Bristol Trials Centre, Clinical Trials and Evaluation Unit
Bristol Medical School
University of Bristol
Bristol Royal Infirmary
Bristol. BS2 8HW

Tel: 0117 342 2507
Fax: 0117 342 3288

btc-mailbox@bristol.ac.uk
www.bristol.ac.uk/health-sciences/research/clinical-trials/

# Adalimumab vs placebo as add-on to Standard Therapy for autoimmune Uveitis: Tolerability, Effectiveness and cost-effectiveness: a randomized controlled trial.

## The ASTUTE trial

| | |
|---|---|
| IRAS ID | 271051 |
| ISRCTN No | ISRCTN31474800 |
| EUDRACT no. | 2020-000754-97 |

**This protocol has regard for the Health Research Authority guidance**

***Details of Sponsor***

University Hospitals Bristol NHS Foundation Trust
R&D Office
Level 3, Education Centre
Upper Maudlin Street
Bristol BS2 8AE

Tel: 0117 342 0233
Fax: 0117 342 0239

***Chief Investigator& Research Team Contact Details***

*Chief Investigator*
Professor Andrew Dick
University of Bristol
Tel: 0117 342 4854
Email: a.dick@bristol.ac.uk

*Senior Methodologist and co-applicant*
Professor Barnaby Reeves
University of Bristol
Tel: 01173423143
Email: barney.reeves@bristol.ac.uk

*Co-Lead clinical investigator*
Dr Srilakshmi Sharma
Oxford University Hospitals NHS Foundation

*Consultant ophthalmologist and co-applicant*
Dr Alastair Denniston
University Hospitals Birmingham NHS

Trust
Tel: 01865 594 299
Email: srilakshmi.sharma@ouh.nhs.uk

*Research fellow and co-applicant*
Dr Lucy Culliford
University of Bristol
Tel: 01173422526
Email: lucy.culliford@bristol.ac.uk

*Consultant ophthalmologist and co-applicant*
Mr Carlos Pavesio
Moorfields Eye Hospital NHS Foundation Trust
Tel: 07739 706 258
Email: Carlos.Pavesio@moorfields.nhs.uk

*Senior Health Economist*
Professor Sarah Wordsworth
University of Oxford
Tel: 01865 289 268
Email: sarah.wordsworth@dph.ox.ac.uk

*Public health consultant*
Dr Robert Wilson
Public Health England
Email: robert.wilson15@nhs.net

*Director of the Central Angiographic Resource Facility, NetwORC UK*
Professor Tunde Peto
Queen's University Belfast
Tel: +44 (0)28 9097 6400
Email: t.peto@qub.ac.uk

*Trial Manager*
Miss Hana Tabusa
University of Bristol
Tel: 01173422526
Email: hana.tabusa@bristol.ac.uk

Foundation Trust
Tel: 0121 371 6905
Email: a.denniston@bham.ac.uk

*Bristol Trials Centre Director*
Professor Chris Rogers
University of Bristol
Tel: 01173422507
Email: chris.rogers@bristol.ac.uk

*Consultant ophthalmologist and co-applicant*
Dr Nicholas Beare
Royal Liverpool & Broadgreen University Hospitals NHS Trust
Email: N.Beare@liverpool.ac.uk

*Senior grader, Moorfields reading centre*
Dr Pearse Keane
University College London
Tel: 020 7566 2255
Email: pearse.keane@moorfields.nhs.uk

*Patient and public representative*
Ms Annie Folkard
The Birdshot Uveitis Society
Email: annie@birdshot.org.uk

*Trial Manager*
Dr Abby O'Connell
University of Bristol
Tel: 01173422987
Email: abby.oconnell@bristol.ac.uk

## Table of contents

## Glossary / abbreviations

| | |
|---|---|
| ANIU | Autoimmune non-infectious uveitis |
| AE | Adverse event - any undesirable event in a subject receiving treatment according to the protocol, including occurrences which are not necessarily caused by or related to administration of the research procedures. |
| ASTUTE | Adalimumab vs placebo as add-on to Standard Therapy for autoimmune Uveitis: Tolerability, Effectiveness and cost-effectiveness. The ASTUTE pragmatic randomized controlled trial. |
| BCVA | Best corrected visual acuity |
| BTC CTEU | Bristol Trials Centre, Clinical Trials and Evaluation Unit |
| BUS | Birdshot Uveitis Society |
| CMO | Cystoid macular oedema |
| CMT | Central macular thickness |
| CRF | Case report form |
| CS | corticosteroid |
| DMSC | Data monitoring and safety committee |
| ECG | Graphical representation of electrical activity of the heart over time, as recorded by an electrocardiograph |
| EQ-5D-5L | EuroQol-5 Dimensions, 5-level version |
| ETDRS | Early Treatment of Diabetic Retinopathy Study |
| HIV | Human immunodeficiency virus |
| HLA | Human leukocyte antigen |
| HR | Hazard ration |
| HRQoL | Health-related quality of life |
| ICF | Informed consent form |
| ICH-GCP | International conference for harmonisation of good clinical practice |
| IFR | Individual funding request |
| IL | Interleukin |
| IMP | Investigative medicinal product |
| IMT | Immunomodulatory treatment |
| MHC | Minor histocompatibility complex |
| MLHF | Minnesota living with heart failure |
| MRI | Magnetic resonance imaging |
| NHS | National Health Service |
| NIHR | National Institute for Health Research |
| OCT | Optical coherence tomography |
| PIL | Patient information leaflet |
| PPI | Patient and public involvement |
| RCT | Randomised controlled trial |
| REC | Research ethics committee |
| RSI | Reference safety information |
| SAE | Serious adverse event - events which result in death, are life threatening, require hospitalisation or prolongation of hospitalisation, result in persistent or significant disability or incapacity. |
| SAR | Serious adverse reaction |
| SOP | Standard operating procedure |
| SmPC | Summary of product characteristics |
| SSAR | Suspected serious adverse reaction |

| | |
|---|---|
| SUSAR | Suspected unexpected serious adverse reaction - an untoward medical occurrence suspected to be related to a medicinal product that is not consistent with the applicable product information and is serious. |
| TF | Treatment failure |
| TMG | Trial management group |
| TNF | Tissue necrosis factor |
| TRI | Treatment run-in |
| TSC | Trial steering committee |
| VCM1 | Vision-related quality of life core questionnaire |
| VFQ | 25-item National Eye Institute Visual Functioning Questionnaire |
| UK | United Kingdom |
| UH Bristol | University Hospitals Bristol NHS Foundation Trust |
| WHO | World Health Organisation |
| WPAI-SHP | Work Productivity and Activity Impairment Questionnaire: Specific Health Problem V2.0 |

# 1. Trial summary

## 1.1 Scientific summary

| | |
|---|---|
| *Design*: | Phase IV pragmatic placebo-controlled, randomised controlled trial (RCT) with a 'treatment run-in' (TRI). After the TRI, responders only (inactive disease with <=5mg/day corticosteroid (CS), estimated 50%) will be randomised (1:1) to adalimumab or placebo. An internal pilot (phase 1; 18 months (m) including 6 months (6m) set up) will determine recruitment and responder rates among eligible patients; progression to phase 2 will depend on a) randomising >=80% (n=41) of the target number at this time (n=51), b) having at least 10 sites recruiting to the trial by month 18 and c) <15% of responders at the end of the TRI unwilling to be randomised. The full RCT will evaluate the effectiveness and relative cost-effectiveness of adalimumab vs placebo as add-on therapy to standard care. |
| *Setting*: | UK tertiary centres treating autoimmune non-infectious uveitis (ANIU). |
| *Target population*: | Adults with active (incident) or inactive (prevalent) ANIU, requiring/starting >5mg/day corticosteroid (CS) to treat disease activity. |
| *Inclusion criteria*: | Patients with sight threatening ANIU in either or both eyes. ANIU will be diagnosed on the basis of the criteria used to define treatment failure. |
| *Exclusion criteria*: | Untreated or active tuberculosis, uncontrolled glaucoma, multiple sclerosis, HIV positive, hepatitis B or C, syphilis, Lyme disease, Behcet's disease, heart failure (NYHA III/IV), cancer diagnosed <5 years ago or monitoring of cancer where oncologist has concern about anti-TNF, anti-TNF drug within 90 days, ocular CS implant within 12 months or an intravitreal steroid injection within the previous 3 months, pregnant, allergy or hypersensitivity to adalimumab or any of its excipients. |
| *Health technologies being assessed*: | 80mg subcutaneous injection of Imraldi™ (licensed biosimilar for adalimumab) at the start of the TRI, then fortnightly 40mg injections starting one week after the initial dose, up to 16 weeks (end of TRI); after randomisation, fortnightly 40mg injections of drug or placebo to the end of the trial (follow-up 12m to 30m). In the event of treatment failure (TF), open label drug will be restarted as per TRI for 16 weeks and, if a participant responds, allocation will be switched and trial treatment restarted, maintaining masking. |
| *Measurement of outcomes*. Primary outcome: | TF, defined as need for >5mg/day CS to maintain inactive disease (decisions to increase CS made by masked clinicians) or treat active disease (see 5.8.1), [1] excluding isolated anterior uveitis and including an increase in cystoid macular oedema (see flow diagram). Clinical TF events will be validated by retinal imaging. Follow-up will be censored when all participants have at least 12m follow-up; following participants recruited earlier to the end of the trial will maintain masking and avoid the ethical issue of withdrawing treatment for participants after 12m follow-up. |

| | |
|---|---|
| Secondary outcomes include: | Patient reported outcomes (visual function [2], generic [3], and symptoms of side effects), individual TF components, retinal morphology, adverse events (AEs), changes in employment, NHS resource use and costs. |
| *Cost-effectiveness analysis:* | The main outcome measure for the economic evaluation will be quality adjusted life years (QALYs), estimated using the EuroQol EQ-5D 5L, administered at every visit. Valuations derived from published UK population tariffs will be assigned. The mean number of QALYs per group and incremental QALYs will be calculated. |
| *Sample size*: | Hazard ratios (HRs) in 2 trials of adalimumab to treat active and inactive ANIU were 0.50 and 0.57 respectively [1, 4]. The TRI design should improve effectiveness and we have set a target HR of 0.5. Assuming that 27% in the placebo group survive free from TF at 12m (estimated from placebo groups of the 2 trials with 40:60 active: inactive disease), 174 participants will allow a HR=0.5 (27% vs 52% survival free from TF at 12 months) to be detected with 90% power and 5% 2-tailed significance, with <=10% loss to follow-up. |
| *Project timetable*: | 48 months comprising 3 months set-up; 23 months recruitment (which includes 4 months TRI and 4 months randomising last recruited participants at end of TRI); minimum 12 months follow-up (allowing 14 months after the last randomisation); 2 months data checks, followed by database lock; 3 months data analyses and 3 months reporting. |
| *Expertise in team*: | The multidisciplinary team includes ophthalmologists who treat ANIU, a patient with ANIU, an imaging expert, clinical trials researchers with expertise conducting ophthalmic trials and a health economist. |

## 1.2 Plain English summary

Autoimmune uveitis is a term for several rare eye diseases in which the body's own immune system causes sight-threatening damage to the light sensitive retina at the back of the eye. Uveitis causes sight loss from inflammation inside the eye, damage to blood vessels in the retina or leakage of fluid into the central, most sensitive area of the retina. Two in 10,000 people are at risk of serious sight loss from uveitis. Usual treatment for autoimmune uveitis involves low dose steroids and one or two other drugs to reduce inflammation. Unfortunately, many patients do not respond to or tolerate usual treatment, or they need high dose steroids to control the uveitis. Long term high dose steroids increase the risk of heart attack, stroke, and infection and affect physical and mental health. Adalimumab is a drug that targets chemicals released by inflamed tissue, neutralising their damage to the body. It was first approved in Europe to treat uveitis in 2016.

Two recent studies suggest fortnightly adalimumab is, on average, an effective way to treat uveitis in some patients. However, drugs like adalimumab can have serious side effects and more evidence is required to identify which patients with uveitis benefit the most from adalimumab, both with respect to their vision and quality of life, including treatment side effects. In 2017, NICE recommended that it should be used in the National Health Service (NHS) but only for a minority of patients with uveitis. Several very similar (biosimilar) drugs are now available, reducing the cost of treatment, and ophthalmologists believe that many more patients

could benefit but have no way to identify those most likely to benefit. This study is designed to evaluate one of these biosimilar drugs, now being purchased by the UK NHS for usual care.

This study aims, first, to identify patients who are most likely to benefit from adalimumab. All eligible patients who consent will be given adalimumab for a 16-week trial period, if necessary in combination with low dose of steroids; these patients will include those with impaired vision due to uveitis, requiring high dose steroids to bring the disease under control, and those with better vision but who require high dose steroids to keep the uveitis under control. Over the 16 weeks, doctors will aim to reduce the steroid dose to a low level that should not cause side effects.

Then, patients who are successfully treated with adalimumab and low dose steroids will enter the main study. They will be given adalimumab or a dummy treatment, in combination with their other medications (including low dose steroids). Chance will determine who receives which treatment and neither patients nor their eye doctors will know. Regular eye examinations, tests and questionnaires will be used to assess how well patients are doing. This part of the study, which will treat and follow up patients for 12 to 30 months, will find out whether adalimumab is better at preventing recurrence of uveitis than the dummy treatment and whether adalimumab is cost-effective compared to the dummy treatment.

Patients with uveitis have contributed to the study from the start, helping to: design the protocol to ensure it applies to uveitis patients who may benefit; co-authoring the lay summary; helping to draft the application, providing feedback on the trial design and participating in a national survey to assess support for the study. They will continue to contribute in these ways and provide support to patients, if funding is awarded. The research team includes eye doctors and researchers with expertise in doing eye studies. A registered clinical trials unit, ophthalmology research networks and patient groups will collaborate to conduct the study. The results will be disseminated through NHS England, patient societies, newsletters to participants and through medical journals.

## 2. Background

### 2.1 The problem addressed by the trial

Uveitis is defined as inflammation of the vascular uveal tract of the eye, including the iris, ciliary body, and choroid; however, adjacent structures such as the retina, optic nerve, and sclera may also be affected. Therefore, in practice, any intraocular inflammation involving compromise of the blood ocular barrier is considered to be in the same group of disorders. In 2010, the World Health Organisation (WHO) estimated that 285 million people were visually impaired; of these, 39 million were blind, and approximately 10% was due to uveitis [5]. In the United States and Europe, uveitis accounts for 10-20% of severe visual handicaps, and 10% of blindness, in working age adults [6-10].

Clinically, uveitis is classified anatomically as anterior, intermediate, posterior or panuveitis, depending on which anatomical structures of the eye are involved [11]. All these forms are characterised by a cellular inflammatory infiltrate, which ophthalmologists visualise directly in a clinic setting using a biomicroscope. The anterior chamber of the eye is filled with optically clear aqueous fluid, allowing the practitioner to clearly see infiltrating leukocytes that are counted and scored in accordance with standardized grading systems [11]. This process also applies to vitreous gel, which fills the posterior segment of the eye.

The clinical phenotype of non-infectious intraocular inflammation is replicated in experimental animal models that are driven by immune responses to self antigen [12]. The animal models

support a role for autoimmunity, albeit experimentally inflammation is often shaped by the presence of mycobacterial protein. However, unlike other classical systemic autoimmune disorders, there are no clearly defined serological markers to assist diagnosis (e.g. autoantibodies) within the majority of uveitis entities, except high human leukocyte antigen (HLA) association (HLA-A29 and Birdshot chorioretinopathy). Markers are also not predictive of either severity or prognosis.

Idiopathic autoimmunity arises following the activation and expansion of retinal antigen-specific T lymphocytes. Experimentally, the triggering event can happen at sites distant to the affected organ, although whether this occurs in human disease is rarely known. The dominant paradigm is that of a CD4+ T helper cell-driven process. The relevance of this to human disease is supported by the association of sympathetic ophthalmia and Vogt–Koyanagi–Harada disease with specific HLA class II alleles [13, 14], as well as the identification of ocular antigen-responsive T cells in both the peripheral blood and eyes of patients [15, 16]. The strong minor histocompatibility complex (MHC) association with autoimmunity arises both through the need for specific autoantigen presentation [17] and through the selection of a potentially pathogenic T cell repertoire [18].

In animal models, the CD4 T cell paradigm is further refined, with both Th1 and Th17 T helper cells implicated as important inducers of autoimmune disease [19]. When CD4+ T cells were purified from the retinas of animals with uveitis induced by peripheral immunisation, and then studied ex vivo, both Th1 and Th17 cells were found. Cytokines produced by these cells condition the local microenvironment, and activate macrophages (especially IFN-γ produced by Th1 cells) to secrete TNF alpha, recruit neutrophils, and potentially restructure the local environment (e.g., through IL-17 produced from Th17 cells; [20]). Differentiated T cell subpopulations also have a role in controlling local inflammation when they acquire a T regulatory phenotype. The normal ocular microenvironment favours differentiation to Foxp3+ regulatory T cells, but when the eye is already inflamed this is not the case [21]. One of the most marked consequences of autoimmune T cell ocular responses is the resultant increased TNFα production [22-24]. TNFα production within the eye (infiltrating monocytes, macrophages and retinal pigment epithelium) critically mediates retinal tissue damage in uveitis by influencing mononuclear cell trafficking into the retina and initiation of a cascade of inflammatory pathways resulting in direct retinal tissue injury [25]. The central role of TNFα in relation to severity is evidenced by the degree of improvement of uveitis and limitation of tissue destruction following TNFα inhibition [25]. In humans, soluble TNFα is increased in paired serum and aqueous humour with uveitis and is reduced upon remission [26-29].

In summary, the pathophysiology of uveitis is underpinned by autoimmune pathophysiology: (a) central tolerance; (b) recognition of cognate retinal antigens by T helper (Th1 and Th17) cells; and (c) increased ocular production of the cytokine, TNF alpha which perpetuates chronic inflammation, causing end-organ ocular tissue damage which results in blindness.
Unlike other rare diseases treated with biologic drugs, such as associated vasculitides or pulmonary immune-mediated diseases, there is less clear evidence for a dominant, single therapeutic target causing tissue damage. For uveitis, much knowledge has accrued through interrogating immunopathological processes in animal models of uveitis (see above), with results that eloquently illuminate specific targets. Overall, the models have demonstrated a pivotal role for TNF-alpha, as well as activated CD4 T cells, their signature cytokines, and their ability to influence trafficking of cells. This mechanism has been substantiated by the recent findings from the VISUAL trials (NCT01138657; NCT01124838) [1, 4].

## 2.2 Reasons why this research is important

ANIU affects 115.3/100,000 patients; the incidence is 52.4/100,000 [30]. Despite its rarity, ANIU is the third leading cause of blindness in the western world [5]. For about 20% of patients with sight-threatening ANIU, usual care is immunomodulatory treatment (IMT) to maintain remission with low dose or no corticosteroids (CS) [31, 32]. However, usual care fails for 40% of patients with sight-threatening ANIU [33-35]. Due to lack of alternative therapies, they are treated with long term high dose CS to maintain disease remission and prevent sight loss but at the cost of significant morbidity [36, 37]. Patients may also be intolerant of high levels of one or more conventional IMTs.

Adalimumab is licensed to treat ANIU refractory to CS or if CS is contraindicated. We estimate that 3800 patients in England do not respond to usual care, which includes IMT. IMT may be effective, well tolerated and used in conjunction with adalimumab to achieve low dose CS when IMT alone is not successful. There are no RCTs specifically evaluating adalimumab as an add-on therapy. This research will collect patient reported outcome measures in association with clinical measures and conduct a cost-effectiveness analysis alongside the trial, which is essential for commissioning.

Sight loss in ANIU is due to cystoid macular oedema (CMO), vitritis, retinal hypoperfusion, retinal scarring or ocular complications [5, 38]. Patients are affected in several ways: sight loss impairs activities that depend on vision (e.g. driving) and, combined with drug side effects, reduces health-related quality of life (HRQoL), increasing the risk of depression [39-41]. Also, 70-90% of ANIU patients are of working age (20-60 years), 43% of them at risk of losing, or having lost, their jobs [42]. CS have serious morbidity and mortality risks; >7.5mg/day prednisolone increases the risk of heart attack, stroke, other systemic and ocular comorbidities [37, 43, 44]. In one UK cross–sectional study, 61% of ANIU patients were taking 40mg/day CS [45]. Published patient reported outcome measures developed for patients with visual loss and validated for uveitis show that visual loss in one or both eyes in uveitis are associated with significant impairment in psychological well-being, social activities, visual function such as walking down stairs or driving, dependence including being forced to stay at home most of the time while improvement in vision is correlated with an improvement in visual quality of life scores [40, 41, 46]. Poorer visual function, and current oral corticosteroid use, are associated with depression in people with ANIU [39].

Patient surveys conducted by the patient groups developing this trial with the trial organisers (Birdshot Uveitis Society (BUS)) found that, after visual loss, co-morbidities due to treatments for uveitis, in particular steroids, are the greatest cause of poor health, well-being and quality of life. We conducted a patient panel and a nationwide survey of patients with uveitis to establish views about the possible role of biologic therapies. There was unanimous agreement from patients surveyed and panel members for a trial evaluating adalimumab as add-on therapy and agreement that the proposed trial as designed is both equitable and acceptable.

## 2.3 Evidence that there is a current need for the trial

The importance of ANIU in relation to the commissioning brief is evidenced by a response to a Freedom of Information request by the research team before applying for funding 10/08/2016). The response stated that 50% of all individual funding requests (IFRs) to NHS England for biologic therapy for autoimmune disease from 01/04/2013 to 31/03/2016 were for uveitis. Most will have been for anti-TNFalpha drugs such as adalimumab, which is effective for ANIU [1, 4].

Although there is a high level of requests, there is no commissioning policy for adalimumab in England for adults. Adalimumab cost £11,000/year when first licensed [47] but the availability of

biosimilars have recently reduced this to about £6,600/year (60%), a significant cost-saving to the public if this therapy is commissioned. The cost of sight loss from any cause in 2008 was £17,549 and the cost of ANIU complications is high [37, 48]. This research is needed to provide evidence that adalimumab is effective as an add-on therapy to existing safe doses of immunosuppression, to identify disease phenotypes which may respond, and to produce commissioning guidelines for this high cost therapy.

Systematic reviews of anti-TNFa drugs conclude that adalimumab is beneficial for ANIU refractory to IMT [49, 50]. There is evidence from studies other than RCTs of the benefit of anti-TNFa drugs in small numbers of patients with specific ANIU syndromes, e.g. multifocal choroiditis, punctate inner choroidopathy and Birdshot Uveitis [51]. Unlike other rare diseases treated with biologics, there is strong evidence that TNFa is a major therapeutic target, increasing the likelihood of anti TNFa drugs being effective for ANIU [30]. Two recent multicentre RCTs reported in 2016 that, compared to placebo, adalimumab delays treatment failure (TF) for active and inactive ANIU (respectively, VISUAL 1, hazard ratio (HR)=0.5; 95% CI, 0.36-0.70; p<0.001 and VISUAL II, HR=0·57, 95% CI 0·39-0·84; p=0·004) [1, 4].

The applicability of these results to patients in the United Kingdom (UK) with refractory ANIU is uncertain. The trials did not study adalimumab as add-on therapy and the most important sight-threatening complication of uveitis, CMO, was not an eligibility criterion or a TF event. Furthermore, the presence of inflammation in the front part of the eye (anterior chamber) was considered a failure, whereas in routine clinical practice, it is acceptable to attempt to maintain remission by using adjunctive topical corticosteroid use which is effective and safe for most patients. The trial design for ASTUTE allows topical corticosteroid therapy.

## 3. Rationale

The trial arises because of the views of ophthalmologists that adalimumab is effective in a wider range of patients with ANIU than covered by the technology appraisal published by NICE [52]. Adalimumab is also ineffective in a proportion of patients covered by the technology appraisal [1, 4]. The design of the trial sought to include features to promote its acceptability to patients affected by uveitis and representatives of organisations representing them. These features are:

A. The offer of a period of treatment with adalimumab to any patient meeting the eligibility criteria for the trial (wider ranging than the criteria published by NICE [52]), i.e. to satisfy the need for the trial to be equitable, with subsequent participation in the randomized phase of the trial being contingent on demonstration of a therapeutic response to the drug.
B. The use of a biosimilar approved by the NHS.
C. In the event of treatment failing in the randomized phase of the trial, the offer to switch treatment to the alternative group without unmasking, so that a participant originally allocated to placebo who relapses could then receive treatment (albeit still masked to allocation).
D. The application of objective clinical criteria to assess whether a therapeutic response has been achieved at the end of the treatment run-in phase of the trial.

To the extent that the trial has been designed to model a future commissioning policy, it also addresses a NHS priority, namely obtaining better evidence to guide effective provision of expensive biologic treatments.

The acceptability of the design features of the trial to patients affected by uveitis was discussed at a patient and public involvement (PPI) meeting with patients and representatives of the Birdshot Uveitis Society and Fight for Sight. The meeting was chaired by Annie Folkard, a co-author on this protocol. The meeting was supported by a subsequent poll of members of the Birdshot Uveitis Society. Conclusions from these consultations were that:

- The trial was considered to be equitable and the broad eligibility criteria were welcomed.
- A minority (<20%) expressed some or strong concern about using a biosimilar approved by the NHS for treating patients with ANIU, because they were of the view that the biosimilar would not be identical to the original drug.
- The offer of switching to the alternative treatment in the event of treatment failure was appreciated; up to two switches was considered optimal.
- Patients would be likely to respect the decisions about patients' therapeutic responses made on the basis of objective clinical criteria at the end of the treatment run-in period.
- The duration of participation in the study was not considered a negative feature.

## 4. Aims and objectives

The ASTUTE pragmatic trial will compare the effectiveness and cost-effectiveness of adalimumab when used to treat ANIU in either or both eyes in patients taking less than or equal to 5mg of steroids per day and other IMT drugs, as required. Specifically, we will test the hypothesis that adalimumab reduces the hazard of TF in patients with ANIU, after weaning of CS to <=5mg/day in a treatment run-in period (TRI).

Specific objectives are:

A. To estimate the hazard of TF in the group allocated to adalimumab compared with the group allocated to placebo.

B. To estimate differences between groups with respect to a range of secondary outcomes including: separate components of the composite TF outcome, visual function, ocular and retinal signs of disease activity, health-related quality of life (HRQoL), resource use and costs, adverse events (AEs).

C. To estimate the cost-effectiveness of adalimumab compared to usual care.

D. To investigate associations between patient factors and ocular and retinal signs at the start of the TRI with responder status at 16 weeks, and to explore emerging participant phenotypes associated with TF during follow-up in the main trial.

