are advised to consult specialists experienced in the use of Humira. Prescribers are furthermore advised to consider discontinuation of Humira if any of these disorders develop. SmPC sections 4.2 and 4.4. were updated accordingly. Furthermore, demyelinating events should be followed in future PSURs.

Other previously identified safety concerns for Humira included infections and malignancies. Occasional malignancies were also reported in the adalimumab treated patients in the uveitis program but considering the limited duration of treatment in these cases, an association with adalimumab was considered unlikely. Similarly, cases of malignancies reported during the open-label extension study were difficult to interpret in terms of causality. Serious infections were also more frequently reported following adalimumab treatment compared to placebo, both for short (2.8% vs 1.6% placebo) and long term use (5.8%). Altogether, these findings were consistent with the known safety profile of Humira.

Uncertainty in the knowledge about the unfavourable effects

The safety analysis for use of Humira in the treatment of non-infectious uveitis was based on a relatively limited patient population and there are limited long-term data. However, at the same time, there is substantial experience with the long-term use of Humira in other, already approved indications. These data were considered relevant and supportive for the present application.

Based on the experience in other indications, the safety profile of Humira combined with low dose CS long-term, and medium dose CS short-term is well known. However, there was limited information for use of Humira in combination with CS >15 mg/day (high dose) and in long-term treatment with 7.5 to 15 mg/day. Similarly, there is experience with Humira in combination with MTX (approved for treatment in RA) as well as with azathioprine (IBD). In contrast, the safety profile is not known for the combination of Humira with other IMMs (ciclosporin, mycophenolate mofetil and tacrolimus). The choice and dosing of concomitant medication for treatment of uveitis patients is different compared to other previously approved indications of Humira and depending on the exact diagnosis, combination of Humira with one or several IMMs can be expected at least in a subset of the uveitis population. Therefore, uncertainties arose from the limited information on concomitant use of CS and other IMMs, including risks associated with immunosuppression. As an increased risk of opportunistic infections has been shown for IBD patients treated with triple medication of IMMs, TNF-α antagonist and high dose CS, the CHMP considered that the risk of infections, in particular fatal opportunistic infections (e.g. pneumocystis, legionellosis) following Humira and IMM triple medication, should be further monitored in future PSURs and in the RMP. Further data are expected to be obtained from the ongoing open label extension study.

Effects Table

Table 46 – Effects Table for Humira in the Treatment of Non-Infectious Intermediate, Posterior and Pan-Uveitis

Effect	Short Description	Unit	Ada	Plc	Uncertainties/ Strength of evidence
Favourable Effects*					
Prevention of treatment failures	Time to treatment failure on or after Week 2 (inactive uveitis)/ Week 6	Months (median) *Active uveitis*	5.6	3.0	Statistical significance in both active and inactive uveitis. Marked risk reduction of 50% (active uveitis) and 43%

Effect	Short Description	Unit	Ada	Plc	Uncertainties/ Strength of evidence
	(active uveitis) if meeting pre-defined criteria: new active lesions, VH grade, AC cell grade and/or BCVA loss[1]	*Inactive uveitis*	NE (>18)	8.3	(inactive uveitis). Active uveitis: Statistically significant results for each component of the composite endpoint. Moderate effect size of <3 months difference, but more convincing 24% absolute difference in treatment failures. Inactive uveitis: Statistically significant results for the BCVA component only, but associated with worsening in other components. Modest absolute difference in treatment failures (15%). Extension study[3]: Time to treatment failure for active uveitis 12.5 months (median) and not estimable in inactive uveitis. Failure rates of 54% (active uveitis) and 12% (inactive uveitis). Caveats due to uncontrolled design and high drop-out rate.
	Treatment failure rate[1]	N (%) *Active uveitis* *Inactive uveitis*	60 (54.5) 45 (39.1)	84 (78.5) 61 (55.0)	
Steroid sparing effect	Proportions of patients in steroid-free quiescence at various time points[2]	N (%) *Active uveitis* Week 16 Week 36 Week 52 *Inactive uveitis* Week 20 Week 40 Week 52	 25 (31.1) 18 (20.0) 12 (13.3) 48 (53.9) 35 (39.3) 34 (38.2)	 18 (18.9) 6 (6.3) 4 (4.2) 31 (33.0) 20 (21.3) 18 (19.1)	Statistically convincing at most (active uveitis) or at all (inactive uveitis) time points. Limited number of patients at later time points. Modest differences between treatment arms (active uveitis). Extension study: Mean daily dose of CS was reduced from 14 to 4 mg/day at Month 12 (active uveitis) and was maintained at <2mg/day (inactive uveitis). Caveats apply; see above.
	Proportion of patients off CS at Month 12 in the long-term extension study	N (%) *Active uveitis* *Inactive uveitis*	83 (48%) 40 (73%)	n/a n/a	
Unfavourable Effects**					
Infections	• All	E/100PY	146.9	143.6	Incidence rates (E/100PY) in the All Adalimumab Analysis Set (long-term safety): 105.8 (all infections), 4.6 (serious infections), 0.3 (opportunistic infections) and 0.3 (active TB)
	• Serious infections		4.8	4.2	
	• Opportunistic infections excl. TB		0	0	
	• Active TB		0.6	0	
Malignancies	• All	E/100PY	2.4	0	Incidence rates for the All Adalimumab Set (E/100PY): 1.7 (all), 0.1 (lymphoma), 0 (melanoma), 0.7 (NMSC)
	• Lymphoma		0	0	
	• Melanoma		0	0	
	• NMSC		0.6	0	
Demyelinating disorders		E/100PY	0.6	0	Not all cases confirmed with MRI. Incidence rate in the All Adalimumab Set: 0.8 E/100PY
Sarcoidosis		E/100PY	4.8	3.3	Incidence rate in the All Adalimumab Set: 1.5 E/100PY