## 5. Plan of Investigation

### 5.1 Conceptual framework

The trial needs to be placebo-controlled because participants will be administering injections themselves and reporting important secondary outcomes, e.g. AEs and the impact of ANIU (which we hypothesise will be effectively treated by adalimumab) on health and employment (including the EQ-5D 5L questionnaire, which will provide the primary outcome for the economic evaluation); these outcomes are likely to be biased if participants know their allocations. The most secure way to mask allocation is to dispense placebo in pre-filled pens that are indistinguishable to the pre-filled pens containing active drug. The manufacturer of the biosimilar used in the trial (Biogen Inc) is supplying placebo pre-filled pens for the trial which are identical to the pre-filled pens containing the licensed adalimumab biosimilar (Imraldi$^{TM}$) which Biogen also manufactures. The only difference is that the Imraldi$^{TM}$ pre-filled pens will have a commercial label and the placebo pre-filled pens will be supplied without the commercial label. The Imraldi$^{TM}$ and placebo pre-filled pens will therefore be over-labelled, with both described only as investigative medicinal product (IMP) to mask the allocation.

An important requirement of the funder was that the trial design should be “both efficient and most likely to provide an answer for a broad range of patients.” To satisfy this requirement, we have specified (a) a more inclusive study population than recruited to previous trials of adalimumab for treating ANIU [1, 4] and (b) included a TRI, with subsequent randomization being contingent on a participant having a therapeutic response. The more inclusive population reflects the population which ophthalmologists want to treat and which they believe is likely to benefit (on average). The TRI is intended as a model for a potential commissioning strategy. It provides an opportunity for all patients in a more inclusive patient population to access treatment, avoiding difficult decisions about eligibility against stricter eligibility criteria and reassuring patients about equitable access, while limiting longer term treatment to only those patients who show a favourable response in the short term (TRI phase). In effect, we are using short term responsiveness to “personalise” treatment, given that there are no proven biomarkers

for responsiveness to adalimumab in patients with ANIU. If objective D (see paragraph 4 above) identifies clear markers for responder status or TF, this would allow eligibility for an 'initial treatment trial' in a commissioning policy to be modified.

Ophthalmological trials usually follow participants for a set duration after randomisation. However, this approach poses a dilemma about how to treat the first randomised participants when they reach the end of their follow-up, long before the end of the trial when the results will be known. This challenge is especially acute if follow-up stops when a participant experiences the primary outcome. When evaluating an intervention that is not available outside a trial, this means either stopping an intervention that may be effective or providing open label treatment outside the trial. Both approaches risk anecdotal information about the effects of treatment (from the usual care follow-up of participants who have completed follow-up) becoming available before the trial reports, potentially biasing trial personnel. Withdrawing treatment that may be effective from participants at the end of follow-up may also be considered unethical and inappropriate when participants have volunteered to contribute to the evidence base for the intervention. To avoid this dilemma, we intend to try to keep participants in the trial until all participants have a minimum of 12 months follow-up and the trial will be close to reporting [53]. This approach is consistent with how adalimumab is used in practice in patients who are maintained on it successfully, so will contribute valuable longer-term evidence about the intervention, but it requires more IMP. It is likely to foster better commitment among participants and was supported by the PPI consultation.

Following participants until all have completed a minimum duration of follow-up requires a strategy for managing repeated TFs. In the event of a TF in either eye, a participant will stop taking the IMP and re-start open label treatment with adalimumab. In effect, this is the same as re-entering the protocol for the TRI (with other medications, including CS being prescribed at the discretion of the treating ophthalmologist). If the participant again meets the criteria for being a "responder" at 16 weeks, he/she will re-start trial follow-up but switch to the alternative IMP to the one provided at randomisation. If the participant does not meet the criteria for "responder" at 16 weeks, he/she will be withdrawn from the trial, without unmasking allocation. Consistent with the PPI consultation, a maximum of two switches will be allowed, i.e. adalimumab-placebo-adalimumab or placebo-adalimumab-placebo.

Although this feature may appear complicated, it has important advantages. It was considered equitable and welcomed during the PPI consultation because it ensures that a participant (classified as a "responder" at the end of the TRI) who is allocated to placebo and suffers TF has a chance to receive active drug. We anticipate that the opportunity to receive the opposite IMP in the event of TF will encourage a participant to accept: (a) initial randomisation, (b) that adalimumab is "truly not for them" in the event of multiple TFs and (c) not disclosing allocation until the trial reports, even after withdrawal. It has elements of a cross-over design (considered impracticable because of the long time-course of remission and TF, and controlling disease activity in the event of TF) so provides extra information in a (non-random) subset of participants about outcome with both adalimumab and placebo.

## 5.2 Trial schema

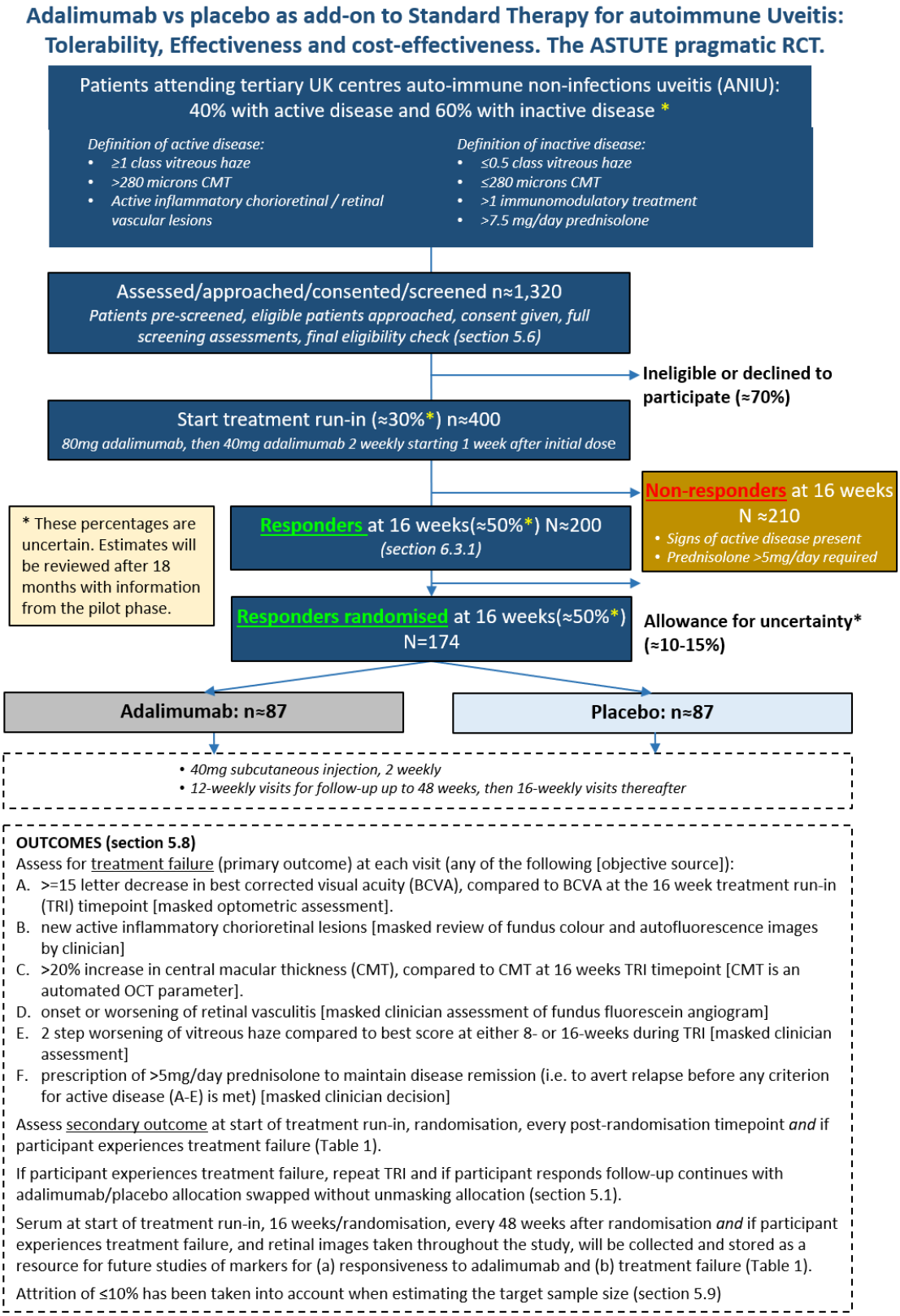



**Figure 1 Trial Schema**

## 5.3 Trial design

The study design is a multi-centre, parallel group, placebo-controlled, pragmatic randomised controlled trial (RCT) with a TRI; only those participants who are classified as "responders" (see 5.1) after 16 weeks of active, open label treatment during the TRI will be randomised. Participants, doctors and all members of the research team except for the study statistician will be masked to allocation. The study will include two phases: an internal pilot (months 1 to 18, including 6 months set up), primarily to establish that recruitment to time and target is possible, and the main trial (months 19 to 48). Progression to phase 2 will depend on: a) having randomised >=80% (n=41) of the target number at the end of the internal pilot (n=51); b) having at least 10 sites recruiting to the trial by month 18; and c) <15% of responders at the end of the TRI unwilling to be randomised. The full RCT will evaluate the effectiveness and relative cost-effectiveness of adalimumab vs placebo as add-on therapy to standard care.

Participants starting the TRI will be seen at 4-5 weeks, 8-9 weeks and 16-17 weeks after starting adalimumab treatment. Participants classified as responders (see 6.3.1) who agree to continue in the RCT, will be randomized at the 16-17 week visit (see 6.1). Follow-up visits will be scheduled at 12 weekly intervals (11 to 13 weeks) up to 48 weeks and 16 weekly intervals (15 to 17 weeks) thereafter, consistent with usual care for patients with ANIU.

**Visit windows**

Treatment run-in weeks 4, 8 and 16: +7 days

RCT all visits: ±7 days

## 5.4 Setting

This study will take place across NHS tertiary UK ophthalmology departments, which have specialist uveitis services.

## 5.5 Key design features to minimise bias

The placebo-controlled trial design (including concealed randomisation) will protect against bias arising from the randomisation process. It will also protect against bias due to deviations from intended interventions and bias in measurement of outcomes, since participants, clinicians and other staff caring for participants, members of the research team (except the study statistician) and participants will be masked to participants' allocations [54]. The success of masking will be assessed (participants and their care team may become unmasked due to side effects). The allocation will be stratified by centre to minimise confounding due to centre-specific factors. Applying standard protocols, pre-defining procedures for participant follow-up/data collection and applying the procedures to all participants in the same way will help to minimise bias due to deviations from intended interventions and bias in measurement of outcomes in the event of instances of unmasking. Adherence to all aspects of the protocol will be monitored.

Bias due to missing outcome data, i.e. systematic differences in withdrawals between the groups, will be minimised by: i) the offer of a switch in allocation in the event of TF; ii) maintaining regular contact with participants throughout the duration of the trial to maximise the proportion of participants for whom all outcome data are available. The Data Monitoring and Safety Committee (DMSC) will monitor attrition by group.

We will minimise bias in selection of the reported result by pre-specifying outcomes (see 5.8) and by writing a detailed statistical analysis plan in advance of locking the database at the end of data collection (see 7.1).

## 5.6 Trial population

The target population is adults with active or controlled ANIU. We will define ANIU in relation to anatomic descriptors of intermediate, posterior and panuveitis, because these features cause most sight loss [11, 45]. This will allow treatment results to be applied across specific diseases, increasing applicability to UK patients with ANIU who do not respond to usual care [1, 4, 55, 56]. There is a potential trade-off with efficacy, but it is not feasible to recruit to separate trials for different autoimmune diseases and the TRI design should offset any average loss of efficacy.

The frequency of different specific diseases in the trial population is expected to be similar to other trials: ocular autoimmune (idiopathic) 60%; Birdshot Uveitis 30%; multifocal choroiditis 4%; PIC 5%; Vogt Kayanagi Harada 1% [4]; and sarcoidosis where the mechanism is autoimmune and TNFa is a critical cytokine.

To inform a commissioning policy for all patients in whom add-on adalimumab is indicated, we need to recruit patients to the TRI who:

(a) present with active sight-threatening ANIU in either or both eyes and who are taking steroids >5mg/day or being started on >5mg/day, or
(b) patients already being treated for ANIU and taking >5mg/day of steroids and other IMT drugs as required.

In the subgroup presenting with new active disease, remission will be induced with high dose CS; CS will be tapered to <=5mg/day over 16 weeks in both groups. The treatment goal in the TRI is the same for both groups, i.e. disease remission with <=5mg/day CS (see 6.3.1). If achieved by the end of the TRI, participants will be eligible for randomisation.

### *5.6.1 Inclusion criteria*

A participant may take part in the study if **ALL** of the following apply:

1. Participant is aged 18 years or over;
2. Participant has sight threatening ANIU and is prescribed CS >5.0mg/day. ANIU will be diagnosed on the basis of the criteria used to define TF (see 5.8.1);
3. Women must have a negative pregnancy test and be willing to use effective contraception* for the duration of the participation in the trial and for 5 months after, or be surgically sterile or post-menopausal for >12 months.
4. Participant is able to provide informed consent.

* This includes: progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action, male or female condom with or without spermicide cap, diaphragm or sponge with spermicide, combined (eostrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal or transdermal), progestogen-only hormonal contraception associated with inhibition of ovulation: (oral, injectable, implantable), intrauterine device, intrauterine hormone-releasing system, bilateral tubal occlusion, vasectomised partner, sexual abstinence.
  NB. A pregnancy test only needs to be repeated if there is reason to suspect the participant has become pregnant. If a participant becomes pregnant during the trial the treating clinician must discuss the options with the patient on whether or not to continue in the trial, referring to the current SmPC for guidance on pregnancy and Imraldi™.
  There are no special precautions/contraceptive requirements for male participants with female partners of child-bearing potential.

*5.6.2 Exclusion criteria*

A participant may not enter the study if any of the following apply:

1. Participant has controlled ANIU and is maintained on CS ≤5.0mg/day at the time of screening;
2. Participant has untreated or active tuberculosis;
3. Participant has severe infection, sepsis or opportunistic infection;
4. Participant has uncontrolled glaucoma;
5. Participant has multiple sclerosis;
6. Participant is HIV positive;
7. Participant has hepatitis B or hepatitis C;
8. Participant has syphilis;
9. Participant has Lyme disease;
10. Participant has Behcet's disease;
11. Participant has heart failure (NYHA III/IV);
12. Participant has been diagnosed with cancer <5 years ago;
13. Participant is undergoing monitoring for recurrence of cancer / tumour growth where their oncologist has concern that a TNFalpha inhibitor would be contraindicated;
14. Participant is taking another biologic drug;
15. Participant has taken an anti-TNF drug within the previous 90 days (anakinra and abatacept are contraindicated);
16. Participant has an ocular CS implant within the previous 12 months or an intravitreal steroid injection within the previous 3 months;
17. Participant is pregnant;
18. Participant has a known allergy or hypersensitivity to adalimumab or any of its excipients (refer to summary of product characteristics (SmPC) for list of excipients; Appendix 1 section 6.1);
19. Participant is taking part in another interventional study.

## 5.7 Trial interventions

The technology being evaluated is fortnightly 40mg subcutaneous injection of Imraldi™, a licensed biosimilar for adalimumab.

The comparator intervention will be subcutaneous injections of placebo. The placebo for the trial will be provided by Biogen GmbH. It will be identical in all respects to the commercially-available Imraldi™ product, with the exception of adalimumab content and the commercial Imraldi™ label will not be applied. It will be over-labelled to identify the placebo as IMP (see 5.1).

The TRI feature of the study will evaluate a policy of treating all eligible patients with adalimumab for 16 weeks but only continuing treatment beyond 16 weeks in the subset that are successfully maintained with inactive disease in both eyes on <=5mg CS at 16 weeks. In accordance with the marketing authorisation for adalimumab, the TRI will commence with an 80mg subcutaneous dose of adalimumab (using two pre-filled pens) and continue with fortnightly 40mg injections starting one week after the initial 80mg dose, (weeks 1, 3, 5, 7, 9, 11, 13 and 15). If an injection date is missed, the advice to patients is to administer the missed injection immediately upon remembering. The patient should then adhere to their original injection schedule, i.e. administer their next injection 2 weeks after the date their previous injection was due had they not taken a dose late. The TRI will end at 16 weeks when response will be assessed. Responders (see 6.3.1) who remain eligible and confirm consent at 16 weeks will be randomly allocated to adalimumab or placebo.

After randomisation, participants will self-medicate with fortnightly 40mg injections of drug or placebo to the end of the trial (follow-up 48 weeks to 128 weeks (approx. 30 months)). In the event of TF in either or both eyes, open label drug will be restarted as per the TRI for 16 weeks and, if a participant responds, allocation will be switched (up to two times) and trial treatment restarted, maintaining masking (see 5.1). Details of the drug are described in the summary of product characteristics (SmPC; Appendix 1) for Imraldi™. The manufacture, quality assurance, labelling and packaging of the placebo are described in the IMP dossier.

Study medication will be stored by an NHS pharmacy department in accordance with Good Clinical Practice and pharmacy department SOPs. Study medication will be transferred to a third party organisation (Healthcare at Home Ltd) to dispense the medication and distribute it directly to participants' homes. Drug accountability including stock control, ordering, and prescribing will be managed by an IMP tracker database [57].

Healthcare at Home Ltd will use their network of trained nurses to deliver training to participants in their homes about self-administration of the study medication at the start of the TRI period. Healthcare at Home Ltd will use their fully traceable, cold-chain supply network to deliver study medication to participants' homes for the duration of the trial. Healthcare at Home Ltd deliver commercial Imraldi™ and train patients who receive the drug as part of standard NHS care and as such are experienced in providing these services and have processes in place for reporting AEs or issues with specific pre-filled pens to patients' care teams (i.e. hospital sites).

Both the IMP and placebo will be labelled in accordance with Annex 13. The contents of the label will be submitted to the MHRA for approval. Storage of the IMP, both drug and placebo, will be in accordance with the SmPC/dossier (Appendix 1). The IMP will be accounted for according to NHS pharmacy standards.

The SmPC Imraldi 40mg solution for injection in a pre-filled pen, dated 12 Sept 2019, will be used as the reference Safety Information (RSI). The currently approved SmPC will be attached to the pdf version of the protocol.

In accordance with the SmPC, participants cannot be administered live vaccines for the duration of their time on the trial intervention.

## 5.8 Primary and secondary outcomes

### *5.8.1 Primary outcome*

The primary outcome is time to the first treatment failure (TF), for a participant, i.e. TF may occur in either eye and may be triggered by incident ANIU in an eye that did not previously have ANIU. TF is defined as a composite of standard criteria reflecting clinical decision-making, including visual acuity and clinical signs of active inflammation which have been used successfully in other ANIU trials [1, 4, 58]. Our definition of TF will modify the composite endpoint used in the VISUAL trials [1,2] by: (i) excluding isolated anterior uveitis as a TF event (it can be treated effectively and safely with low dose, low frequency topical CS); and (ii) including a clinically important deterioration in CMO as a TF event [11], because it is an ANIU complication causing visual loss in a third of patients [59] which has often studied as a TF event in other trials of ANIU. Participants will be assessed for TF at each visit after randomisation. Any of the following criteria in one or both eyes, where applicable, will constitute TF:

i. >=15 letter decrease in best corrected visual acuity (BCVA), compared to BCVA measured by an optometrist masked to treatment allocation at the 16 week TRI visit;

ii. new active inflammatory chorioretinal lesions (masked review of fundus colour and autofluorescence images by clinician);
iii. >20% increase in central macular thickness (CMT), compared to CMT at the 16 week TRI timepoint (CMT is a parameter that is measured by an automated algorithm when doing optical coherence tomography (OCT));
iv. onset or worsening of retinal vasculitis (masked clinician assessment of fundus fluoroscein angiogram);
v. 2 step worsening of vitreous haze cf. compared to best score at either the 8- or 16-week TRI visit (masked clinician assessment);
vi. prescription by a masked clinician of >5mg/day CS to maintain disease remission (i.e. to avert relapse before any of the above criteria for manifest active disease (i-v))

The arrangements for managing a participant's continued follow-up in the trial have been described above, including switching treatment allocation without unmasking allocation (see 5.1 and 5.7).

*5.8.2 Secondary outcomes*

Secondary outcomes will include:

a) Individual TF components, assessed at each trial visit;
b) Retinal morphology (OCT; macular and retinal nerve fibre layer), assessed at each trial visit;
c) AEs, assessed at each trial visit;
d) HRQoL measured using the EQ-5D-5L questionnaire [3][7] at the start of TRI, at 16 weeks immediately before randomisation, then 12-weekly after randomization up to week 48 and 16-weekly thereafter;
e) Patient-reported symptoms of side-effects at each trial visit after starting the TRI and at any interim attendance prompted by an AE;
f) Patient-reported visual function [2], at the start of TRI, at 16 weeks immediately before randomisation, 12-weekly up to week 48 and 16 weekly thereafter;
g) Employment status at the start of TRI, at 16 weeks immediately before randomisation, 12-weekly up to week 48 and 16 weekly thereafter;
h) Resource use during follow-up after randomisation, at the start of TRI, at 16 weeks immediately before randomisation, 12-weekly up to week 48 and 16 weekly thereafter.

## 5.9 Sample size justification

We hypothesise that participants randomised to receive adalimumab will have a lower risk of TF than those allocated to receive placebo. The sample size has been chosen to test this hypothesis. In estimating the sample size, we have considered the results observed in previous studies; hazard ratios (HRs) for time to first TF in two previous trials of adalimumab (in patients with active and inactive ANIU, respectively) were 0.50 and 0.57 [1, 4]. As our study will only randomise participants who are found to respond to treatment in the TRI phase, we anticipate that we will observe a greater benefit than in these trials, which included both responders and non-responders. Therefore, we have set the target HR at 0.5. Assuming that 27% in the placebo group survive free from TF 12 months after randomisation (estimated from placebo groups of the two trials with 40% active and 60% inactive disease), we have set a target sample size of 174 randomised participants. A study of this size will have 90% power to detect a HR 0.5 at a 5% two-sided significance level, allowing for 10% loss-to-follow-up in the first 12 months.

# 6. Trial methods

## 6.1 Description of randomisation

Eligibility will be checked, and consent obtained to the whole study at the beginning of the TRI, with both being confirmed at the 16-week visit when responder status has been ascertained and eligibility for the trial has been confirmed. Randomisation will be carried out at this visit so that the appropriate IMP can be prescribed at the same time. Randomisation will be performed by a member of the local research team on the delegation log who is authorised to do so using a secure internet-based randomisation system ensuring allocation concealment. Participants will be allocated in a 1:1 ratio to either adalimumab or placebo.

The random allocations will be computer-generated by a statistician in the trials unit in blocks of varying size (unknown to trial personnel) and stratified by centre, before the trial starts to recruit. The allocations will be embedded in the trial database and concealed from all clinical and research personnel until a participant has been recruited. Key data to characterise a participant's current clinical status at will be collected at the time of randomisation.

## 6.2 Masking and unmasking

Participants, their clinical care team (i.e. their ophthalmologist and other members of eye care team) and the research nurse(s) responsible for participant follow-up, will all be masked to participants' allocations. Except for the study statistician, clinical trials staff managing the trial will also be masked to allocation. The randomisation system will provide a unique code which the study pharmacy (Healthcare at Home, Ltd) will use to identify the pens to be dispensed. It will not be possible to distinguish between syringes containing drug and placebo dispensed during the RCT on the basis of their appearance or any other characteristics.

The IMP will be injected subcutaneously by participants at home. The prefilled syringes will look identical and we are not aware of any sensation from self-injection of adalimumab that will differ from injection of placebo. Adalimumab may induce side-effects in some patients that will inadvertently unmask participants. We acknowledge this may be a limitation of the study. We will collect information to document the extent to which this happens.

Participants will be made aware before entering the study that they will not be told which treatment they will receive during the RCT. Doctors will prescribe the 'study medication' with a unique code; appropriate pens, corresponding to the code, will be dispensed to participants. Bristol Trials Centre (BTC) and other designated personnel will be able to break the code in the event of an emergency but will not know the allocation in the usual course of dispensing a prescription for trial IMP.

If clinically indicated (i.e. in the event of a serious adverse event (SAE) requiring knowledge of the allocation for treatment) the treatment allocation will be unmasked by the BTC during office hours or by the on-call pharmacist at UH Bristol. Unmasking will be done using the secure web-based IMP-Track IMP management and accountability system [57]. Only authorised personnel will have access to the IMP-Track system. Any request for unmasking will be fully documented, recording the identity of the person asking for the allocation to be unmasked and the reason for unmasking. Instances of unmasking will be monitored throughout the trial.

## 6.3 Research procedures

Dedicated uveitis clinics are run in each centre, which will consider all new referrals. Medical and uveitis history will be recorded, screening investigations will be ordered and eligibility will be assessed.

Potentially eligible patients will be consented (to screening and the full study on one consent form) prior to full screening assessments being done. Patients who are eligible to take part after all required screening assessments are done will be enrolled in the TRI after confirming they are still willing to take part.

Data will be collected on the numbers screened, eligible pre- and post-consent and starting the TRI, including reasons for declining participation. Data will be captured in a purpose-designed secure database, with 'real time' validation, which will be developed by the BTC CTEU to support the trial. Resource use data will be collected using bespoke questionnaires and trial case report forms (CRFs).

Participants starting the TRI will be seen at 4 weeks, 8 weeks and 16 weeks. This visit frequency approximates usual care, when a patient starts treatment with adalimumab. At the 16 week visit, if a participant is classified as a responder (see 6.3.1) and agrees to continue in the randomised trial, he/she will be randomised (see 5.7, 5.8.1 and 6.1). Follow-up visits will be scheduled at 12-weekly intervals up to 48 weeks after randomisation and 16-weekly intervals thereafter, consistent with usual care for patients with ANIU.

### *6.3.1 Responder criteria*

A responder will be defined as meeting ALL of the following criteria at the 16 week TRI visit:

i. No activity on colour fundus or autofluorescence imaging indicative of inflammatory chorioretinal lesions;
ii. CMT ≤ 320μm on any OCT machine [11];
iii. No leakage indicating retinal vasculitis on fundus fluorescein angiography within the first 90 seconds [11];
iv. ≤ 0.5 vitreous haze Binocular Indirect Ophthalmoscopy (BIO) score;
v. Prescription of ≤ 5.0mg/day CS to achieve/maintain disease remission [11].

Investigations relating to eligibility, data about safety of medications, refraction and imaging will be carried out during the TRI. The following investigations will be carried out at all visits after randomisation (see Table 1):

a) Ophthalmic examination, including slit lamp examination with dilated fundoscopy and tonometry;
b) Vital signs / weight (every 24 weeks);
c) Changes in medications, AEs, adherence to medications
d) BCVA (ETDRS letter chart) determined by an optometrist masked to treatment allocation;
e) Retinal imaging, comprising OCT, macular and retinal nerve fibre layer;
f) In addition, the following patient-reported outcome measures will be collected: EQ-5D 5L; VCM1; Work Productivity and Activity Impairment Questionnaire: Specific Health Problem Questionnaire (WPAI-SHP); symptoms of side effects.

In addition, blood will be taken at the start of the TRI, 16 weeks (both responders and non-responders, at the end of the TRI), 48 and 96 weeks after randomisation, and if a participant experiences TF. Serum and DNA will be prepared from the blood samples and stored. These samples, and retinal images taken as part of the study, will be collected and stored as a resource for future studies of markers for (a) responsiveness to adalimumab and (b) TF.

## 6.4 Duration of treatment period

As described in section 5.1, we have chosen to try to keep participants in the trial until all participants have a minimum of 48 weeks follow-up and the trial will be close to reporting [53].

Treating with adalimumab for longer than 48 weeks is consistent with how adalimumab is used in practice in patients who are maintained on it successfully, so will contribute valuable longer term evidence about the intervention. This approach is likely to foster better commitment among participants and is supported by the PPI panel.

### 6.5 Definition of end of trial

The RCT will end for a participant after they have completed follow up for a minimum of 48 weeks up to a maximum of 128 weeks (approx. 30 months) post-randomisation, or earlier if they withdraw from the study completely. The end of the trial as a whole will be after all trial participants have completed follow up, all data queries have been resolved and the database has been locked.

### 6.6 Data collection

Data collection will include the elements described in Table 1.

**Table 1 Schedule of events during the trial**

| | | | Treatment run-in | | | | RCT | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **No.** | **Data item to be collected** | **Screen/ baseline** | **1st injection (time 0)** | **4 w** | **8 w** | **16 w / Rx** | **12 w** | **24 w** | **36 w** | **48 w** | **Then:** |
| 1. | Confirm eligibility | ✓ | | | | ✓ | | | | | |
| 2. | Consent confirmed | ✓ | | | | ✓*3 | | | | | |
| 3. | Medical history | ✓ | | | | | | | | | |
| 4. | Baseline characteristics | ✓ | | | | | | | | | |
| 5. | Vital signs | ✓ | | | | ✓ | ✓ | ✓ | ✓ | ✓ | 16 w+ |
| 6. | Weight | ✓ | | | | ✓ | | ✓ | | ✓ | 16 w+ |
| 7. | History directed medical exam | ✓ | | | | ✓ | ✓ | ✓ | ✓ | ✓ | 16 w+ |
| 8. | Full blood count (FBC) | ✓ | | ✓ | | ✓ | ✓ | ✓ | ✓ | ✓ | 16 w+ |
| 9. | Liver function tests | ✓ | | ✓ | | ✓ | ✓ | ✓ | ✓ | ✓ | 16 w+ |
| 10. | Electrolytes profile | ✓ | | ✓ | | ✓ | ✓ | ✓ | ✓ | ✓ | 16 w+ |
| 11. | Glucose test | ✓ | | ✓ | | | | | | | |
| 12. | TB IGRA test | ✓ | | | | | | | | | |
| 13. | Chest X-ray | ✓ | | | | | | | | | |
| 14. | 12-lead ECG*1 | ✓ | | | | | | | | | |
| 15. | MRI*1 | ✓ | | | | | | | | | |
| 16. | Syphilis test | ✓ | | | | | | | | | |
| 17. | HIV test | ✓ | | | | | | | | | |
| 18. | Hep B / Hep C test | ✓ | | | | | | | | | |
| 19. | Lyme IgG/IgM Antibody Serology*1 | ✓ | | | | | | | | | |
| 20. | Varicella history/antibody test*5 | ✓ | | | | | | | | | |
| 21. | Pregnancy test (women only) | ✓ | | | | | | | | | |
| 22. | BCVA | ✓ | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | 16 w+ |
| 23. | OCT | ✓ | | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | 16 w+ |
| 24. | Fundus colour imaging | ✓ | | | | ✓ | ✓ | ✓ | ✓ | ✓ | 16 w+ |
| 25. | Autofluorescence imaging | ✓ | | | | ✓*2 | ✓*2 | ✓*2 | ✓*2 | ✓*2 | 16 w+*2 |
| 26. | Fundus fluorescein angiogram | ✓ | | | | ✓*2 | ✓*2 | ✓*2 | ✓*2 | ✓*2 | 16 w+*2 |

| | | | Treatment run-in | | | | RCT | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **No.** | **Data item to be collected** | **Screen/ baseline** | **1st injection (time 0)** | **4 w** | **8 w** | **16 w / Rx** | **12 w** | **24 w** | **36 w** | **48 w** | **Then:** |
| 27. | Clinical exam (including slit-lamp examination and indirect ophthalmoscopy) | ✓ | | ✓ | ✓ | | | | | | |
| 28. | Clinical exam for treatment failure (including slit-lamp examination and indirect ophthalmoscopy) | | | | | ✓ | ✓ | ✓ | ✓ | ✓ | 16 w+ |
| 29. | Adverse events | | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| 30. | EQ-5D-5L | ✓ | | | | ✓ | ✓ | ✓ | ✓ | ✓ | 16 w+ |
| 31. | VCM1 | ✓ | | | | ✓ | ✓ | ✓ | ✓ | ✓ | 16 w+ |
| 32. | Symptoms of side-effects | ✓ | | | | ✓ | ✓ | ✓ | ✓ | ✓ | 16 w+ |
| 33. | WPAI-SHP questionnaire | ✓ | | | | ✓ | ✓ | ✓ | ✓ | ✓ | 16 w+ |
| 34. | Blood sample (for serum)*[4] | ✓ | | | | ✓ | ✓*[4] | ✓*[4] | ✓*[4] | ✓ | 48 w+*[4] |
| 35. | Blood sample (for DNA) | ✓ | | | | | | | | | |
| 36. | Resource use | | | | | ✓ | ✓ | ✓ | ✓ | ✓ | 16 w+ |

- Blood tests done as standard care can be accepted for screening up to a maximum of 3 months prior to the date of the screening visit.
- Chest x-ray, MRI and ECG done as standard care can be accepted for screening up to a maximum of 6 months prior to the date of the screening visit.
- Enrolment in the TRI (i.e. writing the TRI prescription) must be done a maximum of 4 weeks after the date of the screening visit.
- TRI follow-ups start from the date of 1st injection (time 0); RCT follow-ups start from the date of randomisation.
- Visit windows: TRI +7 days; RCT ±days.

*[1] Only required if clinically indicated.
*[2] Only required if clinical indicated to support decision about TF.
*[3] Written informed consent will be obtained at the start of the TRI; this consent will be confirmed among responders at the start of the RCT.
*[4] A blood sample for serum will also be taken in the event of treatment failure being detected at a post-randomisation visit.
*[5] If patient has no history of varicella, screen for varicella antibodies.

**BCVA** – best corrected visual acuity; **TF** – treatment failure; **OCT** – optical coherence tomogram; **Rx** – Randomisation; **VCM1** – Visual Function Questionnaire; **WPAI-SHP** – Work Productivity and Activity Impairment Questionnaire: Specific Health Problem Questionnaire; **w** - weekly; **w+** - weekly thereafter

### 6.7 Source data

Source data will differ for different items of data.

- Items 1-22, 27-29 and 36: CRFs designed specifically to capture the required data for the study;
- Items 23-26: OCT, fundus, autofluorescence and fundus fluorescein angiography images submitted for independent grading;
- Items 30-33: Completed questionnaires returned by participants;
- Items 34-35: not applicable; samples for storage only (for future research).

### 6.8 Planned recruitment rate

Projecting recruitment is complicated because: (a) estimates of several parameters are uncertain, (b) participants will be recruited with both incident (active) and prevalent (inactive) ANIU and (c) the TRI design causes a lag. **Table 2** shows our projection with the assumptions described in a footnote.

### 6.9 Participant recruitment

Patients with ANIU present to, and are managed by, specialist ophthalmologists staffing clinics in tertiary hospitals which treat autoimmune ophthalmic diseases. Clinics will include new patients with ANIU and existing patients who are having ongoing treatment monitored. The eligibility criteria allow recruitment of either kind of patient. New patients started on treatment with CS will be eligible, with an attempt being made to reduce CS to <7.5 mg over 16 weeks alongside treatment with adalimumab. Existing patients who are already being treated but who require >5mg/day CS will also be eligible, with an attempt being made to reduce CS to ≤5.0 mg over 16 weeks alongside treatment with adalimumab. Both new patients and existing patients may be prescribed other non-biologic IMT in addition to CS at the discretion of the clinician.

Potential participants will initially be screened from their medical records by the direct care team according to local hospital processes. Patients who are initially eligible will be given or sent an invitation letter and a patient information leaflet (PIL) describing the study. Potential participants will be given time to read the PIL and to ask questions that they may have; the person taking consent will discuss the trial with the potential participant prior to consent. Consent will be taken in clinic. The PIL will describe both the TRI period and the RCT, and the informed consent form (ICF) will include consent to both phases of the trial. Consented participants will undergo further screening assessment to determine their full eligibility to participate. Consented participants who meet all eligibility criteria will be enrolled in the TRI. Eligibility will be confirmed by a clinician on the delegation log. Participants who are classed as responders at the end of the TRI will be asked if they are willing to continue to the randomised phase of the study, before carrying out randomisation; their willingness to continue will be recorded at the time.

**Table 2 projected recruitment of participants with active and inactive ANIU**

| Trial month | Trial phase | Main trial activity | Number of centres | ANIU eligible for TRI | | Number randomised | |
|---|---|---|---|---|---|---|---|
| | | | | Inactive | Active | per month | cumulative |
| 1 to 3 | Pilot | Setup | 0 | 0 | 0 | 0 | 0 |
| 4 | Pilot | Recruit; TRI only | 1 | 2 | 1 | 0 | 0 |
| 5 | Pilot | Recruit; TRI only | 2 | 3 | 1 | 0 | 0 |
| 6 | Pilot | Recruit; TRI only | 3 | 5 | 2 | 0 | 0 |
| 7 | Pilot | Recruit; TRI only | 5 | 9 | 3 | 0 | 0 |
| 8 | Pilot | Recruit & rand'x | 7 | 12 | 4 | 1 | 1 |
| 9 | Pilot | Recruit & rand'x | 9 | 16 | 6 | 2 | 3 |
| 10 | Pilot | Recruit & rand'x | 11 | 19 | 7 | 3 | 6 |
| 11 | Pilot | Recruit & rand'x | 13 | 23 | 8 | 5 | 11 |
| 12 | Pilot | Recruit & rand'x | 14 | 24 | 9 | 7 | 18 |
| 13 | Pilot | Recruit & rand'x | 14 | 24 | 9 | 9 | 27 |
| 14 | Pilot | Recruit & rand'x | 14 | 24 | 9 | 11 | 38 |
| 15 | Pilot | Recruit & rand'x | 14 | 24 | 9 | 13 | 51 |
| 16 | Main RCT | Recruit & rand'x | 14 | 23 | 9 | 14 | 65 |
| 17 | Main RCT | Recruit & rand'x | 14 | 21 | 9 | 14 | 79 |
| 18 | Main RCT | Recruit & rand'x | 14 | 19 | 9 | 14 | 93 |
| 19 | Main RCT | Recruit & rand'x | 14 | 16 | 9 | 14 | 107 |
| 20 | Main RCT | Recruit & rand'x | 14 | 12 | 9 | 13 | 121 |
| 21 | Main RCT | Recruit & rand'x | 14 | 9 | 9 | 13 | 133 |
| 22 | Main RCT | Recruit & rand'x | 14 | 0 | 9 | 10 | 143 |
| 23 | Main RCT | Rand'x only | 14 | 0 | 0 | 10 | 154 |
| 24 | Main RCT | Rand'x only | 14 | 0 | 0 | 9 | 162 |
| 25 | Main RCT | Rand'x only | 14 | 0 | 0 | 7 | 170 |
| 26 | Main RCT | Rand'x only | 14 | 0 | 0 | 4 | 174 |
| 27 to 39 | Main RCT | Follow-up only | 14 | 0 | 0 | 0 | 174 |
| 40 | Main RCT | follow-up | 14 | 0 | 0 | 0 | 174 |
| 42 | Main RCT | d-b lock | 14 | 0 | 0 | 0 | 174 |
| 43 to 45 | Main RCT | analysis | 14 | 0 | 0 | 0 | 0 |
| 43 to 48 | Main RCT | write-up | 14 | 0 | 0 | 0 | 0 |
| **Total** | | | | **285** | **129** | **174** | |

Footnote: rand'x – randomise; annual incidence, 0.0003 [30]; prevalence, 0.00083 [30]; ANIU proportion >20yrs, 0.763; total incident cases,12541; total prevalent cases, 34696; centres treating ANIU, 30; incident ANIU/centre/year, 418; prevalent ANIU/centre/year, 1157; p("eligible"), 0.06; p(approached), 1.00, p(ineligible after approach), 0.20; p(consenting for TRI), 0.40; p(responding), 0.50; p(available to randomise at end of TRI), 0.15; number of centres, 14.

### 6.10 Discontinuation/withdrawal of participants

As described in section 5.1, we will try to keep all participants in the study until the last participant has completed the 48-week visit. Each participant has the right to withdraw at any time. In addition, the investigator may withdraw the participant from treatment with adalimumab/placebo if continuation is considered not to be in the best interests of the participant, e.g. following a SAE or pregnancy. Participants must also stop treatment with

adalimumab/placebo after a maximum of two treatment switches (see section 5.1). In all instances of stopping treatment with adalimumab/placebo we will request that participants continue to attend the scheduled research visits so that the relevant data can be collected. All data and samples collected will be analysed and stored unless a participant expressly requests that his/her data or samples be destroyed.

### 6.11 Frequency and duration of follow up

The follow-up schedule is described in Table 1, Section 6.6.

### 6.12 Likely rate of loss to follow-up

Assuming that 27% in the placebo group are free from TF 12 months after randomisation (estimated from placebo groups of the two trials with 40% active and 60% inactive disease [1, 4]), we have set a target sample size of 174 randomised participants. A study of this size will have 90% to detect a HR 0.5 at the 5% two-sided significance level, allowing for 10% loss-to-follow-up in the first 12 months.

There are no special features to minimise bias due to missing outcome data. Established methods will be used to maximise the proportion of participants for whom all outcome data are available and the proportion of participants who receive the intervention to which they were allocated. However, ANIU is a debilitating condition for patients who are affected and, subject to other comorbidities they experience, we expect participants to attend their follow-up visits as scheduled; these are set at the same frequency as required for usual care so extra research-only visits should be unnecessary.

### 6.13 Expenses

The schedule of follow-up visits has been designed to be the same as for usual care for a patient with ANIU. Therefore, it is not expected that participants will be reimbursed for travel expenses. Participants may be reimbursed for the cost of parking if a visit takes longer than a usual care visit as a direct result of research-specific procedures (i.e. assessments they would not have had if they were not taking part in the trial).

## 7. Statistical analyses

### 7.1 Plan of analysis

The data will be analysed according to intention to treat (ITT) and follow CONSORT reporting guidelines. Analyses will be adjusted for centre. The primary outcome, time from randomisation to first TF, will be compared using survival methods, allowing for censoring of any participant who is lost to follow-up. Secondary outcomes up to the time of TF will be compared using a mixed linear or logistic regression model as appropriate, adjusted for baseline measures when available. These outcomes will be modelled jointly with the time to first TF. Changes in treatment effect with time will be assessed by adding a treatment x time interaction to the model and comparing models using a likelihood ratio test. Model fit will be assessed and alternative models and/or transformations (e.g. to induce normality) will be explored where appropriate. Frequencies of AEs will be described. Treatment differences will be reported with 95% CIs.

A secondary analysis will include follow-up time after the first TF. A participant who experiences a first TF will restart adalimumab (repeating the TRI) for 16 weeks. If after 16 weeks the participant satisfies the criteria for being a responder, he/she will re-enter the trial treated with the opposite treatment to the one originally allocated (placebo if originally on intervention, or vice versa). Restarting treatment will become the time origin for the second period of follow-up.

(This process can be repeated another time, in the event of a second TF, generating up to three discrete "disconnected" periods of follow-up. Follow-up will cease after a third TF.)

The allocation group (and other important covariates) will be updated when "study" treatment (intervention or placebo) is restarted. We will analyse multiple periods of treatment exposure within participants with survival models. The primary analysis, i.e. time to first TF will be unbiased. Analyses of subsequent follow-up periods must be considered to be non-randomised, and potentially biased, since participants' characteristics are likely to predict TF. Therefore, if adalimumab is effective, second and third follow-up periods will not be distributed in a balanced way across the original randomly assigned groups and it will be necessary to consider important covariates. Nevertheless, switches will provide a within-subject comparison of survival free from TF between intervention and placebo.

A detailed analysis plan will be prepared.

### 7.2 Subgroup analyses

No subgroup analyses are planned.

### 7.3 Frequency of analyses

The primary analysis will take place when follow-up is complete for all recruited participants. No formal interim analysis is planned. Safety data will be reported to the Data Monitoring and Safety Committee (DMSC) every 3 months, together with any additional analyses the committee request. In these reports the data will be presented by group, but the allocation will remain masked.

Interim analyses will be decided in advance in discussion with the Data Monitoring and Safety Committee (DMSC). There is no intention to compare any outcomes between groups at the end of the internal pilot phase; the only analyses will be descriptive statistics to summarise eligibility and recruitment to decide whether the trial satisfies the progression criteria.

### 7.4 Criteria for the termination of the trial

The trial may be terminated early by the Trial Steering Committee. A decision to terminate may arise from a recommendation by the DMSC to stop the trial, for example based on *an interim analysis of the data from the trial* or if the results of another study make the completion of the trial unnecessary.

### 7.5 Economic issues

The within-trial economic evaluation will aim to determine the relative cost-effectiveness of adalimumab compared to usual care. We will carry out the cost-effectiveness analysis largely from the perspective of the UK NHS but will also aim to explore costs to society in the form of productivity cost changes.

Established guidelines will be used for the conduct of the economic evaluation [60]. The main outcome measure for the economic evaluation will be quality adjusted life years (QALYs), estimated using the EuroQol EQ-5D 5L, administered at baseline (start of the TRI; n≈400), at 16 weeks (time of exiting the study because of non-response or randomisation; n≈400), then at each subsequent visit (n<=174), i.e. 3-monthly up to 12 months and 4 monthly thereafter). Respondents will be assigned valuations derived from published UK population tariffs [61] and the mean number of QALYs per trial arm and incremental QALYs will be calculated.

For the costing component, resource use data will be collected by adding questions to the trial CRFs. Resource use information will be collected on quantities of drugs of financial significance administered in the two alternative trial arms and resources associated with treating any of these drug side-effects, including hospital admissions and additional outpatient visits and GP visits. We will also collect information on patient employment status during the trial in order to estimate productivity cost changes. Unit costs to be added to the resource use information will be taken from nationally published sources such as the BNF and Emit for drug costs and the NHS Reference Costs for any hospital admissions.

The analysis will calculate the average cost and outcome on a per patient basis and use this information to estimate the incremental cost-effectiveness ratios for the different trial arms will be derived, producing an incremental cost per QALY. Probabilistic sensitivity analysis will be used to demonstrate the impact of the variation around the key parameters in the analysis on the baseline cost-effectiveness results. A key sensitivity analysis will be the cost of adalimumab, where we will explore the use of potentially cheaper biosimilars. Results will be expressed in terms of a cost-effectiveness acceptability curve.

## 8. Trial management

University Hospitals Bristol NHS Foundation Trust (UHB) will act as Sponsor. Responsibility for running the RCT will be delegated via an agreement with the University of Bristol. Agreements between the Sponsor and participating centres will be required, as well as standard site-initiation documents, before recruitment commences. The study will be conducted in accordance with Good Clinical Practice (GCP) guidelines, the European Union Directive 2001/20/EC on clinical trials, the Data Protection Act and the UK Policy Framework for Health and Social Care Research. The trial will be registered on an open access clinical trial database (ISRCTN). Clinical trial documents will be archived and held by the Sponsor for 15 years after study closure in accordance with the standard operating procedures of the Sponsor and in compliance with the principles of GCP.

The study will be managed by the CI, clinical and BTC co-applicants, PPI representative and the trial manager, and fully supported by the wider BTC (a UK Clinical Research Network registered clinical trial unit, Reg. No 11 (registered as the Clinical Trials and Evaluation Unit (CTEU). The CTEU has been assimilated into the BTC). The BTC has an established track record of designing, conducting, managing and reporting multi-centre clinical trials in ophthalmology, including trials of investigational medicinal products (e.g. the IVAN and VICI trials, NIHR refs 07/36/01 and 13/94/15). The BTC has experience in building study database systems and providing randomisation services.

The CI and BTC team will work with the co-applicants to prepare the final protocol, submitting the Ethics/HRA, MHRA and local application packs for each site, preparing trial manuals, providing the randomisation service and designing and implementing the data management system. The CI, BTC team and project Sponsor will endeavour to ensure that the trial runs according to the pre-agreed timetable, recruitment targets are met, the CRFs are completed accurately, complies with relevant ethical and other regulatory standards, and that all aspects of the study are performed to the highest quality. Clinical co-applicants and BTC team members will also train investigators at participating centres, check that centres are ready to start (“green light”) and monitor their progress during the study. The trial manager will be the contact point to provide support and guidance to the participating centres/specialties throughout the study.

### 8.1 Day-to-day management

The trial will be managed by a Trial Management Group (TMG), which will meet face-to-face or by teleconference approximately monthly. The TMG will be chaired by a Chief Investigator and will include all members of the named research team (see Chief Investigator & Research Team Contact Details).

An appropriately qualified person by training will be responsible at each site for identifying potential trial participants, seeking informed participant consent, randomising participants, liaising with pharmacy, collecting trial data and ensuring the trial protocol is adhered to.

### 8.2 Monitoring of sites

*8.2.1 Initiation visit*

Before the study commences, training session(s) will be organised by BTC. These sessions will ensure that personnel at each site involved fully understand the protocol, CRFs and the operational requirements of the study.

*8.2.2 Site monitoring*

The trial coordinating centre will carry out regular monitoring and audit of compliance of centres with GCP and data collection procedures described in section 6.6. Monitoring of data collection will be via the study database (checks for data completeness and routine data query review), which will be carried out on a regular basis. The ISF and CRFs will be monitored by site self-completed checklists at least once in the lifecycle of the trial. The TMG will review accumulating data on, including but not limited to, screening, eligibility, recruitment, data completeness, adherence to follow-up, adverse events and protocol deviations in the form of central monitoring reports generated approximately monthly.

### 8.3 Trial Steering Committee and Data Monitoring and Safety Committee

An independent Trial Steering Committee (TSC) will be established to oversee the conduct of the study. It is anticipated that the TSC will comprise the CI and co-lead investigator, an independent chair and at least two additional independent members, at least one of whom will be a patient/public representative. The TSC will develop terms of reference outlining their responsibilities and operational details. The TSC will meet before recruitment begins and regularly (at intervals to be agreed by the TSC but a minimum of once per year) during the course of the study.

An independent DMSC will be established to review safety data during the course of the study and will advise on interim analyses. The DMSC will develop a charter outlining their responsibilities and operational details. The DMSC will meet (before or jointly with the TSC) before the trial begins and they will meet regularly thereafter (at intervals to be agreed by the DMSC but a minimum of once per year). Stopping rules for the trial will be discussed at the first DMSC meeting, and decisions documented in the DMSC Charter.

## 9. Safety reporting

SAEs and AEs will be recorded and reported in accordance with GCP guidelines and BTC CTEU's Serious Adverse Events and Safety Reporting Standard Operating Procedure (SOP-GE-012) (see Figure 2).

Expected events are those associated with adalimumab and are listed in the SmPC (see section 9.1 and Appendix 1). Events that are fatal or life threatening will follow the same reporting procedure as for unexpected events.

All AEs will be recorded on CRFs. The investigator will notify all SAEs to the Bristol Trials Centre within 24 hours of knowledge of the event. The Bristol Trials Centre will report all SAEs to the Sponsor within 24 hours of being notified of the event by the investigator. If the event is expected or is unexpected but not causally related to the intervention, the Bristol Trials Centre will report to the REC, MHRA and DMSC at least annually. If the event is unexpected and causally related to the intervention (suspected unexpected serious adverse reaction (SUSAR)) reporting will be expedited according to the schedule in Figure 2; the Sponsor will report to the MHRA and the Bristol Trials Centre will report to the REC and the DMSC.

In the event that personnel from Healthcare at Home Ltd are made aware of an adverse event they will report the event to the prescribing investigator according to their standard operating procedure. The investigator will then follow the safety reporting schedule in Figure 2.

The Sponsor delegates assessment of expectedness and relatedness to the investigator but will also review each reported SAE and confirm this assessment.

For all SAEs that are ongoing at the time of the initial report, the participant will be actively followed up, and the investigator (or delegated person) will provide a follow-up report within five working days after the initial report and further follow-up reports as new information becomes available until the SAE has resolved.

Elective surgery or intervention(s) during the trial that were planned prior to recruitment to the trial will not be reported as an SAE.

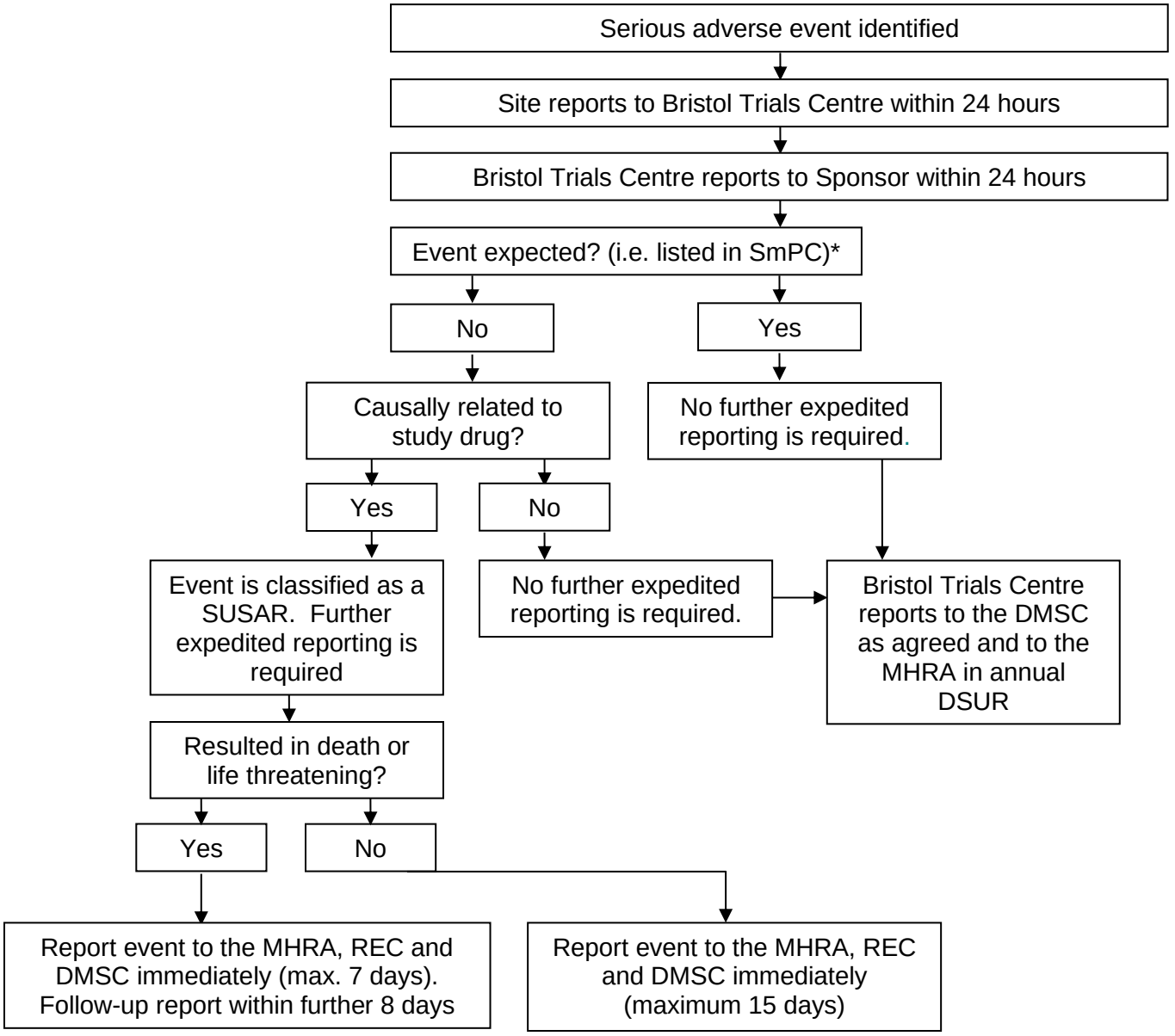
### 9.1 Expected adverse events associated with the study medication

The SmPC for Imraldi™ 40mg solution for injection in using pre-filled pen (Biogen GmbH) dated 12-September-2019 forms the reference safety information and is approved by the MHRA for this trial.