Abbreviations: Ada=adalimumab, HR=hazard ratio, VH=vitreous haze, AC=anterior chamber, BCVA=best corrected visual acuity, CS=corticosteroids, E=Event, N=Number of patients, NMSC=Non-melanoma skin cancer, MRI=magnetic resonance imaging, Plc=Placebo, PY=Patient Year, SUN=Standardization of Uveitis Nomenclature,

TB=Tuberculosis

* Results refer to the main studies M10-877 (active uveitis) and M10-880 (inactive uveitis) unless stated otherwise.

** Rates refer to the uveitis trials (Placebo-Controlled Analysis Set) unless stated otherwise.

(1) VH and AC cell criteria in active uveitis were inability to achieve ≤0.5+ by week 6 and thereafter 2-step increase relative to best state achieved (SUN criteria). In inactive uveitis, a 2-step increase in VH and AC cell criteria relative to baseline (SUN). Visual acuity criteria were worsening of BCVA by ≥15 letters in both studies.

(2) Defined as no active inflammatory lesions and AC cell grade ≤ 0.5 and VH grade ≤ 0.5) at each visit between Baseline through Week 52 without steroids.

(3) Long term extension ongoing, results up to 31 August 2015

Benefit-Risk Balance

Importance of favourable and unfavourable effects

A benefit effect of Humira in the treatment of adult patients with active non-infectious uveitis has been convincingly demonstrated with a compelling statistically significant effect on the primary composite endpoint and with adalimumab being favoured over placebo for the vast majority of secondary endpoints. Given the characteristics of the patient population and the stringent composite endpoint definition, the observed 3 months difference in the median time to treatment failure was considered of clinical relevance, although modest in size. Furthermore, evidence of rapid induction of disease control, albeit in combination with high doses of CS, and maintenance of quiescence with continued adalimumab treatment has been provided. In inactive uveitis, a robust statistical effect was also demonstrated with regards to the primary efficacy endpoint, time to treatment failure, thus showing a beneficial effect in maintaining quiescence over time and preventing recurrences (8 months for placebo and >18 months for adalimumab).

In non-infectious uveitis, the treatment goal is to rapidly control acute inflammation, limit recurrences, reduce both dose and duration of systemic CS and limit decrease in visual acuity. In these regards, a consistent benefit has been shown for adalimumab. From the long-term extension study, it was apparent that with Humira, the disease is controlled over time, both in subjects that entered the study with active and inactive uveitis. With regards to inactive uveitis, the importance of maintaining patients in quiescence over time has to be given weight since with every recurrence there is a risk of irreversible vision loss.

The benefits described above apply to the patient population studied in the clinical development program. Herein, Humira was used as could be anticipated in clinical practice, i.e. in patients receiving established therapies including systemic CS. In these patients, treatment with Humira resulted in less treatment failures after CS tapering compared to placebo and greater proportion of patients maintained quiescence without steroids, although the difference was modest. These data support a role of Humira as second line and steroid-sparing treatment option.

Overall, the safety profile of Humira as observed in the uveitis clinical development program appeared to be in line with the safety profile previously described for other indications including the known important identified risks of malignancies and infections. Of relevance for uveitis was furthermore the risk of demyelinating disorders with Humira, as the scientific literature also suggests an increased risk of demyelination in patients with intermediate uveitis. Other concerns included sarcoidosis and the limited experience with the use of Humira in combination with e.g. high dose CS, ciclosporin, MMF and tacrolimus, which are expected to be used in the uveitis population.