Any updates made to the SmPC will be reviewed by the CI and, in consultation with the Sponsor, a decision made whether the updated document will be submitted to the MHRA for use as the RSI for the trial.

### 9.2 Period for recording serious adverse events

Data on AEs will be collected from the start of the TRI (consented and confirmed eligible to participate in the trial) until 1) the end of the TRI for participants who do not respond and leave the trial at this stage or, 2) the end of the follow-up period in the RCT for all participants who respond and progress into the RCT.




*__NB__ – if the event was fatal or life threatening, should follow the same reporting procedure as for unexpected events.

**Figure 2 Serious adverse event reporting flow chart**

## 10. Ethical considerations

### 10.1 Review by an NHS Research Ethics Committee

The research will be performed subject to a favourable opinion from an NHS REC and Health Research Authority (HRA) approval, including any provisions of a non-NHS site assessment form. Ethics review of the protocol for the trial and other trial related essential documents (e.g. PIL and consent form) will be carried out by a UK NHS REC. Any subsequent amendments to these documents will be submitted to the REC and HRA for approval prior to implementation.

### 10.2 Risks and anticipated benefits

For patients who are not eligible for adalimumab under NICE guidance, the main benefit of participation is the provision of adalimumab for the period of the TRI and, if classified as a responder conditional randomization, subsequently in the RCT. For patients who are eligible for adalimumab under NICE guidance, the main benefit will be knowing more accurately whether they are responders or not and further contributing to the UK cohort of safety and tolerability (which is being maintained for the benefit of all patients being treated with adalimumab).

For patients who are eligible for adalimumab under NICE guidance, the main risk of participation is potential permanent damage from ANIU if a participant is allocated to placebo after being classified as a responder. However, the risk is low as patients with the highest risk of deterioration (e.g. patients with Behcet's disease) will not be included in the study and follow-up visits are frequent enough that treatment failure should be identified before any permanent damage occurs. For all participants, there is also a potential risk of a serious adverse reaction from adalimumab, although such events are rare.

#### *10.2.1 COVID-19 risk/benefit analysis*

In 2020 the COVID-19 pandemic caused significant disruption to the NHS and the provision of non-COVID-19 clinical research. See Table 3 for a risk benefit analysis of the ASTUTE trial in relation to COVID-19.

**Table 3 COVID-19 risk benefit analysis**

| Risk | Benefit |
|---|---|
| ***IMP supply to participants*** | |
| The risk is that participants will not receive their IMP or receive it late due to Healthcare at Home (HaH) being unable to deliver the IMP due to local lock downs.<br><br>We do not anticipate this will be a problem as HaH deliver Imraldi as part of usual NHS care and during the first wave of the pandemic, this service continued as normal. | The benefit of the design of the trial is that the IMP will be delivered to participant's homes by HaH, rather than participants collecting the IMP from the hospital pharmacies. Therefore, participants will not need to wait in the hospital for longer than their appointment time for their IMP to be dispensed by the hospital clinical trials pharmacy, which can sometimes delay patients from being able to leave the hospital. |
| ***Patient on immunosuppressants*** | |
| The risk is the concern that patients on immunosuppressants are at a greater risk if they become infected by COVID-19. | Many of the patients who will be recruited into the ASTUTE trial will already be taking another form of immunosuppressant. Therefore, participating in the trial will not |

| | |
|---|---|
| Based on the first wave of the pandemic, there does not appear to be any additional risk for individual's on immunosuppressants when adopting appropriate "hands, face, space" behaviours.<br><br>There is also no additional risk to participants of having to attend hospital appointments for the research, as the trial visit schedule has been designed to reflect usual care in this population. Care for patients who are eligible for the trial is now being provided face-to-face in a safe clinic environment (as before the pandemic but with extra COVID-19 precautions). | put them at any additional risk from COVID-19. A benefit of the trial is that it may reduce the use of corticosteroids in these participants.<br><br>This was a commissioned call highlighting the importance of this research. Trials are an important part of providing the best possible care to participants. |
| ***Capacity of the research team to conduct the trial*** | |
| The risk is that if research staff are re-deployed to front line services, this will impact the running of the trial and, in particular, prompt identification of adverse events.<br>Based on the first wave of the pandemic, trusts where recruitment had to be stopped due to capacity were nevertheless able to ensure that the reduced research teams focused their efforts on maintaining safety in the trial participants. The safety of participants will remain a top priority even if some research staff are redeployed.<br>A risk to the trial is that recruitment proceeds more slowly or be paused at some sites. | The recently released NIHR guidance for a second wave of the pandemic highlighted that "NIHR funded research staff should not be deployed to front line duties except in exceptional circumstances" [62]. This guidance emphasises the importance of continuing to support non-COVID-19 research.<br><br>As clinical care for sight-threatening uveitis will not pause during a second wave, it is less likely that recruitment will be paused as this trial reflects standard of care. |

### 10.3 Informing potential study participants of possible benefits and known risks

Information about possible benefits and risks of participation will be described in the PIL.

### 10.4 Obtaining informed consent from participants

All participants will be required to give written informed consent. This process, including the information about the trial given to patients in advance of recruitment, is described above in section 6.9.

The PI or members of the team delegated by the PI will be responsible for obtaining informed consent. The consent process will be described in detail in the Trial Manual. Research personnel authorised to obtain consent will be recorded on the Delegation of Responsibilities Log. All individuals obtaining informed consent will have received GCP training. Potential study subjects will be fully apprised of potential risks and benefits of study participation and will be provided with detailed study information prior to written informed consent being sought.

### 10.5 Co-enrolment

Subject to agreement with the Chief Investigator, a participant may be co-enrolled to a non-intervention study as well as to the ASTUTE trial. A participant must not be co-enrolled to another intervention study.

## 11. Research governance

This study will be conducted in accordance with:

- The Medicine for Human Use (Clinical Trial) Regulations 2004
- Good Clinical Practice (GCP) guidelines
- UK Policy Framework for Health and Social Care Research
- European Union Directive 2001/20/EC on clinical trials

### 11.1 Sponsor approval

Any amendments to the trial documents must be approved by the sponsor prior to submission to the REC, HRA and MHRA (if applicable).

### 11.2 NHS confirmation of capacity and capability

Confirmation of capacity and capability is required prior to the start of the trial at each participating site.

Any amendments to the trial documents approved by the REC, HRA and MHRA (if applicable) will be submitted to participating sites for information and implementation, as required.

### 11.3 Investigators' responsibilities

Investigators will be required to ensure that local research approvals have been obtained and that any contractual agreements required have been signed off by all parties before recruiting any participant. Investigators will be required to ensure compliance to the protocol and study manual and with completion of the CRFs. Investigators will be required to allow access to study documentation or source data on request for monitoring visits and audits performed by the Sponsor or BTC CTEU or any regulatory authorities.

Investigators will be required to read, acknowledge and inform their trial team of any amendments to the trial documents approved by the REC, HRA and MHRA (if applicable) that they receive and ensure that the changes are complied with.

### 11.4 Monitoring by sponsor

The study will be monitored and audited in accordance with University Hospitals Bristol's Monitoring and Oversight of Research Activity SOP, which is consistent with the UK Policy Framework for Health and Social Care Research and the Medicines for Human Use (Clinical Trials) Regulations 2004. All study related documents will be made available on request for monitoring and audit by the sponsor (or BTC CTEU if they have been delegated to monitor see 8.2.2), the relevant REC and for inspection by the HRA, MHRA or other licensing bodies. A monitoring plan will be prepared by the Sponsor.

### 11.5 Indemnity

This is an NHS-sponsored research study. For NHS sponsored research if there is negligent harm during the clinical trial when the NHS body owes a duty of care to the person harmed, NHS Indemnity covers NHS staff, medical academic staff with honorary contracts, and those conducting the trial. NHS Indemnity does not offer no-fault compensation and is unable to agree

in advance to pay compensation for non-negligent harm. Ex-gratia payments may be considered in the case of a claim.

### 11.6 Clinical Trial Authorisation

Imraldi™ is classed as an investigational medicinal product and a Clinical Trial Authorisation from the MHRA must be in place before starting the trial.

## 12. Data protection and participant confidentiality

### 12.1 Data protection

Data will be collected and retained in accordance with the UK Data Protection Act 2018 and General Data Protection Regulation (GDPR) 2016.

### 12.2 Data handling, storage and sharing

*12.2.1 Data handling*

The ASTUTE study team will provide the Sponsor with a Data Management Plan prior to the study opening to recruitment.

Data will be entered into a purpose-designed server database hosted on the NHS network. Information capable of identifying individuals and the nature of treatment received will be held in the database with passwords restricted to ASTUTE study staff at the participating site and the co-ordinating centre. Information capable of identifying participants will not be made available in any form to those outside the study. The database and randomisation system will be designed so as to protect patient information in line with data protection legislation. Trial staff will ensure that the participants' anonymity is maintained through protective and secure handling and storage of patient information at participating sites and in accordance with ethics approval. All documents will be stored securely and only accessible by trial staff and authorised personnel. Data will be collected and retained in accordance with data protection legislation.

Access to the database will be via a secure password-protected web-interface. Study data transferred electronically to the University of Bristol network for statistical analyses will be pseudonymised and transferred via a secure network. The participants will be identified using their name and unique study identifier on the secure NHS hosted database.
Data will be entered promptly and data validation and cleaning will be carried out throughout the trial. The trial manual will cover database use, data validation and data cleaning. The manual will be available and regularly maintained.

*12.2.2 Data storage*

All study documentation will be retained in a secure location during the conduct of the study and for 15 years after the end of the study, when all patient identifiable paper records will be destroyed by confidential means. Where trial related information is documented in the medical records, these records will be identified by a label bearing the name and duration of the trial and clearly stating the 'do not destroy before' date. Where electronic records are in use, local site policy will be followed. In compliance with the MRC Policy on Data Sharing, relevant 'meta'-data about the trial and the full dataset, but without any participant identifiers other than the unique participant identifier, will be held indefinitely (University of Bristol server).

*12.2.3 Data sharing*

Data will not be made available for sharing until after publication of the main results of the study. Thereafter, anonymised individual patient data will be made available for secondary research, conditional on assurance from the secondary researcher that the proposed use of the data is compliant with the MRC Policy on Data Sharing regarding scientific quality, ethical requirements and value for money. A minimum requirement with respect to scientific quality will be a publicly available pre-specified protocol describing the purpose, methods and analysis of the secondary research, e.g. a protocol for a Cochrane systematic review. The second file containing patient identifiers would be retained on a secure NHS server for 15 years for record linkage or a similar

purpose, subject to confirmation that the secondary research protocol has been approved by a UK REC or other similar, approved ethics review body. Patient identifiers would not be passed on to any third party.

## 13. Dissemination of findings

The findings will be disseminated by usual academic channels, i.e. presentation at international meetings, as well as by peer-reviewed publications and through patient organisations and newsletters to patients, where available.

## 14. References


1. Jaffe, G.J., et al., *Adalimumab in Patients With Active, Non-infectious Uveitis Requiring High-dose Corticosteroids: the VISUAL-1 Trial*, in *Annals of the Rheumatic Diseases*. 2015. p. 894-850.
2. Frost, N.A., et al., *Development of a questionnaire for measurement of vision-related quality of life.* Ophthalmic Epidemiol, 1998. **5**(4): p. 185-210.
3. Group, E., *EuroQol-a new facility for the measurement of health-related quality of life.* Health Policy, 1990. **16**(3): p. 199-208.
4. Nguyen, Q.D., et al., *Adalimumab for prevention of uveitic flare in patients with inactive non-infectious uveitis controlled by corticosteroids (VISUAL II): a multicentre, double-masked, randomised, placebo-controlled phase 3 trial.* Lancet, 2016. **388**(10050): p. 1183-92.
5. Organization, W.H. *The World Health Report, (2010) Global Data on Visual Impairments*. 04/12/2019]; Available from: http://www.who.int/blindness/GLOBALDATAFINALforweb.pdf.
6. Nussenblatt, R.B., *The natural history of uveitis.* Int Ophthalmol, 1990. **14**(5-6): p. 303-8.
7. Bodaghi, B., et al., *Chronic severe uveitis: etiology and visual outcome in 927 patients from a single center.* Medicine (Baltimore), 2001. **80**(4): p. 263-70.
8. Rothova, A., et al., *Uveitis and systemic disease.* Br J Ophthalmol, 1992. **76**(3): p. 137-41.
9. Darrell, R.W., H.P. Wagener, and L.T. Kurland, *Epidemiology of uveitis. Incidence and prevalence in a small urban community.* Arch Ophthalmol, 1962. **68**: p. 502-14.
10. Suttorp-Schulten, M.S. and A. Rothova, *The possible impact of uveitis in blindness: a literature survey.* Br J Ophthalmol, 1996. **80**(9): p. 844-8.
11. Jabs, D.A., et al., *Standardization of uveitis nomenclature for reporting clinical data. Results of the First International Workshop.* Am J Ophthalmol, 2005. **140**(3): p. 509-16.
12. Agarwal, R.K., P.B. Silver, and R.R. Caspi, *Rodent models of experimental autoimmune uveitis.* Methods Mol Biol, 2012. **900**: p. 443-69.
13. Kilmartin, D.J., et al., *Immunogenetics and clinical phenotype of sympathetic ophthalmia in British and Irish patients.* Br J Ophthalmol, 2001. **85**(3): p. 281-6.
14. Islam, S.M., et al., *HLA class II genes in Vogt-Koyanagi-Harada disease.* Invest Ophthalmol Vis Sci, 1994. **35**(11): p. 3890-6.
15. Gocho, K., I. Kondo, and K. Yamaki, *Identification of autoreactive T cells in Vogt-Koyanagi-Harada disease.* Invest Ophthalmol Vis Sci, 2001. **42**(9): p. 2004-9.
16. Sugita, S., et al., *Ocular infiltrating CD4+ T cells from patients with Vogt-Koyanagi-Harada disease recognize human melanocyte antigens.* Invest Ophthalmol Vis Sci, 2006. **47**(6): p. 2547-54.

17. Todd, J.A., J.I. Bell, and H.O. McDevitt, *HLA-DQ beta gene contributes to susceptibility and resistance to insulin-dependent diabetes mellitus.* Nature, 1987. **329**(6140): p. 599-604.
18. Anderson, A.C., et al., *High frequency of autoreactive myelin proteolipid protein-specific T cells in the periphery of naive mice: mechanisms of selection of the self-reactive repertoire.* J Exp Med, 2000. **191**(5): p. 761-70.
19. Luger, D., et al., *Either a Th17 or a Th1 effector response can drive autoimmunity: conditions of disease induction affect dominant effector category.* J Exp Med, 2008. **205**(4): p. 799-810.
20. Peters, A., et al., *Th17 cells induce ectopic lymphoid follicles in central nervous system tissue inflammation.* Immunity, 2011. **35**(6): p. 986-96.
21. Zhou, R., et al., *The living eye "disarms" uncommitted autoreactive T cells by converting them to Foxp3(+) regulatory cells following local antigen recognition.* J Immunol, 2012. **188**(4): p. 1742-50.
22. Dick, A.D., et al., *The role of tumour necrosis factor (TNF-alpha) in experimental autoimmune uveoretinitis (EAU).* Prog Retin Eye Res, 2004. **23**(6): p. 617-37.
23. McMenamin, P.G., et al., *Ultrastructural pathology of experimental autoimmune uveitis in the rat.* Autoimmunity, 1993. **16**(2): p. 83-93.
24. Papotto, P.H., et al., *Immunotherapeutic strategies in autoimmune uveitis.* Autoimmun Rev, 2014. **13**(9): p. 909-16.
25. Dick, A.D., et al., *Inhibition of tumor necrosis factor activity minimizes target organ damage in experimental autoimmune uveoretinitis despite quantitatively normal activated T cell traffic to the retina.* Eur J Immunol, 1996. **26**(5): p. 1018-25.
26. Santos Lacomba, M., et al., *Aqueous humor and serum tumor necrosis factor-alpha in clinical uveitis.* Ophthalmic Res, 2001. **33**(5): p. 251-5.
27. Valentincic, N.V., et al., *Intraocular and serum cytokine profiles in patients with intermediate uveitis.* Mol Vis, 2011. **17**: p. 2003-10.
28. Murphy, C.C., et al., *Systemic CD4(+) T cell phenotype and activation status in intermediate uveitis.* Br J Ophthalmol, 2004. **88**(3): p. 412-6.
29. Schonermarck, U., E. Csernok, and W.L. Gross, *Pathogenesis of anti-neutrophil cytoplasmic antibody-associated vasculitis: challenges and solutions 2014.* Nephrol Dial Transplant, 2015. **30 Suppl 1**: p. i46-52.
30. Gritz, D.C. and I.G. Wong, *Incidence and prevalence of uveitis in Northern California; the Northern California Epidemiology of Uveitis Study.* Ophthalmology, 2004. **111**(3): p. 491-500; discussion 500.
31. Jabs, D., et al., *Guidelines for the use of immunosuppressive drugs in patients with ocular inflammatory disorders: recommendations of an expert panel.* Am J Ophthalmol, 2000. **130**(4): p. 492-513.
32. Castiblanco, C. and C.S. Foster, *Review of Systemic Immunosuppression for Autoimmune Uveitis.* Ophthalmol Ther, 2014. **3**(1-2): p. 17-36.
33. Daniel, E., et al., *Mycophenolate mofetil for ocular inflammation.* Am J Ophthalmol, 2010. **149**(3): p. 423-32 e1-2.
34. Pasadhika, S., et al., *Azathioprine for ocular inflammatory diseases.* Am J Ophthalmol, 2009. **148**(4): p. 500-509 e2.
35. Hogan, A.C., et al., *Long-term efficacy and tolerance of tacrolimus for the treatment of uveitis.* Ophthalmology, 2007. **114**(5): p. 1000-6.
36. Nguyen, Q.D., et al., *A cross-sectional study of the current treatment patterns in noninfectious uveitis among specialists in the United States.* Ophthalmology, 2011. **118**(1): p. 184-90.

37. Stanbury, R.M. and E.M. Graham, *Systemic corticosteroid therapy--side effects and their management.* Br J Ophthalmol, 1998. **82**(6): p. 704-8.
38. Tundia, N., et al., *Cost of complications for patients with non‐infectious non‐anterior uveitis.*, in *European Association for Vision and Eye Research Conference*. 2014, Wiley.
39. Qian, Y., et al., *Depression and visual functioning in patients with ocular inflammatory disease.* Am J Ophthalmol, 2012. **153**(2): p. 370-378 e2.
40. Naik, R.K., et al., *Normative comparison of patient-reported outcomes in patients with noninfectious uveitis.* JAMA Ophthalmol, 2013. **131**(2): p. 219-25.
41. Murphy, C.C., et al., *Quality of life and visual function in patients with intermediate uveitis.* Br J Ophthalmol, 2005. **89**(9): p. 1161-5.
42. Jalil, A., et al., *Vision-related quality of life and employment status in patients with uveitis of working age: a prospective study.* Ocul Immunol Inflamm, 2012. **20**(4): p. 262-5.
43. Carnahan, M.C. and D.A. Goldstein, *Ocular complications of topical, peri-ocular, and systemic corticosteroids.* Curr Opin Ophthalmol, 2000. **11**(6): p. 478-83.
44. Multicenter Uveitis Steroid Treatment Trial Research, G., et al., *Randomized comparison of systemic anti-inflammatory therapy versus fluocinolone acetonide implant for intermediate, posterior, and panuveitis: the multicenter uveitis steroid treatment trial.* Ophthalmology, 2011. **118**(10): p. 1916-26.
45. Tomkins-Netzer, O., et al., *Long-term clinical outcome and causes of vision loss in patients with uveitis.* Ophthalmology, 2014. **121**(12): p. 2387-92.
46. Mangione, C.M., et al., *Development of the 25-item National Eye Institute Visual Function Questionnaire.* Arch Ophthalmol, 2001. **119**(7): p. 1050-8.
47. Ophthalmology, N.E.S.C.R.G.f.S. *Clinical Commissioning Policy: Infliximab (Remicade) and Adalimumab (Humira) As Anti-TNF Treatment Options For Adult Patients with Severe Refractory Uveitis*. 2015 04/12/2019]; Available from: https://www.engage.england.nhs.uk/consultation/specialised-services-consultation/user_uploads/uveitis-adults-policy.pdf.
48. RNIB, L.A. *The economic impact of partial sight and blindness in the UK adult population*. 2009 04/12/2019]; Available from: http://www.rnib.org.uk/sites/default/files/FSUK_Report.pdf.
49. Levy-Clarke, G., et al., *Expert panel recommendations for the use of anti-tumor necrosis factor biologic agents in patients with ocular inflammatory disorders.* Ophthalmology, 2014. **121**(3): p. 785-96 e3.
50. Cordero-Coma, M., T. Yilmaz, and S. Onal, *Systematic review of anti-tumor necrosis factor-alpha therapy for treatment of immune-mediated uveitis.* Ocul Immunol Inflamm, 2013. **21**(1): p. 19-27.
51. Pasadhika, S. and J.T. Rosenbaum, *Update on the use of systemic biologic agents in the treatment of noninfectious uveitis.* Biologics, 2014. **8**: p. 67-81.
52. Excellence, N.I.f.H.a.C. *Adalimumab and dexamethasone for treating non-infectious uveitis*. 2017 04/12/2019]; Available from: Nice.org.uk/guidance/ta460.
53. Foss, A.J., et al., *Comparing different dosing regimens of bevacizumab in the treatment of neovascular macular degeneration: study protocol for a randomised controlled trial.* Trials, 2015. **16**: p. 85.
54. Higgins, J., et al. *Revised Cochrane risk-of-bias tool for randomized trials (RoB 2)*. 04/12/2019]; Available from: https://sites.google.com/site/riskofbiastool/welcome/rob-2-0-tool.
55. Suhler, E.B., et al., *Adalimumab therapy for refractory uveitis: results of a multicentre, open-label, prospective trial.* Br J Ophthalmol, 2013. **97**(4): p. 481-6.
56. Suhler, E.B., et al., *A prospective trial of infliximab therapy for refractory uveitis: preliminary safety and efficacy outcomes.* Arch Ophthalmol, 2005. **123**(7): p. 903-12.

57. Bristol Trials Centre, U.o.B. *IMP-Track User Manual*. 2018; Available from: https://cpb-eu-w2.wpmucdn.com/blogs.bristol.ac.uk/dist/4/628/files/2020/07/imp-track-user-manual-v10.pdf.
58. Trusko, B., et al., *The Standardization of Uveitis Nomenclature (SUN) Project. Development of a clinical evidence base utilizing informatics tools and techniques.* Methods Inf Med, 2013. **52**(3): p. 259-65, S1-6.
59. Okhravi, N. and S. Lightman, *Cystoid macular edema in uveitis.* Ocul Immunol Inflamm, 2003. **11**(1): p. 29-38.
60. Excellence, N.I.f.H.a.C., *Guide to the Methods of Technology Appraisal*, in *Process and Methods Guides*. 2013: London.
61. Dolan, P., et al., *A Social Tariff for EuroQol: Results from a UK General Population Survey.* University of York: Center for Health Economics, 1995. **138**.
62. NIHR. 2020; Available from: https://www.nihr.ac.uk/news/nihr-issues-guidance-to-ensure-research-protected-in-a-second-wave/25858.

## 15. Amendments to protocol

| Amendment number (i.e. REC and/or MHRA amendment number) | Previous version | Previous date | New version | New date | Brief summary of change | Date of ethical approval (or NA if non-substantial) |
|---|---|---|---|---|---|---|
| N/A (pre-approvals) Changes made following initial REC review. | 2.0 | 11/03/2020 | 3.0 | 20/05/2020 | Added ISRCTN number<br>5.6.2 Updated exclusion criteria<br>6.13 Added further detail about expense claims | 03/06/2020 |
| N/A (pre-approvals) Changes made following initial MHRA review. | 3.0 | 20/05/2020 | 4.0 | | 5.7 Clarified live vaccines cannot be administered<br>10.2.1 Added COVID-19 risk/benefit analysis | |

The ASTUTE Trial is funded by the NIHR HTA Programme (project reference 16/24/09). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

FUNDED BY
NIHR | National Institute for Health Research

## 16. Appendix 1

**Approved SmPC – this will be attached in the pdf version of the protocol**

# Imraldi 40mg solution for injection in pre-filled pen

Summary of Product Characteristics Updated 12-Sep-2019 | Biogen Biosimilars

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

## 1. Name of the medicinal product

Imraldi 40 mg solution for injection in pre-filled syringe

Imraldi 40 mg solution for injection in pre-filled pen

## 2. Qualitative and quantitative composition

Imraldi 40 mg solution for injection in pre-filled syringe

Each 0.8 ml single dose pre-filled syringe contains 40 mg of adalimumab.

Imraldi 40 mg solution for injection in pre-filled pen

Each 0.8 ml single dose pre-filled pen contains 40 mg of adalimumab.

Adalimumab is a recombinant human monoclonal antibody produced in Chinese Hamster Ovary cells.

Excipient(s) with known effect

This medicinal product contains 20.0 mg sorbitol.

For the full list of excipients, see section 6.1.

## 3. Pharmaceutical form

Solution for injection.

Clear, colourless solution.

## 4. Clinical particulars

### 4.1 Therapeutic indications

Rheumatoid arthritis

Imraldi in combination with methotrexate, is indicated for:

- the treatment of moderate to severe, active rheumatoid arthritis in adult patients when the response to disease-modifying anti-rheumatic drugs including methotrexate has been inadequate.

- the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with methotrexate.

Imraldi can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate.

Adalimumab has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function, when given in combination with methotrexate.

Juvenile idiopathic arthritis

*Polyarticular juvenile idiopathic arthritis*

Imraldi in combination with methotrexate is indicated for the treatment of active polyarticular juvenile idiopathic arthritis, in patients from the age of 2 years who have had an inadequate response to one or more disease-modifying anti-rheumatic drugs (DMARDs). Imraldi can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate (for the efficacy in monotherapy see section 5.1). Adalimumab has not been studied in patients aged less than 2 years.

*Enthesitis-related arthritis*

Imraldi is indicated for the treatment of active enthesitis-related arthritis in patients, 6 years of age and older, who have had an inadequate response to, or who are intolerant of, conventional therapy (see section 5.1).

Axial spondyloarthritis

*Ankylosing spondylitis (AS)*

Imraldi is indicated for the treatment of adults with severe active ankylosing spondylitis who have had an inadequate response to conventional therapy.

*Axial spondyloarthritis without radiographic evidence of AS*

Imraldi is indicated for the treatment of adults with severe axial spondyloarthritis without radiographic evidence of AS but with objective signs of inflammation by elevated CRP and / or MRI, who have had an inadequate response to, or are intolerant to nonsteroidal anti-inflammatory drugs.

Psoriatic arthritis

Imraldi is indicated for the treatment of active and progressive psoriatic arthritis in adults when the response to previous disease-modifying anti-rheumatic drug therapy has been inadequate.

Adalimumab has been shown to reduce the rate of progression of peripheral joint damage as measured by X-ray in patients with polyarticular symmetrical subtypes of the disease (see Section 5.1) and to improve physical function.

Psoriasis

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

Paediatric plaque psoriasis

Imraldi is indicated for the treatment of severe chronic plaque psoriasis in children and adolescents from 4 years of age who have had an inadequate response to or are inappropriate candidates for topical therapy and phototherapies.

Hidradenitis suppurativa (HS)

Imraldi is indicated for the treatment of active moderate to severe hidradenitis suppurativa (acne inversa) in adults and adolescents from 12 years of age with an inadequate response to conventional systemic HS therapy (see sections 5.1 and 5.2).

Crohn's disease

Imraldi is indicated for treatment of moderately to severely active Crohn's disease, in adult patients who have not responded despite a full and adequate course of therapy with a corticosteroid and/or an immunosuppressant; or who are intolerant to or have medical contraindications for such therapies.

Paediatric Crohn's disease

Imraldi is indicated for the treatment of moderately to severely active Crohn's disease in paediatric patients (from 6 years of age) who have had an inadequate response to conventional therapy including primary nutrition therapy and a corticosteroid and/or an immunomodulator, or who are intolerant to or have contraindications for such therapies.

Ulcerative colitis

Imraldi is indicated for treatment of moderately to severely active ulcerative colitis in adult patients who have had an inadequate response to conventional therapy including corticosteroids and 6-mercaptopurine (6-MP) or azathioprine (AZA), or who are intolerant to or have medical contraindications for such therapies.

Uveitis

Imraldi 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.

Paediatric Uveitis

Imraldi is indicated for the treatment of paediatric chronic non-infectious anterior uveitis in patients from 2 years of age who have had an inadequate response to or are intolerant to conventional therapy, or in whom conventional therapy is inappropriate.

### 4.2 Posology and method of administration

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

After proper training in injection technique, patients may self-inject with Imraldi if their physician determines that it is appropriate and with medical follow-up as necessary.

During treatment with Imraldi, other concomitant therapies (e.g., corticosteroids and/or immunomodulatory agents) should be optimised.

Posology

*Rheumatoid arthritis*

The recommended dose of Imraldi for adult patients with rheumatoid arthritis is 40 mg adalimumab administered every other week as a single dose via subcutaneous injection. Methotrexate should be continued during treatment with Imraldi.

Glucocorticoids, salicylates, nonsteroidal anti-inflammatory drugs, or analgesics can be continued during treatment with Imraldi. Regarding combination with disease modifying anti-rheumatic drugs other than methotrexate see sections 4.4 and 5.1.

In monotherapy, some patients who experience a decrease in their response to Imraldi 40 mg every other week dosing may benefit from an increase in dosage to 40 mg adalimumab every week or 80 mg every other week.

Available data suggest that the clinical response is usually achieved within 12 weeks of treatment. Continued therapy should be reconsidered in a patient not responding within this time period.

*Dose interruption*

There may be a need for dose interruption, for instance before surgery or if a serious infection occurs.

Available data suggest that re-introduction of adalimumab after discontinuation for 70 days or longer resulted in the same magnitudes of clinical response and similar safety profile as before dose interruption.

*Ankylosing spondylitis, axial spondyloarthritis without radiographic evidence of AS and psoriatic arthritis*

The recommended dose of Imraldi for patients with ankylosing spondylitis, axial spondyloarthritis without radiographic evidence of AS and for patients with psoriatic arthritis is 40 mg adalimumab administered every other week as a single dose via subcutaneous injection.

Available data suggest that the clinical response is usually achieved within 12 weeks of treatment. Continued therapy should be reconsidered in a patient not responding within this time period.

*Psoriasis*

The recommended dose of Imraldi for adult patients is an initial dose of 80 mg administered subcutaneously, followed by 40 mg subcutaneously given every other week starting one week after the initial dose.

Continued therapy beyond 16 weeks should be carefully reconsidered in a patient not responding within this time period.

Beyond 16 weeks, patients with inadequate response to Imraldi 40 mg every other week may benefit from an increase in dosage to 40 mg every week or 80 mg every other week. The benefits and risks of continued 40 mg weekly or 80 mg every other week therapy should be carefully reconsidered in a patient with an inadequate response after the increase in dosage (see section 5.1). If adequate response is achieved with 40 mg every week or 80 mg every other week, the dosage may subsequently be reduced to 40 mg every other week.

*Hidradenitis suppurativa*

The recommended Imraldi dose regimen for adult patients with hidradenitis suppurativa (HS) is 160 mg initially at Day 1 (given as four 40 mg injections in one day or as two 40 mg injections per day for two consecutive days), followed by 80 mg two weeks later at Day 15 (given as two 40 mg injections in one day). Two weeks later (Day 29) continue with a dose of 40 mg every week or 80 mg every other week (given as two 40 mg injections in one day). Antibiotics may be continued during treatment with Imraldi if necessary. It is recommended that the patient should use a topical antiseptic wash on their HS lesions on a daily basis during treatment with Imraldi.

Continued therapy beyond 12 weeks should be carefully reconsidered in a patient with no improvement within this time period.

Should treatment be interrupted, Imraldi 40 mg every week or 80 mg every other week may be re-introduced (see section 5.1).

The benefit and risk of continued long-term treatment should be periodically evaluated (see section 5.1).

*Crohn's disease*

The recommended Imraldi induction dose regimen for adult patients with moderately to severely active Crohn's disease is 80 mg at week 0 followed by 40 mg at week 2. In case there is a need for a more rapid response to therapy, the regimen 160 mg at week 0 (given as four 40 mg injections in one day or as two 40 mg injections per day for two consecutive days), 80 mg at week 2 (given as two 40 mg injections in one day), can be used with the awareness that the risk for adverse events is higher during induction.

After induction treatment, the recommended dose is 40 mg every other week via subcutaneous injection. Alternatively, if a patient has stopped Imraldi and signs and symptoms of disease recur, Imraldi may be re-administered. There is little experience from re-administration after more than 8 weeks since the previous dose.

During maintenance treatment, corticosteroids may be tapered in accordance with clinical practice guidelines.

Some patients who experience decrease in their response to Imraldi 40 mg every other week may benefit from an increase in dosage to 40 mg Imraldi every week or 80 mg every other week.

Some patients who have not responded by week 4 may benefit from continued maintenance therapy through week 12. Continued therapy should be carefully reconsidered in a patient not responding within this time period.

*Ulcerative colitis*

The recommended Imraldi induction dose regimen for adult patients with moderate to severe ulcerative colitis is 160 mg at week 0 (given as four 40 mg injections in one day or as two 40 mg injections per day for two consecutive days) and 80 mg at week 2 (given as two 40 mg injections in one day). After induction treatment, the recommended dose is 40 mg every other week via subcutaneous injection.

During maintenance treatment, corticosteroids may be tapered in accordance with clinical practice guidelines.

Some patients who experience decrease in their response to Imraldi 40 mg every other week may benefit from an increase in dosage to 40 mg Imraldi every week or 80 mg every other week.

Available data suggest that the clinical response is usually achieved within 2-8 weeks of treatment. Imraldi therapy should not be continued in patients failing to respond within this time period.

*Uveitis*

The recommended dose of Imraldi 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 Imraldi alone. Treatment with Imraldi 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 Imraldi.

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

Special populations

*Elderly*

No dose adjustment is required.

*Renal and/or hepatic impairment*

Adalimumab has not been studied in these patient populations. No dose recommendations can be made.

*Paediatric population*

*Juvenile idiopathic arthritis*

Polyarticular juvenile idiopathic arthritis from 2 years of age

The recommended dose of Imraldi for patients with polyarticular juvenile idiopathic arthritis from 2 years of age is based on body weight (Table 1). Imraldi is administered every other week via subcutaneous injection.

**Table 1. Imraldi Dose for Patients with Polyarticular Juvenile Idiopathic Arthritis**

| Patient Weight | Dosing Regimen |
|---|---|
| 10 kg to < 30 kg | 20 mg every other week |
| ≥ 30 kg | 40 mg every other week |

Available data suggest that clinical response is usually achieved within 12 weeks of treatment. Continued therapy should be carefully reconsidered in a patient not responding within this time period.

There is no relevant use of adalimumab in patients aged less than 2 years for this indication.

*Enthesitis-related arthritis*

The recommended dose of Imraldi for patients with enthesitis-related arthritis from 6 years of age is based on body weight (Table 2). Imraldi is administered every other week via subcutaneous injection.

**Table 2. Imraldi Dose for Patients with Enthesitis-Related Arthritis**

| Patient Weight | Dosing Regimen |
|---|---|
| 15 kg to < 30 kg | 20 mg every other week |
| ≥ 30 kg | 40 mg every other week |

Adalimumab has not been studied in patients with enthesitis-related arthritis aged less than 6 years.

*Paediatric plaque psoriasis*

The recommended Imraldi dose for patients with plaque psoriasis from 4 to 17 years of age is based on body weight (Table 3). Imraldi is administered via subcutaneous injection.

**Table 3. Imraldi Dose for Paediatric Patients with Plaque Psoriasis**

| Patient Weight | Dosing Regimen |
|---|---|
| 15 kg to < 30 kg | Initial dose of 20 mg, followed by 20 mg given every other week starting one week after the initial dose |
| ≥ 30 kg | Initial dose of 40 mg, followed by 40 mg given every other week starting one week after the initial dose |

Continued therapy beyond 16 weeks should be carefully considered in a patient not responding within this time period.

If retreatment with Imraldi is indicated, the above guidance on dose and treatment duration should be followed.

The safety of adalimumab in paediatric patients with plaque psoriasis has been assessed for a mean of 13 months.

There is no relevant use of adalimumab in children aged less than 4 years for this indication.

*Adolescent hidradenitis suppurativa (from 12 years of age, weighing at least 30 kg)*

There are no clinical trials with adalimumab in adolescent patients with HS. The posology of adalimumab in these patients has been determined from pharmacokinetic modelling and simulation (see section 5.2).

The recommended Imraldi dose is 80 mg at week 0 followed by 40 mg every other week starting at week 1 via subcutaneous injection.

In adolescent patients with inadequate response to Imraldi 40 mg every other week, an increase in dosage to 40 mg every week or 80 mg every other week may be considered.

Antibiotics may be continued during treatment with Imraldi if necessary. It is recommended that the patient should use a topical antiseptic wash on their HS lesions on a daily basis during treatment with Imraldi.

Continued therapy beyond 12 weeks should be carefully reconsidered in a patient with no improvement within this time period.

Should treatment be interrupted, Imraldi may be re-introduced as appropriate.

The benefit and risk of continued long-term treatment should be periodically evaluated (see adult data in section 5.1).

There is no relevant use of adalimumab in children aged less than 12 years in this indication.

*Paediatric Crohn's disease*

The recommended dose of Imraldi for patients with Crohn's disease from 6 to 17 years of age is based on body weight (Table 4). Imraldi is administered via subcutaneous injection.

**Table 4. Imraldi Dose for Paediatric Patients with Crohn's disease**

| Patient Weight | Induction Dose | Maintenance Dose Starting at Week 4 |
|---|---|---|
| < 40 kg | • 40 mg at week 0 and 20 mg at week 2<br><br>In case there is a need for a more rapid response to therapy with the awareness that the risk for adverse events may be higher with use of the higher induction dose, the following dose may be used:<br>• 80 mg at week 0 and 40 mg at week 2 | 20 mg every other week |
| ≥ 40 kg | • 80 mg at week 0 and 40 mg at week 2<br><br>In case there is a need for a more rapid response to therapy with the awareness that the risk for adverse events may be higher with use of the higher induction dose, the following dose may be used:<br>• 160 mg at week 0 and 80 mg at week 2 | 40 mg every other week |

Patients who experience insufficient response may benefit from an increase in dosage:

• < 40 kg: 20 mg every week

• ≥ 40 kg: 40 mg every week or 80 mg every other week

Continued therapy should be carefully considered in a subject not responding by week 12.

There is no relevant use of adalimumab in children aged below 6 years for this indication.

*Paediatric ulcerative colitis*

The safety and efficacy of adalimumab in children aged 4-17 years have not yet been established. No data are available. There is no relevant use of Imraldi in children aged less than 4 years for this indication.

*Psoriatic arthritis and axial spondyloarthritis including ankylosing spondylitis*

There is no relevant use of adalimumab in the paediatric population for the indications of ankylosing spondylitis and psoriatric arthritis.

*Paediatric uveitis*

The recommended dose of Imraldi for paediatric patients with uveitis from 2 years of age is based on body weight (Table 5). Imraldi is administered via subcutaneous injection.

In paediatric uveitis, there is no experience in the treatment with adalimumab without concomitant treatment with methotrexate.

**Table 5 Imraldi Dose for Paediatric Patients with Uveitis**

| | |
|---|---|

| Patient Weight | Dosing Regimen |
|---|---|
| < 30 kg | 20 mg every other week in combination with methotrexate |
| ≥ 30 kg | 40 mg every other week in combination with methotrexate |

When Imraldi therapy is initiated, a loading dose of 40 mg for patients < 30 kg or 80 mg for patients ≥ 30 kg may be administered one week prior to the start of maintenance therapy. No clinical data are available on the use of an adalimumab loading dose in children < 6 years of age (see section 5.2).

There is no relevant use of adalimumab in children aged less than 2 years in this indication.

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

Method of administration

Imraldi is administered by subcutaneous injection. Full instructions for use are provided in the package leaflet.

A 40 mg pre-filled syringe and pre-filled pen are available for patients to administer a full 40 mg dose.

**4.3 Contraindications**

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Active tuberculosis or other severe infections such as sepsis, and opportunistic infections (see section 4.4).

Moderate to severe heart failure (NYHA class III/IV) (see section 4.4).

**4.4 Special warnings and precautions for use**

Traceability

In order to improve traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Infections

Patients taking TNF-antagonists are more susceptible to serious infections. Impaired lung function may increase the risk for developing infections. Patients must therefore be monitored closely for infections, including tuberculosis, before, during and after treatment with Imraldi. Because the elimination of adalimumab may take up to four months, monitoring should be continued throughout this period.

Treatment with Imraldi should not be initiated in patients with active infections including chronic or localised infections until infections are controlled. In patients who have been exposed to tuberculosis and patients who have travelled in areas of high risk of tuberculosis or endemic mycoses, such as histoplasmosis, coccidioidomycosis, or blastomycosis, the risk and benefits of treatment with Imraldi should be considered prior to initiating therapy (see *Other opportunistic infections*).

Patients who develop a new infection while undergoing treatment with Imraldi, should be monitored closely and undergo a complete diagnostic evaluation. Administration of Imraldi should be discontinued if a patient develops a new serious infection or sepsis, and appropriate antimicrobial or antifungal therapy should be initiated until the infection is controlled. Physicians should exercise caution when considering the use of Imraldi in patients with a history of recurring infection or with underlying conditions which may predispose patients to infections, including the use of concomitant immunosuppressive medications.

*Serious infections*

Serious infections, including sepsis, due to bacterial, mycobacterial, invasive fungal, parasitic, viral, or other opportunistic infections such as listeriosis, legionellosis and pneumocystis have been reported in patients receiving adalimumab.

Other serious infections seen in clinical trials include pneumonia, pyelonephritis, septic arthritis and septicaemia. Hospitalisation or fatal outcomes associated with infections have been reported.

*Tuberculosis*

Tuberculosis, including reactivation and new onset of tuberculosis, has been reported in patients receiving adalimumab. Reports included cases of pulmonary and extra-pulmonary (i.e. disseminated) tuberculosis.

Before initiation of therapy with Imraldi, all patients must be evaluated for both active or inactive (“latent”) tuberculosis infection. This evaluation should include a detailed medical assessment of patient history of tuberculosis or possible previous exposure to people with active tuberculosis and previous and/or current immunosuppressive therapy. Appropriate screening tests (i.e. tuberculin skin test and chest X-ray) should be performed in all patients (local recommendations may apply). It is recommended that the conduct and results of these tests are recorded in the Patient Reminder Card. Prescribers are reminded of the risk of false negative tuberculin skin test results, especially in patients who are severely ill or immunocompromised.

If active tuberculosis is diagnosed, Imraldi therapy must not be initiated (see section 4.3).

In all situations described below, the benefit/risk balance of therapy should be very carefully considered.

If latent tuberculosis is suspected, a physician with expertise in the treatment of tuberculosis should be consulted.

If latent tuberculosis is diagnosed, appropriate treatment must be started with anti-tuberculosis prophylaxis treatment before the initiation of Imraldi, and in accordance with local recommendations.

Use of anti-tuberculosis prophylaxis treatment should also be considered before the initiation of Imraldi in patients with several or significant risk factors for tuberculosis despite a negative test for tuberculosis and in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed.

Despite prophylactic treatment for tuberculosis, cases of reactivated tuberculosis have occurred in patients treated with adalimumab. Some patients who have been successfully treated for active tuberculosis have redeveloped tuberculosis while being treated with adalimumab.

Patients should be instructed to seek medical advice if signs/symptoms suggestive of a tuberculosis infection (e.g., persistent cough, wasting/weight loss, low grade fever, listlessness) occur during or after therapy with Imraldi.

*Other opportunistic infections*

Opportunistic infections, including invasive fungal infections have been observed in patients receiving adalimumab. These infections have not consistently been recognised in patients taking TNF-antagonists and this has resulted in delays in appropriate treatment, sometimes resulting in fatal outcomes.

For patients who develop the signs and symptoms such as fever, malaise, weight loss, sweats, cough, dyspnoea, and/or pulmonary infiltrates or other serious systemic illness with or without concomitant shock an invasive fungal infection should be suspected and administration of Imraldi should be promptly discontinued. Diagnosis and administration of empiric antifungal therapy in these patients should be made in consultation with a physician with expertise in the care of patients with invasive fungal infections.

Hepatitis B reactivation

Reactivation of hepatitis B has occurred in patients receiving a TNF-antagonist including adalimumab, who are chronic carriers of this virus (i.e. surface antigen positive). Some cases have had a fatal outcome. Patients should be tested for HBV infection before initiating treatment with Imraldi. For patients who test positive for hepatitis B infection, consultation with a physician with expertise in the treatment of hepatitis B is recommended.

Carriers of HBV who require treatment with Imraldi should be closely monitored for signs and symptoms of active HBV infection throughout therapy and for several months following termination of therapy. Adequate data from treating patients who are carriers of HBV with anti-viral therapy in conjunction with TNF-antagonist therapy to prevent HBV reactivation are not available. In patients who develop HBV reactivation, Imraldi should be stopped and effective anti-viral therapy with appropriate supportive treatment should be initiated.

Neurological events

TNF-antagonists including adalimumab 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 Imraldi in patients with pre-existing or recent-onset central or peripheral nervous system demyelinating disorders; discontinuation of Imraldi 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 Imraldi therapy and regularly during treatment to assess for pre-existing or developing central demyelinating disorders.

Allergic reactions

Serious allergic reactions associated with adalimumab were rare during clinical trials. Non-serious allergic reactions associated with adalimumab were uncommon during clinical trials. Reports of serious allergic reactions including anaphylaxis have been received following adalimumab administration. If an anaphylactic reaction or other serious allergic reaction occurs, administration of Imraldi should be discontinued immediately and appropriate therapy initiated.

Immunosuppression

In a study of 64 patients with rheumatoid arthritis that were treated with adalimumab, there was no evidence of depression of delayed-type hypersensitivity, depression of immunoglobulin levels, or change in enumeration of effector T-, B, - NK-cells, monocyte/macrophages, and neutrophils.

Malignancies and lymphoproliferative disorders

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. There is an increased background risk for lymphoma and leukaemia in rheumatoid arthritis patients with long-standing, highly active, inflammatory disease, which complicates the risk estimation. With the current knowledge, a possible risk for the development of lymphomas, leukaemia, and other malignancies in patients treated with a TNF-antagonist cannot be excluded.

Malignancies, some fatal, have been reported among children, adolescents and young adults (up to 22 years of age) treated with TNF-antagonists (initiation of therapy ≤18 years of age), including adalimumab in the post marketing setting.

Approximately half the cases were lymphomas. The other cases represented a variety of different malignancies and included rare malignancies usually associated with immunosuppression. A risk for the development of malignancies in children and adolescents treated with TNF-antagonists cannot be excluded.

Rare postmarketing cases of hepatosplenic T-cell lymphoma have been identified in patients treated with adalimumab. This rare type of T-cell lymphoma has a very aggressive disease course and is usually fatal. Some of these hepatosplenic T-cell lymphomas with adalimumab have occurred in young adult patients on concomitant treatment with azathioprine or 6-mercaptopurine used for inflammatory bowel disease. The potential risk with the combination of azathioprine or 6-mercaptopurine and adalimumab should be carefully considered. A risk for the development of hepatosplenic T-cell lymphoma in patients treated with Imraldi cannot be excluded (see section 4.8).

No studies have been conducted that include patients with a history of malignancy or in whom treatment with adalimumab is continued following development of malignancy. Thus additional caution should be exercised in considering adalimumab treatment of these patients (see section 4.8).

All patients, and in particular patients with a medical history of extensive immunosuppressant therapy or psoriasis patients with a history of PUVA treatment should be examined for the presence of non-melanoma skin cancer prior to and during treatment with Imraldi. Melanoma and Merkel cell carcinoma have also been reported in patients treated with TNF-antagonists including adalimumab (see section 4.8).

In an exploratory clinical trial evaluating the use of another TNF-antagonist, infliximab, in patients with moderate to severe chronic obstructive pulmonary disease (COPD), more malignancies, mostly in the lung or head and neck, were reported in infliximab-treated patients compared with control patients. All patients had a history of heavy smoking. Therefore, caution should be exercised when using any TNF-antagonist in COPD patients, as well as in patients with increased risk for malignancy due to heavy smoking.

With current data it is not known if adalimumab treatment influences the risk for developing dysplasia or colon cancer. All patients with ulcerative colitis who are at increased risk for dysplasia or colon carcinoma (for example, patients with long-standing ulcerative colitis or primary sclerosing cholangitis), or who had a prior history of dysplasia or colon carcinoma should be screened for dysplasia at regular intervals before therapy and throughout their disease course. This evaluation should include colonoscopy and biopsies per local recommendations.

Haematologic reactions

Rare reports of pancytopenia including aplastic anaemia have been reported with TNF-antagonists. Adverse events of the haematologic system, including medically significant cytopenia (e.g. thrombocytopenia, leukopenia) have been reported with adalimumab. All patients should be advised to seek immediate medical attention if they develop signs and symptoms suggestive of blood dyscrasias (e.g. persistent fever, bruising, bleeding, pallor) while on Imraldi. Discontinuation of Imraldi therapy should be considered in patients with confirmed significant haematologic abnormalities.

Vaccinations

Similar antibody responses to the standard 23-valent pneumococcal vaccine and the influenza trivalent virus vaccination were observed in a study in 226 adult subjects with rheumatoid arthritis who were treated with adalimumab or placebo. No data are available on the secondary transmission of infection by live vaccines in patients receiving adalimumab.

It is recommended that paediatric patients, if possible, be brought up to date with all immunisations in agreement with current immunisation guidelines prior to initiating adalimumab therapy.

Patients on adalimumab may receive concurrent vaccinations, except for live vaccines. Administration of live vaccines (e.g., BCG vaccine) to infants exposed to adalimumab in utero is not recommended for 5 months following the mother's last adalimumab injection during pregnancy.

Congestive heart failure

In a clinical trial with another TNF-antagonist worsening congestive heart failure and increased mortality due to congestive heart failure have been observed. Cases of worsening congestive heart failure have also been reported in patients receiving adalimumab. Imraldi should be used with caution in patients with mild heart failure (NYHA class I/II). Imraldi is contraindicated in moderate to severe heart failure (see section 4.3). Treatment with Imraldi must be discontinued in patients who develop new or worsening symptoms of congestive heart failure.

Autoimmune processes

Treatment with Imraldi may result in the formation of autoimmune antibodies. The impact of long-term treatment with adalimumab on the development of autoimmune diseases is unknown. If a patient develops symptoms suggestive of a lupus-like syndrome following treatment with Imraldi and is positive for antibodies against double-stranded DNA, further treatment with Imraldi should not be given (see section 4.8).

Concurrent administration of biologic DMARDS or TNF-antagonists

Serious infections were seen in clinical studies with concurrent use of anakinra and another TNF-antagonist, etanercept, with no added clinical benefit compared to etanercept alone. Because of the nature of the adverse events seen with the combination of etanercept and anakinra therapy, similar toxicities may also result from the combination of anakinra and other TNF-antagonists. Therefore, the combination of adalimumab and anakinra is not recommended. (See section 4.5).

Concomitant administration of adalimumab with other biologic DMARDS (e.g, anakinra and abatacept) or other TNF-antagonists is not recommended based upon the possible increased risk for infections, including serious infections and

other potential pharmacological interactions. (See section 4.5).

Surgery

There is limited safety experience of surgical procedures in patients treated with adalimumab. The long half-life of adalimumab should be taken into consideration if a surgical procedure is planned. A patient who requires surgery while on Imraldi should be closely monitored for infections, and appropriate actions should be taken. There is limited safety experience in patients undergoing arthroplasty while receiving adalimumab.