Benefit-risk balance

Based on the available data and subject to amendments to the product information and the RMP, the CHMP concluded that the benefits of Humira in the treatment of non-infectious intermediate, posterior and pan-uveitis in adult patients who have had an inadequate response to corticosteroids, in patients

in need of corticosteroid-sparing, or in whom corticosteroid treatment is inappropriate, outweighed its risks. The benefit-risk balance was thus considered favourable.

Discussion on the Benefit-Risk Balance

Based on the available data, use of Humira as first line treatment option for non-infectious uveitis was not considered acceptable by the CHMP. Rather, based on the study population, who received, at least initially, systemic CS, use of Humira in adult patients with inadequate response to CS, in need of CS sparing or in whom CS treatment is inappropriate, was supported. Evidence for a beneficial effect of Humira in patients with inadequate response to CS was available from the clinical trials' data which also supported a benefit of Humira as steroid-sparing option. Further, while not actually studied, the CHMP was of the view that there was no reason to believe that the efficacy or safety profile of Humira should be significantly different in a population where CS should be avoided and thus it was considered acceptable to include this population in the indication.

The decision to restrict the indication to second-line therapy also took into account the safety profile of Humira and advice from an expert panel. The experts were asked to discuss the clinical relevance of the effects shown in the clinical development program and to comment on a suitable place in therapy for Humira. Taking into account the totality of the data, the experts considered that a beneficial effect of Humira had been convincingly demonstrated and that the second line indication was reasonable.

Further restriction of the use of Humira such as to active disease, last line treatment or in terms of treatment duration was not considered justified. This view was supported by additional analyses presented in the course of the assessment including data showing similar efficacy in patients with and without additional IMMs as well as interim data from the extension study showing maintenance of the effect in the long-term. While, overall, there was sufficient support for persistence of the beneficial effect of Humira in the long-term, the CHMP considered that continuation of treatment should be re-evaluated by physicians on an annual basis taking into account the benefits and risks of long-term treatment. This approach was agreed by the experts.

The CHMP was furthermore of the view that Humira treatment should only be initiated in combination with CS and/or IMMs as there was insufficient evidence that disease control with Humira alone could be obtained as quickly and to the same extent as in combination therapy with CS. Thereafter, Humira could be used both in combination and monotherapy. CS may be tapered in accordance with clinical practice starting two weeks after treatment initiation with Humira.

With regards to the dose regimen, the CHMP concluded that the proposed posology of an initial loading dose of 80 mg adalimumab, followed by 40 mg every other week was acceptable. However, the available data and simulations suggested that this regimen was sub-optimal and that a weekly maintenance dose of 40 mg adalimumab may result in an increased beneficial effect. Therefore, the CHMP recommended for the MAH to study the weekly dose regimen in uveitis patients post approval.

With regards to safety, some uncertainties including a potentially increased risk for serious infection, in particular in combination therapy, remained. However, the available educational material, which also includes information on demyelinating disorders, was considered of importance for the new group of prescribers and patients. The risk of demyelinating events was also highlighted by the experts, who stated that they would not use Humira in patients with demyelinating disease or signs of development of such disease. This view was reflected in an update of the warning in SmPC section 4.4.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II, IIIA and IIIB

Extension of Indication to include treatment of non-infectious intermediate, posterior and panuveitis in adult patients who have had an inadequate response to corticosteroids, in patients in need of corticosteroid-sparing, or in whom corticosteroid treatment is inappropriate; as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC were updated. The warning in SmPC section 4.4 on neurological events was extended to provide additional advice on the monitoring and possible need for discontinuation in case of demyelinating disorders. The Package Leaflet was updated in accordance. Furthermore, the PI is being brought in line with the latest QRD template version 10 and the MAH took the opportunity to make editorial amendments throughout the PI.

The variation leads to amendments to the Summary of Product Characteristics, Annex II, Labelling and Package Leaflet as well as to the Risk Management Plan (RMP).

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module "*steps after the authorisation*" will be updated as follows:

Scope

Extension of Indication to include treatment of non-infectious intermediate, posterior and panuveitis in adult patients who have had an inadequate response to corticosteroids, in patients in need of corticosteroid-sparing, or in whom corticosteroid treatment is inappropriate; as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC were updated. The warning in SmPC section 4.4 on neurological events was extended to provide additional advice on the monitoring and possible need for discontinuation in case of demyelinating disorders. The Package Leaflet was updated in accordance. Furthermore, the PI is being brought in line with the latest QRD template version 10 and the MAH took the opportunity to make editorial amendments throughout the PI.

Summary

Please refer to the published Assessment Report Humira H-481-II-146-AR.