Small bowel obstruction

Failure to respond to treatment for Crohn's disease may indicate the presence of fixed fibrotic stricture that may require surgical treatment. Available data suggest that adalimumab does not worsen or cause strictures.

Elderly

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

Paediatric population

See Vaccinations above.

Excipients with known effects

This medicinal product contains 20 mg sorbitol in each pre-filled syringe/pre-filled pen. Patients with rare hereditary problems of fructose intolerance should not take this medicinal product.

Also, this medicinal product contains less than 1 mmol of sodium (23 mg) per 0.8 ml dose, i.e. essentially 'sodium-free'.

**4.5 Interaction with other medicinal products and other forms of interaction**

Adalimumab has been studied in rheumatoid arthritis, polyarticular juvenile idiopathic arthritis and psoriatic arthritis patients taking adalimumab as monotherapy and those taking concomitant methotrexate. Antibody formation was lower when adalimumab was given together with methotrexate in comparison with use as monotherapy. Administration of adalimumab without methotrexate resulted in increased formation of antibodies, increased clearance and reduced efficacy of adalimumab (see section 5.1).

The combination of Imraldi and anakinra is not recommended (see section 4.4 “Concurrent administration of biologic DMARDS or TNF-antagonists”).

The combination of Imraldi and abatacept is not recommended (see section 4.4 “Concurrent administration of biologic DMARDS or TNF-antagonists”).

**4.6 Fertility, pregnancy and lactation**

Women of child bearing potential

Women of childbearing potential should consider the use of adequate contraception to prevent pregnancy and continue its use for at least five months after the last Imraldi treatment.

Pregnancy

A large number (approximately 2,100) of prospectively collected pregnancies exposed to adalimumab resulting in live birth with known outcomes, including more than 1,500 exposed during the first trimester, does not indicate an increase in the rate of malformation in the newborn.

In a prospective cohort registry, 257 women with rheumatoid arthritis (RA) or Crohn's disease (CD) treated with adalimumab at least during the first trimester and 120 women with RA or CD not treated with adalimumab were enrolled. The primary endpoint was the birth prevalence of major birth defects. The rate of pregnancies ending with at least one live born infant with a major birth defect was 6/69 (8.7 %) in the adalimumab-treated women with RA and 5/74 (6.8 %) in the untreated women with RA (unadjusted OR 1.31, 95 % CI 0.38-4.52) and 16/152 (10.5 %) in the adalimumab-treated women with CD and 3/32 (9.4 %) in the untreated women with CD (unadjusted OR 1.14, 95 % CI 0.31-4.16). The adjusted OR (accounting for baseline differences) was 1.10 (95 % CI 0.45-2.73) with RA and CD combined. There were no distinct differences between adalimumab-treated and untreated women for the secondary endpoints spontaneous abortions, minor birth defects, preterm delivery, birth size and serious or opportunistic infections and no stillbirths or malignancies were reported. The interpretation of data may be impacted due to methodological limitations of the study, including small sample size and non-randomized design.

In a developmental toxicity study conducted in monkeys, there was no indication of maternal toxicity, embryotoxicity or teratogenicity. Preclinical data on postnatal toxicity of adalimumab are not available (see section 5.3).

Due to its inhibition of TNFα, adalimumab administered during pregnancy could affect normal immune responses in the newborn. Adalimumab should only be used during pregnancy if clearly needed.

Adalimumab may cross the placenta into the serum of infants born to women treated with adalimumab during pregnancy. Consequently, these infants may be at increased risk for infection. Administration of live vaccines (e.g., BCG vaccine) to

infants exposed to adalimumab in utero is not recommended for 5 months following the mother's last adalimumab injection during pregnancy.

Breast feeding

Limited information from the published literature indicates that adalimumab is excreted in breast milk at very low concentrations with the presence of adalimumab in human milk at concentrations of 0.1 % to 1 % of the maternal serum level. Given orally, immunoglobulin G proteins undergo intestinal proteolysis and have poor bioavailability. No effects on the breastfed newborns/infants are anticipated. Consequently, adalimumab can be used during breastfeeding.

Fertility

Preclinical data on fertility effects of adalimumab are not available.

### 4.7 Effects on ability to drive and use machines

Imraldi may have a minor influence on the ability to drive and use machines. Vertigo and visual impairment may occur following administration of Imraldi (see section 4.8).

### 4.8 Undesirable effects

Summary of the safety profile

Adalimumab was studied in 9,506 patients in pivotal controlled and open label trials for up to 60 months or more. These trials included rheumatoid arthritis patients with short term and long standing disease, juvenile idiopathic arthritis (polyarticular juvenile idiopathic arthritis and enthesitis-related arthritis) as well as axial spondyloarthritis (ankylosing spondylitis and axial spondyloarthritis without radiographic evidence of AS), psoriatic arthritis, Crohn's disease, ulcerative colitis, psoriasis, hidradenitis suppurativa, and uveitis patients. The pivotal controlled studies involved 6,089 patients receiving adalimumab and 3,801 patients receiving placebo or active comparator during the controlled period.

The proportion of patients who discontinued treatment due to adverse events during the double-blind, controlled portion of pivotal studies was 5.9 % for patients taking adalimumab and 5.4 % for control treated patients.

The most commonly reported adverse reactions 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 adverse reactions have been reported for adalimumab. TNF-antagonists, such as adalimumab affect the immune system and their use may affect the body's defense against infection and cancer.

Fatal and life-threatening infections (including sepsis, opportunistic infections and TB), HBV reactivation and various malignancies (including leukaemia, lymphoma and HSTCL) have also been reported with use of adalimumab.

Serious haematological, neurological and autoimmune reactions have also 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.

*Paediatric population*

In general, the adverse events in paediatric patients were similar in frequency and type to those seen in adult patients.

Tabulated list of adverse reactions

The following list of adverse reactions is based on experience from clinical trials and on postmarketing experience and are displayed by system organ class and frequency in Table 6 below:

very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥ 1/10,000 to <1/1,000); and not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. The highest frequency seen among the various indications has been included. An asterisk (*) appears in the System Organ Class (SOC) column if further information is found elsewhere in sections 4.3, 4.4 and 4.8.

**Table 6**

**Undesirable Effects**

| System Organ Class | Frequency | Adverse Reaction |
|---|---|---|
| Infections and infestations* | Very common | Respiratory tract infections (including lower and upper respiratory tract infection, pneumonia, sinusitis, pharyngitis, nasopharyngitis and pneumonia herpes viral) |
| | Common | Systemic infections (including sepsis, candidiasis and influenza), intestinal infections (including gastroenteritis viral), skin and soft tissue infections (including paronychia, cellulitis, impetigo, necrotising fasciitis and herpes zoster), ear infections, oral infections (including herpes simplex, oral herpes and tooth infections), reproductive tract |

| | | |
|---|---|---|
| | | infections (including vulvovaginal mycotic infection), urinary tract infections (including pyelonephritis), fungal infections, joint infections |
| | Uncommon | Neurological infections (including viral meningitis), opportunistic infections and tuberculosis (including coccidioidomycosis, histoplasmosis and mycobacterium avium complex infection), bacterial infections, eye infections, diverticulitis[1)] |
| Neoplasms benign, malignant and unspecified (including cysts and polyps)* | Common | Skin cancer excluding melanoma (including basal cell carcinoma and squamous cell carcinoma), benign neoplasm |
| | Uncommon | Lymphoma**, solid organ neoplasm (including breast cancer, lung neoplasm and thyroid neoplasm), melanoma** |
| | Rare | Leukaemia[1)] |
| | Not known | Hepatosplenic T-cell lymphoma[1)]<br>Merkel cell carcinoma (neuroendocrine carcinoma of the skin)[1)] |
| Blood and the lymphatic system disorders* | Very common | Leukopenia (including neutropenia and agranulocytosis), anaemia |
| | Common | Leukocytosis, thrombocytopenia |
| | Uncommon | Idiopathic thrombocytopenic purpura |
| | Rare | Pancytopenia |
| Immune system disorders* | Common | Hypersensitivity, allergies (including seasonal allergy) |
| | Uncommon | Sarcoidosis[1)],<br>vasculitis |
| | Rare | Anaphylaxis[1)] |
| Metabolism and nutrition disorders | Very common | Lipids increased |
| | Common | Hypokalaemia, uric acid increased, blood sodium abnormal, hypocalcaemia, hyperglycaemia, hypophosphatemia, dehydration |
| Psychiatric disorders | Common | Mood alterations (including depression), anxiety, Insomnia |
| Nervous system disorders* | Very common | Headache |
| | Common | Paraesthesias (including hypoesthesia), migraine, nerve root compression |
| | Uncommon | Cerebrovascular accident[1)],<br>tremor,<br>neuropathy |
| | Rare | Multiple sclerosis, demyelinating disorders (e.g. optic neuritis, Guillain-Barré syndrome)[1)] |
| Eye disorders | Common | Visual impairment, conjunctivitis, blepharitis, eye swelling |
| | Uncommon | Diplopia |
| Ear and labyrinth disorders | Common | Vertigo |
| | Uncommon | Deafness, tinnitus |
| Cardiac disorders* | Common | Tachycardia |
| | Uncommon | Myocardial infarction[1)], arrhythmia, congestive heart failure |
| | Rare | Cardiac arrest |
| | | |

| | | |
|---|---|---|
| Vascular disorders | Common | Hypertension, flushing, haematoma |
| | Uncommon | Aortic aneurysm, vascular arterial occlusion, thrombophlebitis |
| Respiratory, thoracic and mediastinal disorders* | Common | Asthma, dyspnoea, cough |
| | Uncommon | Pulmonary embolism[1)], interstitial lung disease, chronic obstructive pulmonary disease, pneumonitis, pleural effusion[1)] |
| | Rare | Pulmonary fibrosis[1)] |
| Gastrointestinal disorders | Very common | Abdominal pain, nausea and vomiting |
| | Common | GI haemorrhage, dyspepsia, gastroesophageal reflux disease, sicca syndrome |
| | Uncommon | Pancreatitis, dysphagia, face oedema |
| | Rare | Intestinal perforation[1)] |
| Hepatobiliary disorders* | Very common | Elevated liver enzymes |
| | Uncommon | Cholecystitis and cholelithiasis, hepatic steatosis, bilirubin increased |
| | Rare | Hepatitis<br>reactivation of hepatitis B[1)]<br>autoimmune hepatitis[1)] |
| | Not Known | Liver failure[1)] |
| Skin and subcutaneous tissue disorders | Very common | Rash (including exfoliative rash) |
| | Common | Worsening or new onset of psoriasis (including palmoplantar pustular psoriasis)[1)], urticaria, bruising (including purpura), dermatitis (including eczema), onychoclasis, hyperhidrosis, alopecia[1)], pruritus |
| | Uncommon | Night sweats,<br>scar |
| | Rare | Erythema multiforme[1)], Stevens-Johnson syndrome[1)], angioedema[1)], cutaneous vasculitis[1)]<br>lichenoid skin reaction[1)] |
| | Not known | Worsening of symptoms of dermatomyositis[1)] |
| Musculoskeletal and connective tissue disorders | Very common | Musculoskeletal pain |
| | Common | Muscle spasms (including blood creatine phosphokinase increased) |
| | Uncommon | Rhabdomyolysis, systemic lupus erythematosus |
| | Rare | Lupus-like syndrome[1)] |
| Renal and urinary disorders | Common | Renal impairment, haematuria |
| | Uncommon | Nocturia |
| Reproductive system and breast disorders | Uncommon | Erectile dysfunction |
| General disorders and administration site conditions* | Very common | Injection site reaction (including injection site erythema) |
| | Common | Chest pain, oedema, pyrexia[1)] |
| | Uncommon | Inflammation |
| | | |

| | | |
|---|---|---|
| Investigations* | Common | Coagulation and bleeding disorders (including activated partial thromboplastin time prolonged), autoantibody test positive (including double stranded DNA antibody), blood lactate dehydrogenase increased |
| Injury, poisoning and procedural complications | Common | Impaired healing |

* further information is found elsewhere in sections 4.3, 4.4 and 4.8

** including open label extension studies

1) including spontaneous reporting data

Hidradenitis suppurativa

The safety profile for patients with HS treated with adalimumab weekly was consistent with the known safety profile of adalimumab.

Uveitis

The safety profile for patients with uveitis treated with adalimumab every other week was consistent with the known safety profile of adalimumab.

Description of selected adverse reactions

*Injection site reactions*

In the pivotal controlled trials in adults and children, 12.9 % of patients treated with adalimumab developed injection site reactions (erythema and/or itching, haemorrhage, pain or swelling), compared to 7.2 % of patients receiving placebo or active control. Injection site reactions generally did not necessitate discontinuation of the medicinal product.

*Infections*

In the pivotal controlled trials in adults and children, the rate of infection was 1.51 per patient year in the adalimumab treated patients and 1.46 per patient year in the placebo and active control-treated patients. The infections consisted primarily of nasopharyngitis, upper respiratory tract infection, and sinusitis. Most patients continued on adalimumab after the infection resolved.

The incidence of serious infections was 0.04 per patient year in adalimumab treated patients and 0.03 per patient year in placebo and active control-treated patients.

In controlled and open label adult and paediatric studies with adalimumab, serious infections (including fatal infections, which occurred rarely) have been reported, which include reports of tuberculosis (including miliary and extra-pulmonary locations) and invasive opportunistic infections (e.g. disseminated or extrapulmonary histoplasmosis, blastomycosis, coccidioidomycosis, pneumocystis, candidiasis, aspergillosis and listeriosis). Most of the cases of tuberculosis occurred within the first eight months after initiation of therapy and may reflect recrudescence of latent disease.

*Malignancies and lymphoproliferative disorders*

No malignancies were observed in 249 paediatric patients with an exposure of 655.6 patient years during adalimumab trials in patients with juvenile idiopathic arthritis (polyarticular juvenile idiopathic arthritis and enthesitis-related arthritis). In addition, no malignancies were observed in 192 paediatric patients with an exposure of 498.1 patient years during adalimumab trials in paediatric patients with Crohn's disease. No malignancies were observed in 77 paediatric patients with an exposure of 80.0 patient years during an adalimumab trial in paediatric patients with chronic plaque psoriasis. No malignancies were observed in 60 paediatric patients with an exposure of 58.4 patient years during an adalimumab trial in paediatric patients with uveitis.

During the controlled portions of pivotal adalimumab trials in adults of at least 12 weeks in duration in patients with moderately to severely active rheumatoid arthritis, ankylosing spondylitis, axial spondyloarthritis without radiographic evidence of AS, psoriatic arthritis, psoriasis, hidradenitis suppurativa, Crohn's disease, ulcerative colitis, and uveitis, malignancies, other than lymphoma and non-melanoma skin cancer, were observed at a rate (95% confidence interval) of 6.8 (4.4, 10.5) per 1,000 patient-years among 5,291 adalimumab treated patients *versus* a rate of 6.3 (3.4, 11.8) per 1,000 patient-years among 3,444 control patients (median duration of treatment was 4.0 months for adalimumab and 3.8 months for control-treated patients). The rate (95% confidence interval) of non-melanoma skin cancers was 8.8 (6.0, 13.0) per 1,000 patient-years among adalimumab-treated patients and 3.2 (1.3, 7.6) per 1,000 patient-years among control patients. Of these skin cancers, squamous cell carcinomas occurred at rates (95% confidence interval) of 2.7 (1.4, 5.4) per 1,000 patient-years among adalimumab-treated patients and 0.6 (0.1, 4.5) per 1,000 patient-years among control patients. The rate (95 % confidence interval) of lymphomas was 0.7 (0.2, 2.7) per 1,000 patient-years among adalimumab-treated patients and 0.6 (0.1, 4.5) per 1,000 patient-years among control patients.

When combining controlled portions of these trials and ongoing and completed open label extension studies with a median duration of approximately 3.3 years including 6,427 patients and over 26,439 patient-years of therapy, the observed rate of malignancies, other than lymphoma and non-melanoma skin cancers is approximately 8.5 per 1,000 patient years. The observed rate of non-melanoma skin cancers is approximately 9.6 per 1,000 patient years, and the observed rate of lymphomas is approximately 1.3 per 1,000 patient-years.

In post-marketing experience from January 2003 to December 2010, predominantly in patients with rheumatoid arthritis, the reported rate of malignancies is approximately 2.7 per 1,000 patient treatment years. The reported rates for non-melanoma skin cancers and lymphomas are approximately 0.2 and 0.3 per 1,000 patient treatment years, respectively (see section 4.4).

Rare post-marketing cases of hepatosplenic T-cell lymphoma have been reported in patients treated with adalimumab (see section 4.4).

*Autoantibodies*

Patients had serum samples tested for autoantibodies at multiple time points in rheumatoid arthritis studies I − V. In these trials, 11.9 % of patients treated with adalimumab and 8.1% of placebo and active control − treated patients that had negative baseline anti-nuclear antibody titres reported positive titres at week 24. Two patients out of 3,441 treated with adalimumab in all rheumatoid arthritis and psoriatic arthritis studies developed clinical signs suggestive of new-onset lupus-like syndrome. The patients improved following discontinuation of therapy. No patients developed lupus nephritis or central nervous system symptoms.

*Hepato-biliary events*

In controlled Phase 3 trials of adalimumab in patients with rheumatoid arthritis and psoriatic arthritis with a control period duration ranging from 4 to 104 weeks, ALT elevations ≥3 ×ULN occurred in 3.7 % of adalimumab-treated patients and 1.6 % of control-treated patients.

In controlled Phase 3 trials of adalimumab in patients with polyarticular juvenile idiopathic arthritis who were 4 to 17 years and enthesitis-related arthritis who were 6 to 17 years, ALT elevations ≥3 × ULN occurred in 6.1 % of adalimumab-treated patients and 1.3 % of control-treated patients. Most ALT elevations occurred with concomitant methotrexate use. No ALT elevations ≥3 × ULN occurred in the Phase 3 trial of adalimumab in patients with polyarticular juvenile idiopathic arthritis who were 2 to <4 years.

In controlled Phase 3 trials of adalimumab in patients with Crohn's disease and ulcerative colitis with a control period ranging from 4 to 52 weeks. ALT elevations ≥3 × ULN occurred in 0.9% of adalimumab-treated patients and 0.9 % of controlled-treated patients.

In the Phase 3 trial of adalimumab in patients with paediatric Crohn's disease which evaluated efficacy and safety of two body weight adjusted maintenance dose regimens following body weight adjusted induction therapy up to 52 weeks of treatment, ALT elevations ≥3 × ULN occurred in 2.6 % (5/192) of patients of whom 4 were receiving concomitant immunosuppressants at baseline.

In controlled Phase 3 trials of adalimumab in patients with plaque psoriasis with a control period duration ranging from 12 to 24 weeks, ALT elevations ≥3 × ULN occurred in 1.8% of adalimumab-treated patients and 1.8 % of control-treated patients.

No ALT elevations ≥3 × ULN occurred in the Phase 3 trial of adalimumab in paediatric patients with plaque psoriasis.

In controlled trials of adalimumab (initial doses of 160 mg at week 0 and 80 mg at week 2, followed by 40 mg every week starting at week 4), in patients with hidradenitis suppurativa with a control period duration ranging from 12 to 16 weeks, ALT elevations ≥3 × ULN occurred in 0.3 % of adalimumab-treated patients and 0.6 % of control-treated patients.

In controlled trials of adalimumab (initial doses of 80 mg at week 0 followed by 40 mg every other week starting at week 1) in adult patients with uveitis up to 80 weeks with a median exposure of 166.5 days and 105.0 days in adalimumab-treated and control-treated patients, respectively, ALT elevations ≥3 × ULN occurred in 2.4 % of adalimumab-treated patients and 2.4 % of control-treated patients.

Across all indications in clinical trials patients with raised ALT were asymptomatic and in most cases elevations were transient and resolved on continued treatment. However, there have also been post-marketing reports of liver failure as well as less severe liver disorders that may precede liver failure, such as hepatitis including autoimmune hepatitis in patients receiving adalimumab.

Concurrent treatment with azathioprine/6-mercaptopurine

In adult Crohn's disease studies, higher incidences of malignant and serious infection-related adverse events were seen with the combination of adalimumab and azathioprine/6-mercaptopurine compared with adalimumab alone.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via:

**United Kingdom**

Yellow Card Scheme

Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store

**Ireland**

HPRA Pharmacovigilance

Website: www.hpra.ie

**Malta**

ADR Reporting

Website: www.medicinesauthority.gov.mt/adrportal

### 4.9 Overdose

No dose-limiting toxicity was observed during clinical trials. The highest dose level evaluated has been multiple intravenous doses of 10 mg/kg, which is approximately 15 times the recommended dose.

## 5. Pharmacological properties

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, Tumour Necrosis Factor alpha (TNF-α) inhibitors.

ATC code: L04AB04

Imraldi is a biosimilar medicinal product. Detailed information is available on the website of the European Medicines Agency http://www.ema.europa.eu.

Mechanism of action

Adalimumab binds specifically to TNF and neutralises the biological function of TNF by blocking its interaction with the p55 and p75 cell surface TNF receptors.

Adalimumab also modulates biological responses that are induced or regulated by TNF, including changes in the levels of adhesion molecules responsible for leukocyte migration (ELAM-1, VCAM-1, and ICAM-1 with an $IC_{50}$ of 0.1-0.2 nM).

Pharmacodynamic effects

After treatment with adalimumab, a rapid decrease in levels of acute phase reactants of inflammation (C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR)) and serum cytokines (IL-6) was observed, compared to baseline in patients with rheumatoid arthritis. Serum levels of matrix metalloproteinases (MMP-1 and MMP-3) that produce tissue remodelling responsible for cartilage destruction were also decreased after adalimumab administration. Patients treated with adalimumab usually experienced improvement in haematological signs of chronic inflammation.

A rapid decrease in CRP levels was also observed in patients with polyarticular juvenile idiopathic arthritis, Crohn's disease, ulcerative colitis, and hidradenitis suppurativa after treatment with adalimumab. In patients with Crohn's disease, a reduction of the number of cells expressing inflammatory markers in the colon including a significant reduction of expression of TNFα was seen. Endoscopic studies in intestinal mucosa have shown evidence of mucosal healing in adalimumab treated patients.

Clinical efficacy and safety

*Rheumatoid arthritis*

Adalimumab was evaluated in over 3,000 patients in all rheumatoid arthritis clinical trials. The efficacy and safety of adalimumab were assessed in five randomised, double-blind and well-controlled studies. Some patients were treated for up to 120 months duration.

RA study I evaluated 271 patients with moderately to severely active rheumatoid arthritis who were ≥18 years old, had failed therapy with at least one disease-modifying, anti-rheumatic drug and had insufficient efficacy with methotrexate at doses of 12.5 to 25 mg (10 mg if methotrexate-intolerant) every week and whose methotrexate dose remained constant at 10 to 25 mg every week. Doses of 20, 40 or 80 mg of adalimumab or placebo were given every other week for 24 weeks.

RA study II evaluated 544 patients with moderately to severely active rheumatoid arthritis who were ≥18 years old and had failed therapy with at least one disease-modifying, anti-rheumatic drugs. Doses of 20 or 40 mg of adalimumab were given by subcutaneous injection every other week with placebo on alternative weeks or every week for 26 weeks; placebo was given every week for the same duration. No other disease-modifying anti-rheumatic drugs were allowed.

RA study III evaluated 619 patients with moderately to severely active rheumatoid arthritis who were ≥18 years old, and who had an ineffective response to methotrexate at doses of 12.5 to 25 mg or have been intolerant to 10 mg of methotrexate every week. There were three groups in this study. The first received placebo injections every week for 52 weeks. The second received 20 mg of adalimumab every week for 52 weeks. The third group received 40 mg of adalimumab every other week with placebo injections on alternate weeks. Upon completion of the first 52 weeks, 457 patients enrolled in an open-label extension phase in which 40 mg of adalimumab/MTX was administered every other week up to 10 years.

RA study IV primarily assessed safety in 636 patients with moderately to severely active rheumatoid arthritis who were ≥ 18 years old. Patients were permitted to be either disease-modifying, anti-rheumatic drug-naïve or to remain on their pre-existing rheumatologic therapy provided that therapy was stable for a minimum of 28 days. These therapies include methotrexate, leflunomide, hydroxychloroquine, sulfasalazine and/or gold salts. Patients were randomised to 40 mg of adalimumab or placebo every other week for 24 weeks.

RA study V evaluated 799 methotrexate-naïve, adult patients with moderate to severely active early rheumatoid arthritis (mean disease duration less than 9 months). This study evaluated the efficacy of adalimumab 40 mg every other

week/methotrexate combination therapy, adalimumab 40 mg every other week monotherapy and methotrexate monotherapy in reducing the signs and symptoms and rate of progression of joint damage in rheumatoid arthritis for 104 weeks. Upon completion of the first 104 weeks, 497 patients enrolled in an open-label extension phase in which 40 mg of adalimumab was administered every other week up to 10 years.

The primary end point in RA studies I, II and III and the secondary endpoint in RA study IV was the percent of patients who achieved an ACR 20 response at week 24 or 26. The primary endpoint in RA study V was the percent of patients who achieved an ACR 50 response at week 52. RA studies III and V had an additional primary endpoint at 52 weeks of retardation of disease progression (as detected by X-ray results). RA study III also had a primary endpoint of changes in quality of life.

*ACR response*

The percent of adalimumab-treated patients achieving ACR 20, 50 and 70 responses was consistent across RA studies I, II and III. The results for the 40 mg every other week dose are summarised in Table 7.

**Table 7**

**ACR Responses in Placebo Controlled Trials**

**(Percent of Patients)**

| Response | RA study I[a]** | | RA study II[a]** | | RA study III[a]** | |
|---|---|---|---|---|---|---|
| | Placebo/ MTX[c] N=60 | Adalimumab[b]/ MTX[c] N=63 | Placebo N=110 | Adalimumab[b] N=113 | Placebo/ MTX[c] N=200 | Adalimumab[b]/ MTX[c] N=207 |
| **ACR 20** | | | | | | |
| **6 months** | 13.3% | 65.1% | 19.1% | 46.0% | 29.5% | 63.3% |
| **12 months** | - | - | - | - | 24.0% | 58.9% |
| **ACR 50** | | | | | | |
| **6 months** | 6.7% | 52.4% | 8.2% | 22.1% | 9.5% | 39.1% |
| **12 months** | - | - | - | - | 9.5% | 41.5% |
| **ACR 70** | | | | | | |
| **6 months** | 3.3% | 23.8% | 1.8% | 12.4% | 2.5% | 20.8% |
| **12 months** | - | - | - | - | 4.5% | 23.2% |

[a] RA study I at 24 weeks, RA study II at 26 weeks, and RA study III at 24 and 52 weeks

[b] 40 mg adalimumab administered every other week

[c] MTX = methotrexate

**p <0.01, adalimumab *versus* placebo

- Not applicable

In RA studies I-IV, all individual components of the ACR response criteria (number of tender and swollen joints, physician and patient assessment of disease activity and pain, disability index (HAQ) scores and CRP (mg/dl) values) improved at 24 or 26 weeks compared to placebo. In RA study III, these improvements were maintained throughout 52 weeks.

In the open-label extension for RA study III, most patients who were ACR responders maintained response when followed for up to 10 years. Of 207 patients who were randomised to adalimumab 40 mg every other week, 114 patients continued on adalimumab 40 mg every other week for 5 years. Among those, 86 patients (75.4 %) had ACR 20 responses; 72 patients (63.2 %) had ACR 50 responses; and 41 patients (36 %) had ACR 70 responses. Of 207 patients, 81 patients continued on adalimumab 40 mg every other week for 10 years. Among those, 64 patients (79.0 %) had ACR 20 responses; 56 patients (69.1 %) had ACR 50 responses; and 43 patients (53.1 %) had ACR 70 responses.

In RA study IV, the ACR 20 response of patients treated with adalimumab plus standard of care was statistically significantly better than patients treated with placebo plus standard of care (p <0.001).

In RA studies I-IV, adalimumab -treated patients achieved statistically significant ACR 20 and 50 responses compared to placebo as early as one to two weeks after initiation of treatment.

In RA study V with early rheumatoid arthritis patients who were methotrexate naïve, combination therapy with adalimumab and methotrexate led to faster and significantly greater ACR responses than methotrexate monotherapy and adalimumab monotherapy at week 52 and responses were sustained at week 104 (see Table 8).

**Table 8**

**ACR Responses in RA Study V**

**(Percent of Patients)**

| Response | MTX N=257 | Adalimumab N=274 | Adalimumab/ MTX N=268 | p-value[a] | p-value[b] | p-value[c] |
|---|---|---|---|---|---|---|
| **ACR 20** | | | | | | |
| **52 Week** | 62.6% | 54.4% | 72.8% | 0.013 | <0.001 | 0.043 |
| **104 Week** | 56.0% | 49.3% | 69.4% | 0.002 | <0.001 | 0.140 |
| **ACR 50** | | | | | | |
| **52 Week** | 45.9% | 41.2% | 61.6% | <0.001 | <0.001 | 0.317 |
| **104 Week** | 42.8% | 36.9% | 59.0% | <0.001 | <0.001 | 0.162 |
| **ACR 70** | | | | | | |
| **52 Week** | 27.2% | 25.9% | 45.5% | <0.001 | <0.001 | 0.656 |
| **104 Week** | 28.4% | 28.1% | 46.6% | <0.001 | <0.001 | 0.864 |

[a] p-value is from the pairwise comparison of methotrexate monotherapy and adalimumab/methotrexate combination therapy using the Mann-Whitney U test.

[b] p-value is from the pairwise comparison of adalimumab monotherapy and adalimumab/methotrexate combination therapy using the Mann-Whitney U test

[c] p-value is from the pairwise comparison of adalimumab monotherapy and methotrexate monotherapy using the Mann-Whitney U test

In the open-label extension for RA study V, ACR response rates were maintained when followed for up to 10 years. Of 542 patients who were randomised to adalimumab 40 mg every other week, 170 patients continued on adalimumab 40 mg every other week for 10 years. Among those, 154 patients (90.6 %) had ACR 20 responses; 127 patients (74.7 %) had ACR 50 responses; and 102 patients (60.0 %) had ACR 70 responses.

At week 52, 42.9 % of patients who received adalimumab/methotrexate combination therapy achieved clinical remission (DAS28 <2.6) compared to 20.6 % of patients receiving methotrexate monotherapy and 23.4 % of patients receiving adalimumab monotherapy. Adalimumab/methotrexate combination therapy was clinically and statistically superior to methotrexate (p <0.001) and adalimumab monotherapy (p <0.001) in achieving a low disease state in patients with recently diagnosed moderate to severe rheumatoid arthritis. The response for the two monotherapy arms was similar (p = 0.447). Of 342 subjects originally randomized to adalimumab monotherapy or adalimumab/methotrexate combination therapy who entered the open-label extension study, 171 subjects completed 10 years of adalimumab treatment. Among those, 109 subjects (63.7 %) were reported to be in remission at 10 years.

*Radiographic response*

In RA study III, where adalimumab treated patients had a mean duration of rheumatoid arthritis of approximately 11 years, structural joint damage was assessed radiographically and expressed as change in modified Total Sharp Score (TSS) and its components, the erosion score and joint space narrowing score. Adalimumab /methotrexate patients demonstrated significantly less radiographic progression than patients receiving methotrexate alone at 6 and 12 months (see Table 9).

In the open-label extension of RA study III, the reduction in rate of progression of structural damage is maintained for 8 and 10 years in a subset of patients. At 8 years, 81 of 207 patients originally treated with 40 mg adalimumab every other week were evaluated radiographically. Among those, 48 patients showed no progression of structural damage defined by a change from baseline in the mTSS of 0.5 or less. At 10 years, 79 of 207 patients originally treated with 40 mg adalimumab every other week were evaluated radiographically. Among those, 40 patients showed no progression of structural damage defined by a change from baseline in the mTSS of 0.5 or less.

**Table 9**

**Radiographic Mean Changes Over 12 Months in RA Study III**

| | Placebo/MTX[a] | Adalimumab/MTX 40 mg every other week | Placebo/MTX-Adalimumab/MTX (95% Confidence Interval[b]) | p-value |
|---|---|---|---|---|

| | | | | |
|---|---|---|---|---|
| **Total Sharp Score** | 2.7 | 0.1 | 2.6 (1.4, 3.8) | <0.001[c] |
| **Erosion Score** | 1.6 | 0.0 | 1.6 (0.9, 2.2) | <0.001 |
| **JSN[d] Score** | 1.0 | 0.1 | 0.9 (0.3, 1.4) | 0.002 |

[a] methotrexate

[b] 95 % confidence intervals for the differences in change scores between methotrexate and adalimumab.

[c] Based on rank analysis

[d] Joint Space Narrowing

In RA study V, structural joint damage was assessed radiographically and expressed as change in modified Total Sharp Score (see Table 10).

**Table 10**

**Radiographic Mean Changes at Week 52 in RA Study V**

| | **MTX N=257 (95% confidence interval)** | **Adalimumab N=274 (95% confidence interval)** | **Adalimumab /MTX N=268 (95% confidence interval)** | **p-value[a]** | **p-value[b]** | **p-value[c]** |
|---|---|---|---|---|---|---|
| **Total Sharp Score** | 5.7 (4.2-7.3) | 3.0 (1.7-4.3) | 1.3 (0.5-2.1) | <0.001 | 0.0020 | <0.001 |
| **Erosion Score** | 3.7 (2.7-4.7) | 1.7 (1.0-2.4) | 0.8 (0.4-1.2) | <0.001 | 0.0082 | <0.001 |
| **JSN Score** | 2.0 (1.2-2.8) | 1.3 (0.5-2.1) | 0.5 (0-1.0) | <0.001 | 0.0037 | 0.151 |

[a] p-value is from the pairwise comparison of methotrexate monotherapy and adalimumab/methotrexate combination therapy using the Mann-Whitney U test

[b] p-value is from the pairwise comparison of adalimumab monotherapy and adalimumab/methotrexate combination therapy using the Mann-Whitney U test

[c] p-value is from the pairwise comparison of adalimumab monotherapy and methotrexate monotherapy using the Mann-Whitney U test

Following 52 weeks and 104 weeks of treatment, the percentage of patients without progression (change from baseline in modified Total Sharp Score ≤0.5) was significantly higher with adalimumab/methotrexate combination therapy (63.8 % and 61.2 % respectively) compared to methotrexate monotherapy (37.4 % and 33.5 % respectively, p <0.001) and adalimumab monotherapy (50.7 %, p <0.002 and 44.5 %, p <0.001 respectively).

In the open-label extension of RA study V, the mean change from baseline at Year 10 in the modified Total Sharp Score was 10.8, 9.2 and 3.9 in patients originally randomized to methotrexate monotherapy, adalimumab monotherapy and adalimumab/methotrexate combination therapy, respectively. The corresponding proportions of patients with no radiographic progression were 31.3 %, 23.7 % and 36.7 % respectively.

*Quality of life and physical function*

Health-related quality of life and physical function were assessed using the disability index of the Health Assessment Questionnaire (HAQ) in the four original adequate and well-controlled trials, which was a pre-specified primary endpoint at week 52 in RA study III. All doses/schedules of adalimumab in all four studies showed statistically significantly greater improvement in the disability index of the HAQ from baseline to Month 6 compared to placebo and in RA study III the same was seen at week 52. Results from the Short Form Health Survey (SF 36) for all doses/schedules of adalimumab in all four studies support these findings, with statistically significant physical component summary (PCS) scores, as well as statistically significant pain and vitality domain scores for the 40 mg every other week dose. A statistically significant decrease in fatigue as measured by functional assessment of chronic illness therapy (FACIT) scores was seen in all three studies in which it was assessed (RA studies I, III, IV).

In RA study III, most subjects who achieved improvement in physical function and continued treatment maintained improvement through week 520 (120 months) of open-label treatment. Improvement in quality of life was measured up to week 156 (36 months) and improvement was maintained through that time.

In RA study V, the improvement in the HAQ disability index and the physical component of the SF 36 showed greater improvement (p <0.001) for adalimumab/methotrexate combination therapy *versus* methotrexate monotherapy and adalimumab monotherapy at week 52, which was maintained through week 104. Among the 250 subjects who completed the open-label extension study, improvements in physical function were maintained through 10 years of treatment.

*Juvenile idiopathic arthritis (JIA)*

*Polyarticular juvenile idiopathic arthritis (pJIA)*

The safety and efficacy of adalimumab was assessed in two studies (pJIA I and II) in children with active polyarticular or polyarticular course juvenile idiopathic arthritis, who had a variety of JIA onset types (most frequently rheumatoid-factor negative or positive polyarthritis and extended oligoarthritis).

pJIA I

The safety and efficacy of adalimumab were assessed in a multicentre, randomised, double-blind, parallel-group study in 171 children (4-17 years old) with polyarticular JIA. In the open-label lead in phase (OL LI) patients were stratified into two groups, MTX (methotrexate)-treated or non-MTX- treated. Patients who were in the non-MTX stratum were either naïve to or had been withdrawn from MTX at least two weeks prior to study drug administration. Patients remained on stable doses of NSAIDs and or prednisone (≤ 0.2 mg /kg/day or 10 mg/day maximum). In the OL LI phase all patients received 24 mg/m$^2$ up to a maximum of 40 mg adalimumab every other week for 16 weeks. The distribution of patients by age and minimum, median and maximum dose received during the OL LI phase is presented in Table 11.

**Table 11**

**Distribution of patients by age and adalimumab dose received during the OL LI phase**

| Age Group | Number of patients at Baseline N (%) | Minimum, median and maximum dose |
|---|---|---|
| 4 to 7 years | 31 (18.1) | 10, 20 and 25 mg |
| 8 to 12 years | 71 (41.5) | 20, 25 and 40 mg |
| 13 to 17 years | 69 (40.4) | 25, 40 and 40 mg |

Patients demonstrating a Paediatric ACR 30 response at week 16 were eligible to be randomised into the double blind (DB) phase and received either adalimumab 24 mg/m$^2$ up to a maximum of 40 mg, or placebo every other week for an additional 32 weeks or until disease flare. Disease flare criteria were defined as a worsening of ≥30% from baseline in ≥3 of 6 Paediatric ACR core criteria, ≥2 active joints, and improvement of >30% in no more than 1 of the 6 criteria. After 32 weeks or at disease flare, patients were eligible to enrol into the open label extension phase.

**Table 12**

**Paed ACR 30 Responses in the JIA study**

| **Stratum** / **Phase** | **MTX** | | **Without MTX** | |
|---|---|---|---|---|
| OL-LI 16 weeks | | | | |
| Ped ACR 30 response (n/N) | 94.1 % (80/85) | | 74.4 % (64/86) | |
| Efficacy Outcomes | | | | |
| Double Blind 32 weeks | Adalimumab /MTX (N=38) | Placebo / MTX (N=37) | Adalimumab (N=30) | Placebo (N=28) |
| Disease flares at the end of 32 weeks[a] (n/N) | 36.8 % (14/38) | 64.9 % (24/37)[b] | 43.3 % (13/30) | 71.4 % (20/28)[c] |
| Median time to disease flare | >32 weeks | 20 weeks | >32 weeks | 14 weeks |

[a] Ped ACR 30/50/70 responses week 48 significantly greater than those of placebo treated patients

[b] p = 0.015

[c] p = 0.031

Amongst those who responded at week 16 (n=144), the Paediatric ACR 30/50/70/90 responses were maintained for up to six years in the OLE phase in patients who received adalimumab throughout the study. Over all 19 subjects, of which 11 of the baseline age group 4 to 12 and 8 of the baseline age group 13 to 17 years were treated 6 years or longer.

Overall responses were generally better and, fewer patients developed antibodies when treated with the combination of adalimumab and MTX compared to adalimumab alone. Taking these results into consideration, adalimumab is recommended for use in combination with MTX and for use as monotherapy in patients for whom MTX use is not appropriate (see section 4.2).

pJIA II

The safety and efficacy of adalimumab was assessed in an open-label, multicentre study in 32 children (2 - <4 years old or aged 4 and above weighing <15 kg) with moderately to severely active polyarticular JIA. The patients received 24

mg/m$^2$ body surface area (BSA) of adalimumab up to a maximum of 20 mg every other week as a single dose via SC injection for at least 24 weeks. During the study, most subjects used concomitant MTX, with fewer reporting use of corticosteroids or NSAIDs.

At week 12 and week 24, PaedACR30 response was 93.5% and 90.0%, respectively, using the observed data approach. The proportions of subjects with PaedACR50/70/90 at week 12 and week 24 were 90.3%/61.3%/38.7% and 83.3%/73.3%/36.7%, respectively. Amongst those who responded (Paediatric ACR 30) at week 24 (n=27 out of 30 patients), the Paediatric ACR 30 responses were maintained for up to 60 weeks in the OLE phase in patients who received adalimumab throughout this time period. Overall, 20 subjects were treated for 60 weeks or longer.

*Enthesitis-related arthritis*

The safety and efficacy of adalimumab were assessed in a multicentre, randomised, double-blind study in 46 paediatric patients (6 to 17 years old) with moderate enthesitis-related arthritis. Patients were randomised to receive either 24 mg/m$^2$ body surface area (BSA) of adalimumab up to a maximum of 40 mg, or placebo every other week for 12 weeks. The double-blind period is followed by an open-label (OL) period during which patients received 24 mg/m$^2$ BSA of adalimumab up to a maximum of 40 mg every other week subcutaneously for up to an additional 192 weeks. The primary endpoint was the percent change from Baseline to week 12 in the number of active joints with arthritis (swelling not due to deformity or joints with loss of motion plus pain and/or tenderness), which was achieved with mean percent decrease of -62.6% (median percent change -88.9 %) in patients in the adalimumab group compared to -11.6% (median percent change -50.0 %) in patients in the placebo group. Improvement in number of active joints with arthritis was maintained during the OL period through week 156 for the 26 of 31 (84 %) patients in the adalimumab group who remained in the study. Although not statistically significant, the majority of patients demonstrated clinical improvement in secondary endpoints such as number of sites of enthesitis, tender joint count (TJC), swollen joint count (SJC), Paediatric ACR 50 response, and Paediatric ACR 70 response.

*Axial spondyloarthritis*

*Ankylosing spondylitis (AS)*

Adalimumab 40 mg every other week was assessed in 393 patients in two randomised, 24 week double − blind, placebo − controlled studies in patients with active ankylosing spondylitis (mean baseline score of disease activity [Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)] was 6.3 in all groups) who have had an inadequate response to conventional therapy. Seventy-nine (20.1%) patients were treated concomitantly with disease modifying anti − rheumatic drugs, and 37 (9.4%) patients with glucocorticoids. The blinded period was followed by an open − label period during which patients received adalimumab 40 mg every other week subcutaneously for up to an additional 28 weeks. Subjects (n=215, 54.7%) who failed to achieve ASAS 20 at weeks 12, or 16 or 20 received early escape open-label adalimumab 40 mg every other week subcutaneously and were subsequently treated as non-responders in the double-blind statistical analyses.

In the larger AS study I with 315 patients, results showed statistically significant improvement of the signs and symptoms of ankylosing spondylitis in patients treated with adalimumab compared to placebo. Significant response was first observed at week 2 and maintained through 24 weeks (Table 13).

**Table 13**

**Efficacy Responses in Placebo-Controlled AS Study – Study I**

**Reduction of Signs and Symptoms**

| **Response** | **Placebo N=107** | **Adalimumab N=208** |
|---|---|---|
| ASAS[a] 20 | | |
| Week 2 | 16% | 42%*** |
| Week 12 | 21% | 58%*** |
| Week 24 | 19% | 51%*** |
| ASAS 50 | | |
| Week 2 | 3% | 16%*** |
| Week 12 | 10% | 38%*** |
| Week 24 | 11% | 35%*** |
| ASAS 70 | | |
| Week 2 | 0% | 7%** |
| Week 12 | 5% | 23%*** |

| | | |
|---|---|---|
| Week 24 | 8% | 24%*** |
| BASDAI[b] 50 | | |
| Week 2 | 4% | 20%*** |
| Week 12 | 16% | 45%*** |
| Week 24 | 15% | 42%*** |

***,** Statistically significant at p < 0.001, < 0.01 for all comparisons between adalimumab and placebo at weeks 2, 12 and 24

[a] Assessments in Ankylosing Spondylitis

[b] Bath Ankylosing Spondylitis Disease Activity Index

Adalimumab treated patients had significantly greater improvement at week 12 which was maintained through week 24 in both the SF36 and Ankylosing Spondylitis Quality of Life Questionnaire (ASQoL).

Similar trends (not all statistically significant) were seen in the smaller randomised, double − blind, placebo controlled AS study II of 82 adult patients with active ankylosing spondylitis.

*Axial spondyloarthritis without radiographic evidence of AS*

The safety and efficacy of adalimumab were assessed in two randomized, double-blind placebo-controlled studies in patients with non-radiographic axial spondyloarthritis (nr-axSpA). Study nr-axSpA I evaluated patients with active nr-axSpA. Study nr-axSpA II was a treatment withdrawal study in active nr-axSpA patients who achieved remission during open-label treatment with adalimumab.

Study nr-axSpA I

In study nr-axSpA I, adalimumab 40 mg every other week was assessed in 185 patients in a randomised, 12 week double - blind, placebo - controlled study in patients with active nr-axSpA (mean baseline score of disease activity [Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)] was 6.4 for patients treated with adalimumab and 6.5 for those on placebo) who have had an inadequate response to or intolerance to ≥1 NSAIDs, or a contraindication for NSAIDs.

Thirty-three (18 %) patients were treated concomitantly with disease modifying anti-rheumatic drugs, and 146 (79 %) patients with NSAIDs at baseline. The double-blind period was followed by an open-label period during which patients receive adalimumab 40 mg every other week subcutaneously for up to an additional 144 weeks. week 12 results showed statistically significant improvement of the signs and symptoms of active nr-axSpA in patients treated with adalimumab compared to placebo (Table 14).

**Table 14**

**Efficacy Response in Placebo-Controlled Study nr-axSpA I**

| **Double-Blind**<br>**Response at Week 12** | **Placebo**<br>**N=94** | **Adalimumab**<br>**N=91** |
|---|---|---|
| ASAS[a] 40 | 15% | 36%*** |
| ASAS 20 | 31% | 52%** |
| ASAS 5/6 | 6% | 31%*** |
| ASAS partial remission | 5% | 16%* |
| BASDAI[b] 50 | 15% | 35%** |
| ASDAS[c,d,e] | -0.3 | -1.0*** |
| ASDAS Inactive Disease | 4% | 24%*** |
| hs-CRP[d,f,g] | -0.3 | -4.7*** |
| SPARCC[h] MRI Sacroiliac Joints[d,i] | -0.6 | -3.2** |
| SPARCC MRI Spine[d,j] | -0.2 | -1.8** |

[a] Assessments in SpondyloArthritis International Society

[b] Bath Ankylosing Spondylitis Disease Activity Index

[c] Ankylosing Spondylitis Disease Activity Score

[d] mean change from baseline

[e] n=91 placebo and n=87 adalimumab

[f] high sensitivity C-Reactive Protein (mg/L)

[g] n=73 placebo and n=70 adalimumab

[h] Spondyloarthritis Research Consortium of Canada

[i] n=84 placebo and adalimumab

[j] n=82 placebo and n=85 adalimumab

***, **, * Statistically significant at p <0.001, <0.01, and <0.05, respectively, for all comparisons between adalimumab and placebo.

In the open-label extension, improvement in the signs and symptoms was maintained with adalimumab therapy through week 156.

Inhibition of inflammation

Significant improvement of signs of inflammation as measured by hs-CRP and MRI of both Sacroiliac Joints and the Spine was maintained in adalimumab-treated patients through week 156 and week 104, respectively.

Quality of life and physical function

Health-related quality of life and physical function were assessed using the HAQ-S and the SF-36 questionnaires. Adalimumab showed statistically significantly greater improvement in the HAQ-S total score and the SF-36 Physical Component Score (PCS) from baseline to week 12 compared to placebo. Improvement in health-related quality of life and physical function was maintained during the openlabel extension through week 156.

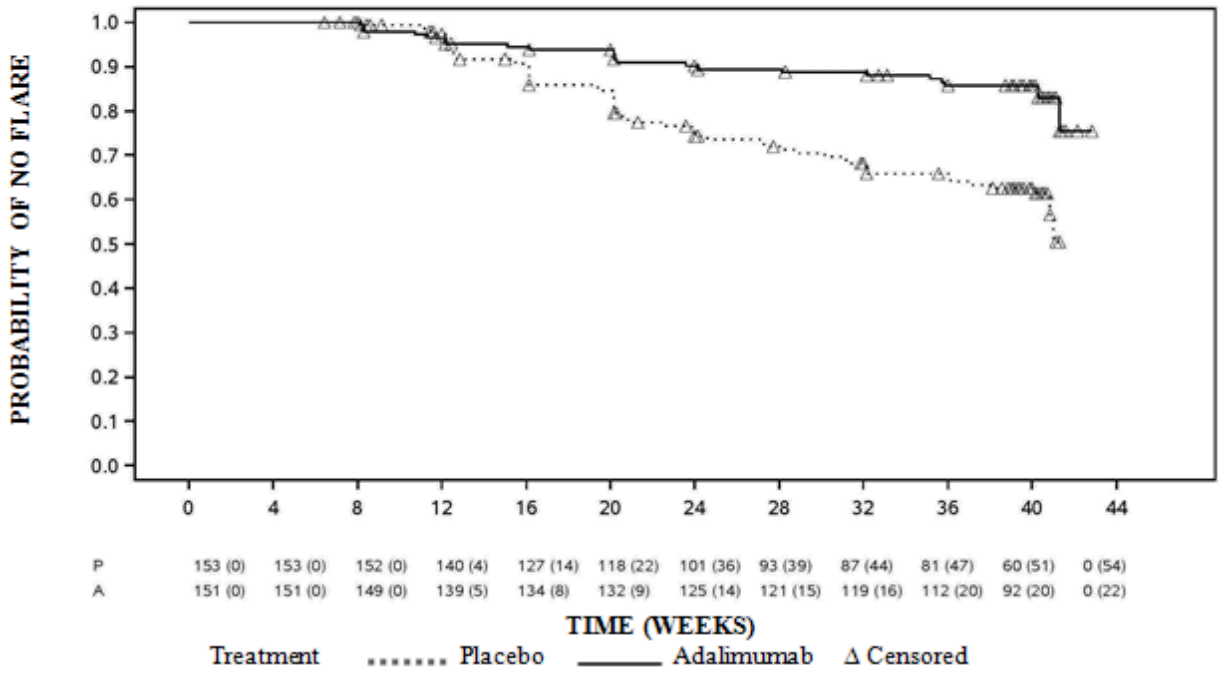
Study nr-axSpA II

673 patients with active nr-axSpA (mean baseline disease activity [BASDAI] was 7.0) who had an inadequate response to ≥ 2 NSAIDs, or an intolerance to or a contraindication for NSAIDs enrolled into the open-label period of study nr-axSpA II during which they received adalimumab 40 mg eow for 28 weeks. These patients also had objective evidence of inflammation in the sacroiliac joints or spine on MRI or elevated hs-CRP. Patients who achieved sustained remission for at least 12 weeks (N=305) (ASDAS < 1.3 at Weeks 16, 20, 24, and 28) during the open-label period were then randomized to receive either continued treatment with adalimumab 40 mg eow (N=152) or placebo (N=153) for an additional 40 weeks in a double-blind, placebo-controlled period (total study duration 68 weeks). Subjects who flared during the double-blind period were allowed adalimumab 40 mg eow rescue therapy for at least 12 weeks.

The primary efficacy endpoint was the proportion of patients with no flare by Week 68 of the study. Flare was defined as ASDAS ≥ 2.1 at two consecutive visits four weeks apart. A greater proportion of patients on adalimumab had no disease flare during the double-blind period, when compared with those on placebo (70.4% vs. 47.1%, p<0.001) (Figure 1).

**Figure 1: Kaplan-Meier Curves Summarizing Time to Flare in Study nr-axSpA II**

**Figure 1: Kaplan-Meier Curves Summarizing Time to Flare in Study nr-axSpA II**




Note: P = Placebo (Number at Risk (flared)); A = Adalimumab (Number at Risk (flared)).

Among the 68 patients who flared in the group allocated to treatment withdrawal, 65 completed 12 weeks of rescue therapy with adalimumab, out of which 37 (56.9%) had regained remission (ASDAS < 1.3) after 12 weeks of restarting the open-label treatment.

By Week 68, patients receiving continuous adalimumab treatment showed statistically significant greater improvement of the signs and symptoms of active nr-axSpA as compared to patients allocated to treatment withdrawal during the double-blind period of the study (Table 15).

**Table 15**

**Efficacy Response in Placebo-Controlled Period for Study nr-axSpA II**

| **Double-Blind**<br>**Response at Week 68** | **Placebo**<br>**N=153** | **Adalimumab**<br>**N=152** |
|---|---|---|
| ASAS[a,b] 20 | 47.1% | 70.4%*** |
| ASAS[a,b] 40 | 45.8% | 65.8%*** |
| ASAS[a] Partial Remission | 26.8% | 42.1%** |
| ASDAS[c] Inactive Disease | 33.3% | 57.2%*** |
| Partial Flare[d] | 64.1% | 40.8%*** |

[a] Assessment of SpondyloArthritis international Society

[b] Baseline is defined as open label baseline when patients have active disease.

[c] Ankylosing Spondylitis Disease Activity Score

[d] Partial flare is defined as ASDAS ≥ 1.3 but < 2.1 at 2 consecutive visits.

***, ** Statistically significant at p < 0.001 and < 0.01, respectively, for all comparisons between adalimumab and placebo.

*Psoriatic arthritis*

Adalimumab, 40 mg every other week, was studied in patients with moderately to severely active psoriatic arthritis in two placebo-controlled studies, PsA studies I and II. PsA study I with 24 week duration, treated 313 adult patients who had an inadequate response to non-steroidal anti-inflammatory drug therapy and of these, approximately 50 % were taking methotrexate. PsA study II with 12-week duration, treated 100 patients who had an inadequate response to DMARD

therapy. Upon completion of both studies, 383 patients enrolled in an open-label extension study, in which 40 mg adalimumab was administered every other week.

There is insufficient evidence of the efficacy of adalimumab in patients with ankylosing spondylitis-like psoriatic arthropathy due to the small number of patients studied.

**Table 16**

**ACR Response in Placebo-Controlled Psoriatic Arthritis Studies**

**(Percent of Patients)**

| | **PsA study I** | | **PsA study II** | |
|---|---|---|---|---|
| **Response** | **Placebo N=162** | **Adalimumab N=151** | **Placebo N=49** | **Adalimumab N=51** |
| ACR 20 | | | | |
| Week 12 | 14% | 58%*** | 16% | 39%* |
| Week 24 | 15% | 57%*** | - | - |
| ACR 50 | | | | |
| Week 12 | 4% | 36%*** | 2% | 25%*** |
| Week 24 | 6% | 39%*** | - | - |
| ACR 70 | | | | |
| Week 12 | 1% | 20%*** | 0% | 14%* |
| Week 24 | 1% | 23%*** | - | - |

*** p < 0.001 for all comparisons between adalimumab and placebo

* p < 0.05 for all comparisons between adalimumab and placebo

- Not applicable

ACR responses in PsA study I were similar with and without concomitant methotrexate therapy.

ACR responses were maintained in the open-label extension study for up to 136 weeks.

Radiographic changes were assessed in the psoriatic arthritis studies. Radiographs of hands, wrists, and feet were obtained at baseline and week 24 during the double-blind period when patients were on adalimumab or placebo and at week 48 when all patients were on open-label adalimumab. A modified Total Sharp Score (mTSS), which included distal interphalangeal joints (i.e. not identical to the TSS used for rheumatoid arthritis), was used.

Adalimumab treatment reduced the rate of progression of peripheral joint damage compared with placebo treatment as measured by change from baseline in mTSS (mean ± SD) 0.8 ± 2.5 in the placebo group (at week 24) compared with 0.0 ± 1.9; (p<0.001) in the adalimumab group (at week 48).

In subjects treated with adalimumab with no radiographic progression from baseline to week 48 (n=102), 84% continued to show no radiographic progression through 144 weeks of treatment.

Adalimumab treated patients demonstrated statistically significant improvement in physical function as assessed by HAQ and Short Form Health Survey (SF 36) compared to placebo at week 24. Improved physical function continued during the open label extension up to week 136.

*Psoriasis*

The safety and efficacy of adalimumab were studied in adult patients with chronic plaque psoriasis (≥10% BSA involvement and Psoriasis Area and Severity Index (PASI) ≥12 or ≥10) who were candidates for systemic therapy or phototherapy in randomised, double-blind studies. 73% of patients enrolled in Psoriasis studies I and II had received prior systemic therapy or phototherapy. The safety and efficacy of adalimumab were also studied in adult patients with moderate to severe chronic plaque psoriasis with concomitant hand and/or foot psoriasis who were candidates for systemic therapy in a randomised double-blind study (Psoriasis study III).

Psoriasis study I (REVEAL) evaluated 1,212 patients within three treatment periods. In period A, patients received placebo or adalimumab at an initial dose of 80 mg followed by 40 mg every other week starting one week after the initial dose. After 16 weeks of therapy, patients who achieved at least a PASI 75 response (PASI score improvement of at least 75 % relative to baseline), entered period B and received open-label 40 mg adalimumab every other week. Patients who maintained ≥PASI 75 response at week 33 and were originally randomised to active therapy in Period A, were re-randomised in period C to receive 40 mg adalimumab every other week or placebo for an additional 19 weeks. Across all

treatment groups, the mean baseline PASI score was 18.9 and the baseline Physician's Global Assessment (PGA) score ranged from “moderate” (53 % of subjects included) to “severe” (41 %) to “very severe” (6 %).

Psoriasis study II (CHAMPION) compared the efficacy and safety of adalimumab *versus* methotrexate and placebo in 271 patients. Patients received placebo, an initial dose of MTX 7.5 mg and thereafter dose increases up to week 12, with a maximum dose of 25 mg or an initial dose of 80 mg adalimumab followed by 40 mg every other week (starting one week after the initial dose) for 16 weeks. There are no data available comparing adalimumab and MTX beyond 16 weeks of therapy. Patients receiving MTX who achieved a ≥PASI 50 response at week 8 and/or 12 did not receive further dose increases. Across all treatment groups, the mean baseline PASI score was 19.7 and the baseline PGA score ranged from “mild” (<1%) to “moderate” (48%) to “severe” (46%) to “very severe” (6%).

Patients participating in all Phase 2 and Phase 3 psoriasis studies were eligible to enrol into an open-label extension trial, where adalimumab was given for at least an additional 108 weeks.

In Psoriasis studies I and II, a primary endpoint was the proportion of patients who achieved a PASI 75 response from baseline at week 16 (see Tables 17 and18).

**Table 17**

**Ps Study I (REVEAL) - Efficacy Results at 16 Weeks**

| | **Placebo N=398 n (%)** | **Adalimumab 40 mg eow N=814 n (%)** |
|---|---|---|
| **≥ PASI 75[a]** | 26 (6.5) | 578 (70.9)[b] |
| **PASI 100** | 3 (0.8) | 163 (20.0)[b] |
| **PGA: Clear/minimal** | 17 (4.3) | 506 (62.2)[b] |

[a] Percent of patients achieving PASI 75 response was calculated as centre-adjusted rate

[b] p<0.001, adalimumab vs. placebo

**Table 18**

**Ps Study II (CHAMPION) Efficacy Results at 16 Weeks**

| | **Placebo N=53 n (%)** | **MTX N=110 n (%)** | **Adalimumab 40 mg eow N=108 n (%)** |
|---|---|---|---|
| **≥ PASI 75** | 10 (18.9) | 39 (35.5) | 86 (79.6)[a, b] |
| **PASI 100** | 1 (1.9) | 8 (7.3) | 18 (16.7)[c, d] |
| **PGA: Clear/minimal** | 6 (11.3) | 33 (30.0) | 79 (73.1)[a, b] |

[a] p<0.001 adalimumab vs. placebo

[b] p<0.001 adalimumab vs. methotrexate

[c] p<0.01 adalimumab vs. placebo

[d] p<0.05 adalimumab vs. methotrexate

In Psoriasis study I, 28 % of patients who were PASI 75 responders and were re-randomised to placebo at week 33 compared to 5 % continuing on adalimumab, p<0.001, experienced “loss of adequate response” (PASI score after week 33 and on or before week 52 that resulted in a <PASI 50 response relative to baseline with a minimum of a 6-point increase in PASI score relative to week 33). Of the patients who lost adequate response after re-randomisation to placebo who then enrolled into the open-label extension trial, 38 % (25/66) and 55 % (36/66) regained PASI 75 response after 12 and 24 weeks of re-treatment, respectively.

A total of 233 PASI 75 responders at week 16 and week 33 received continuous adalimumab therapy for 52 weeks in Psoriasis study I, and continued adalimumab in the open-label extension trial. PASI 75 and PGA of clear or minimal response rates in these patients were 74.7 % and 59.0 %, respectively, after an additional 108 weeks of open-label therapy (total of 160 weeks). In an analysis in which all patients who dropped out of the study for adverse events or lack of efficacy, or who dose-escalated, were considered non-responders, PASI 75 and PGA of clear or minimal response

rates in these patients were 69.6 % and 55.7 %, respectively, after an additional 108 weeks of open-label therapy (total of 160 weeks).

A total of 347 stable responders participated in a withdrawal and retreatment evaluation in an open-label extension study. During the withdrawal period, symptoms of psoriasis returned over time with a median time to relapse (decline to PGA “moderate” or worse) of approximately 5 months. None of these patients experienced rebound during the withdrawal period. A total of 76.5% (218/285) of patients who entered the retreatment period had a response of PGA “clear” or “minimal” after 16 weeks of retreatment, irrespective of whether they relapsed during withdrawal (69.1 %[123/178] and 88.8 % [95/107] for patients who relapsed and who did not relapse during the withdrawal period, respectively). A similar safety profile was observed during retreatment as before withdrawal.

Significant improvements at week 16 from baseline compared to placebo (studies I and II) and MTX (study II) were demonstrated in the DLQI (Dermatology Life Quality Index). In study I, improvements in the physical and mental component summary scores of the SF-36 were also significant compared to placebo.

In an open-label extension study, for patients who dose escalated from 40 mg every other week to 40 mg weekly due to a PASI response below 50 %, 26.4 % (92/349) and 37.8 % (132/349) of patients achieved PASI 75 response at week 12 and 24, respectively.

Psoriasis study III (REACH) compared the efficacy and safety of adalimumab *versus* placebo in 72 patients with moderate to severe chronic plaque psoriasis and hand and/or foot psoriasis. Patients received an initial dose of 80 mg adalimumab followed by 40 mg every other week (starting one week after the initial dose) or placebo for 16 weeks. At week 16, a statistically significantly greater proportion of patients who received adalimumab achieved PGA of 'clear' or 'almost clear' for the hands and/or feet compared to patients who received placebo (30.6% *versus* 4.3%, respectively [p = 0.014]).

Psoriasis study IV compared efficacy and safety of adalimumab *versus* placebo in 217 adult patients with moderate to severe nail psoriasis. Patients received an initial dose of 80 mg adalimumab followed by 40 mg every other week (starting one week after the initial dose) or placebo for 26 weeks followed by open-label adalimumab treatment for an additional 26 weeks. Nail psoriasis assessments included the Modified Nail Psoriasis Severity Index (mNAPSI), the Physician's Global Assessment of Fingernail Psoriasis (PGA-F) and the Nail Psoriasis Severity Index (NAPSI) (see Table 19). Adalimumab demonstrated a treatment benefit in nail psoriasis patients with different extents of skin involvement (BSA≥10 % (60 % of patients) and BSA<10 % and ≥5 % (40 % of patients)).

**Table 19**

**Ps Study IV Efficacy Results at 16, 26 and 52 Weeks**

| Endpoint | Week 16 Placebo-Controlled | | Week 26 Placebo-Controlled | | Week 52 Open-label |
|---|---|---|---|---|---|
| | Placebo N=108 | Adalimumab 40 mg eow N=109 | Placebo N=108 | Adalimumab 40 mg eow N=109 | Adalimumab 40 mg eow N=80 |
| **≥ mNAPSI 75 (%)** | 2.9 | 26.0[a] | 3.4 | 46.6[a] | 65.0 |
| **PGA-F clear/minimal and ≥2-grade improvement (%)** | 2.9 | 29.7[a] | 6.9 | 48.9[a] | 61.3 |
| **Percent Change in Total Fingernail NAPSI (%)** | -7.8 | -44.2[a] | -11.5 | -56.2[a] | -72.2 |

[a] p<0.001, adalimumab vs. placebo

Adalimumab treated patients showed statistically significant improvements at week 26 compared with placebo in the DLQI.

*Paediatric plaque psoriasis*

The efficacy of adalimumab was assessed in a randomised, double-blind, controlled study of 114 paediatric patients from 4 years of age with severe chronic plaque psoriasis (as defined by a PGA ≥4 or >20% BSA involvement or >10 % BSA involvement with very thick lesions or PASI ≥20 or ≥10 with clinically relevant facial, genital, or hand/ foot involvement) who were inadequately controlled with topical therapy and heliotherapy or phototherapy.

Patients received adalimumab 0.8 mg/kg eow (up to 40 mg), 0.4 mg/kg eow (up to 20 mg), or methotrexate 0.1 – 0.4 mg/kg weekly (up to 25 mg). At Week 16, more patients randomised to adalimumab 0.8 mg/kg had positive efficacy responses (e.g., PASI 75) than those randomised to 0.4 mg/kg eow or MTX.

**Table 20**

**Paediatric Plaque Psoriasis Efficacy Results at 16 Weeks**

| | MTX[a] | Adalimumab 0.8 mg/kg eow |
|---|---|---|

| | N=37 | N=38 |
|---|---|---|
| **PASI 75[b]** | 12 (32.4%) | 22 (57.9%) |
| **PGA: Clear/minimal[c]** | 15 (40.5%) | 23 (60.5%) |

[a] MTX = methotrexate

[b] P=0.027, adalimumab 0.8 mg/kg *versus* MTX

[c] P=0.083, adalimumab 0.8 mg/kg *versus* MTX

Patients who achieved PASI 75 and PGA clear or minimal were withdrawn from treatment for up to 36 weeks and monitored for loss of disease control (i.e. a worsening of PGA by at least 2 grades). Patients were then re-treated with adalimumab 0.8 mg/kg eow for an additional 16 weeks and response rates observed during retreatment were similar to the previous double-blind period: PASI 75 response of 78.9 % (15 of 19 subjects) and PGA clear or minimal of 52.6 % (10 of 19 subjects).

In the open label period of the study, PASI 75 and PGA clear or minimal responses were maintained for up to an additional 52 weeks with no new safety findings.

*Hidradenitis suppurativa*

The safety and efficacy of adalimumab were assessed in randomised, double-blind, placebo-controlled studies and an open-label extension study in adult patients with moderate to severe hidradenitis suppurativa (HS) who were intolerant, had a contraindication or an inadequate response to at least a 3-month trial of systemic antibiotic therapy. The patients in HS-I and HS-II had Hurley Stage II or III disease with at least 3 abscesses or inflammatory nodules.

Study HS-I (PIONEER I) evaluated 307 patients with 2 treatment periods. In Period A, patients received placebo or adalimumab at an initial dose of 160 mg at week 0, 80 mg at week 2, and 40 mg every week starting at week 4 to week 11. Concomitant antibiotic use was not allowed during the study. After 12 weeks of therapy, patients who had received adalimumab in Period A were re-randomised in Period B to 1 of 3 treatment groups (adalimumab 40 mg every week, adalimumab 40 mg every other week, or placebo from week 12 to week 35). Patients who had been randomised to placebo in Period A were assigned to receive adalimumab 40 mg every week in Period B.

Study HS-II (PIONEER II) evaluated 326 patients with 2 treatment periods. In Period A, patients received placebo or adalimumab at an initial dose of 160 mg at week 0 and 80 mg at week 2 and 40 mg every week starting at week 4 to week 11. 19.3 % of patients had continued baseline oral antibiotic therapy during the study. After 12 weeks of therapy, patients who had received adalimumab in Period A were re-randomised in Period B to 1 of 3 treatment groups (adalimumab 40 mg every week, adalimumab 40 mg every other week, or placebo from week 12 to week 35). Patients who had been randomised to placebo in Period A were assigned to receive placebo in Period B.

Patients participating in studies HS-I and HS-II were eligible to enrol into an open-label extension study in which adalimumab 40 mg was administered every week. Mean exposure in all adalimumab population was 762 days. Throughout all 3 studies patients used topical antiseptic wash daily.

*Clinical Response*

Reduction of inflammatory lesions and prevention of worsening of abscesses and draining fistulas was assessed using Hidradenitis Suppurativa Clinical Response (HiSCR; at least a 50 % reduction in total abscess and inflammatory nodule count with no increase in abscess count and no increase in draining fistula count relative to Baseline). Reduction in HS-related skin pain was assessed using a Numeric Rating Scale in patients who entered the study with an initial baseline score of 3 or greater on a 11 point scale.

At week 12, a significantly higher proportion of patients treated with adalimumab *versus* placebo achieved HiSCR. At week 12, a significantly higher proportion of patients in study HS-II experienced a clinically relevant decrease in HS-related skin pain (see Table 21). Patients treated with adalimumab had significantly reduced risk of disease flare during the initial 12 weeks of treatment.

**Table 21**

**Efficacy Results at 12 Weeks, HS Studies I and II**

| | **HS study I** | | **HS study II** | |
|---|---|---|---|---|
| | **Placebo** | **Adalimumab 40 mg Weekly** | **Placebo** | **Adalimumab 40 mg Weekly** |
| **Hidradenitis Suppurativa Clinical Response (HiSCR)[a]** | N=154<br>40 (26.0%) | N=153<br>64 (41.8%) * | N=163<br>45 (27.6%) | N=163<br>96 (58.9%) *** |
| **≥ 30% Reduction in Skin Pain[b]** | N=109<br>27 (24.8%) | N=122<br>34 (27.9%) | N=111<br>23 (20.7%) | N=105<br>48 (45.7%) *** |

* p<0.05, ***p<0.001, adalimumab *versus* placebo

[a] Among all randomised patients

[b] Among patients with baseline HS-related skin pain assessment ≥ 3, based on Numeric Rating Scale 0 – 10; 0 = no skin pain, 10 = skin pain as bad as you can imagine

Treatment with adalimumab 40 mg every week significantly reduced the risk of worsening of abscesses and draining fistulas. Approximately twice the proportion of patients in the placebo group in the first 12 weeks of studies HS-I and HS-II, compared with those in the adalimumab group experienced worsening of abscesses (23.0 % vs 11.4 %, respectively) and draining fistulas (30.0 % vs 13.9 %, respectively).

Greater improvements at week 12 from baseline compared to placebo were demonstrated in skin specific health-related quality of life, as measured by the Dermatology Life Quality Index (DLQI; studies HS-I and HS-II), patient global satisfaction with medication treatment as measured by the Treatment Satisfaction Questionnaire - medication (TSQM; studies HS-I and HS-II), and physical health as measured by the physical component summary score of the SF-36 (study HS-I).

In patients with at least a partial response to adalimumab 40 mg weekly at week 12, the HiSCR rate at week 36 was higher in patients who continued weekly adalimumab than in patients in whom dosing frequency was reduced to every other week, or in whom treatment was withdrawn (see Table 22).

**Table 22**

**Proportion of Patients[a] Achieving HiSCR[b] at Weeks 24 and 36 After Treatment Reassignment from Weekly Adalimumab at Week 12**

| | Placebo (treatment withdrawal) N = 73 | Adalimumab 40 mg every other week N = 70 | Adalimumab 40 mg weekly N = 70 |
|---|---|---|---|
| **Week 24** | 24 (32.9%) | 36 (51.4%) | 40 (57.1%) |
| **Week 36** | 22 (30.1%) | 28 (40.0%) | 39 (55.7%) |

[a] Patients with at least a partial response to adalimumab 40 mg weekly after 12 weeks of treatment

[b] Patients meeting protocol-specified criteria for loss of response or no improvement were required to discontinue from the studies and were counted as nonresponders

Among patients who were at least partial responders at week 12, and who received continuous

weekly adalimumab therapy, the HiSCR rate at week 48 was 68.3% and at Week 96 was 65.1%. Longer term treatment with adalimumab 40 mg weekly for 96 weeks identified no new safety findings.

Among patients whose adalimumab treatment was withdrawn at week 12 in studies HS-I and HS-II, the HiSCR rate 12 weeks after re-introduction of adalimumab 40 mg weekly returned to levels similar to that observed before withdrawal (56.0 %).

*Adolescent hidradenitis suppurativa*

There are no clinical trials with adalimumab in adolescent patients with HS. Efficacy of adalimumab for the treatment of adolescent patients with HS is predicted based on the demonstrated efficacy and exposure-response relationship in adult HS patients and the likelihood that the disease course, pathophysiology, and drug effects are substantially similar to that of adults at the same exposure levels. Safety of the recommended adalimumab dose in the adolescent HS population is based on cross-indication safety profile of adalimumab in both adults and paediatric patients at similar or more frequent doses (see section 5.2).

*Crohn's disease*

The safety and efficacy of adalimumab were assessed in over 1,500 patients with moderately to severely active Crohn's disease (Crohn's Disease Activity Index (CDAI) ≥220 and ≤450) in randomised, double-blind, placebo-controlled studies. Concomitant stable doses of aminosalicylates, corticosteroids, and/or immunomodulatory agents were permitted and 80 % of patients continued to receive at least one of these medications.

Induction of clinical remission (defined as CDAI <150) was evaluated in two studies, CD study I (CLASSIC I) and CD study II (GAIN). In CD study I, 299 TNF-antagonist naive patients were randomised to one of four treatment groups; placebo at weeks 0 and 2, 160 mg adalimumab at week 0 and 80 mg at week 2, 80 mg at week 0 and 40 mg at week 2, and 40 mg at week 0 and 20 mg at week 2. In CD study II, 325 patients who had lost response or were intolerant to infliximab were randomised to receive either 160 mg adalimumab at week 0 and 80 mg at week 2 or placebo at weeks 0 and 2. The primary non-responders were excluded from the studies and therefore these patients were not further evaluated.

Maintenance of clinical remission was evaluated in CD study III (CHARM). In CD study III, 854 patients received open-label 80 mg at week 0 and 40 mg at week 2. At week 4 patients were randomised to 40 mg every other week, 40 mg every week, or placebo with a total study duration of 56 weeks. Patients in clinical response (decrease in CDAI ≥70) at

week 4 were stratified and analysed separately from those not in clinical response at week 4. Corticosteroid taper was permitted after week 8.

CD study I and CD study II induction of remission and response rates are presented in Table 23.

**Table 23**

**Induction of Clinical Remission and Response**

**(Percent of Patients)**

| | **CD study I: Infliximab Naive Patients** | | | **CD study II: Infliximab Experienced Patients** | |
|---|---|---|---|---|---|
| | **Placebo N=74** | **Adalimumab 80/40 mg N=75** | **Adalimumab 160/80 mg N=76** | **Placebo N=166** | **Adalimumab 160/80 mg N=159** |
| **Week 4** | | | | | |
| **Clinical remission** | 12% | 24% | 36%* | 7% | 21%* |
| **Clinical response (CR-100)** | 24% | 37% | 49%** | 25% | 38%** |
| All p-values are pairwise comparisons of proportions for adalimumab *versus* placebo<br>* p <0.001<br>** p <0.01 | | | | | |

Similar remission rates were observed for the 160/80 mg and 80/40 mg induction regimens by week 8 and adverse events were more frequently noted in the 160/80 mg group.

In CD study III, at week 4, 58 % (499/854) of patients were in clinical response and were assessed in the primary analysis. Of those in clinical response at week 4, 48 % had been previously exposed to other TNF-antagonists. Maintenance of remission and response rates are presented in Table 24. Clinical remission results remained relatively constant irrespective of previous TNF-antagonist exposure.

Disease-related hospitalisations and surgeries were statistically significantly reduced with adalimumab compared with placebo at week 56.

**Table 24**

**Maintenance of Clinical Remission and Response**

**(Percent of Patients)**

| | **Placebo** | **40 mg Adalimumab every other week** | **40 mg Adalimumab every week** |
|---|---|---|---|
| **Week 26** | **N=170** | **N=172** | **N=157** |
| Clinical remission | 17 % | 40 %* | 47 %* |
| Clinical response (CR-100) | 27 % | 52 %* | 52 %* |
| Patients in steroid-free remission for >=90 days[a] | 3 % (2/66) | 19% (11/58)** | 15% (11/74)** |
| **Week 56** | **N=170** | **N=172** | **N=157** |
| Clinical remission | 12 % | 36 %* | 41 %* |
| Clinical response (CR-100) | 17 % | 41 %* | 48 %* |
| Patients in steroid-free remission for >=90 days[a] | 5 % (3/66) | 29 % (17/58)* | 20 % (15/74)** |
| * p <0.001 for adalimumab *versus* placebo pairwise comparisons of proportions<br>** p <0.02 for adalimumab *versus* placebo pairwise comparisons of proportions<br>[a] Of those receiving corticosteroids at baseline | | | |

Among patients who were not in response at week 4, 43 % of adalimumab maintenance patients responded by week 12 compared to 30 % of placebo maintenance patients. These results suggest that some patients who have not responded by week 4 benefit from continued maintenance therapy through week 12. Therapy continued beyond 12 weeks did not result in significantly more responses (see section 4.2).

117/276 patients from CD study I and 272/777 patients from CD studies II and III were followed through at least 3 years of open-label adalimumab therapy. 88 and 189 patients, respectively, continued to be in clinical remission. Clinical response (CR-100) was maintained in 102 and 233 patients, respectively.

*Quality of life*

In CD study I and CD study II, statistically significant improvement in the disease-specific inflammatory bowel disease questionnaire (IBDQ) total score was achieved at week 4 in patients randomised to adalimumab 80/40 mg and 160/80 mg compared to placebo and was seen at weeks 26 and 56 in CD study III as well among the adalimumab treatment groups compared to the placebo group.

*Paediatric Crohn's disease*

Adalimumab was assessed in a multicentre, randomised, double-blind clinical trial designed to evaluate the efficacy and safety of induction and maintenance treatment with doses dependent on body weight (<40 kg or ≥40 kg) in 192 paediatric subjects between the ages of 6 and 17 (inclusive) years, with moderate to severe Crohn´s disease (CD) defined as Paediatric Crohn's Disease Activity Index (PCDAI) score >30. Subjects had to have failed conventional therapy (including a corticosteroid and/or an immunomodulator) for CD. Subjects may also have previously lost response or been intolerant to infliximab.

All subjects received open-label induction therapy at a dose based on their Baseline body weight: 160 mg at week 0 and 80 mg at week 2 for subjects ≥40 kg, and 80 mg and 40 mg, respectively, for subjects <40 kg.

At week 4, subjects were randomised 1:1 based on their body weight at the time to either the Low Dose or Standard Dose maintenance regimens as shown in Table 25.

**Table 25**

**Maintenance regimen**

| Patient Weight | Low dose | Standard dose |
|---|---|---|
| <40 kg | 10 mg eow | 20 mg eow |
| ≥40 kg | 20 mg eow | 40 mg eow |

*Efficacy results*

The primary endpoint of the study was clinical remission at week 26, defined as PCDAI score ≤10.

Clinical remission and clinical response (defined as reduction in PCDAI score of at least 15 points from Baseline) rates are presented in Table 26. Rates of discontinuation of corticosteroids or immunomodulators are presented in Table 27.

**Table 26**

**Paediatric CD Study**

**PCDAI Clinical Remission and Response**

| | **Standard Dose 40/20 mg eow N=93** | **Low Dose 20/10 mg eow N=95** | **P value*** |
|---|---|---|---|
| **Week 26** | | | |
| Clinical remission | 38.7 % | 28.4 % | 0.075 |
| Clinical response | 59.1 % | 48.4 % | 0.073 |
| **Week 52** | | | |
| Clinical remission | 33.3 % | 23.2 % | 0.100 |
| Clinical response | 41.9 % | 28.4 % | 0.038 |

* p value for Standard Dose *versus* Low Dose comparison

**Table 27**

**Paediatric CD Study**

**Discontinuation of Corticosteroids or Immunomodulators and Fistula Remission**

| | Standard Dose 40/20 mg eow | Low Dose 20/10 mg eow | P value[1] |
|---|---|---|---|
| **Discontinued corticosteroids** | **N=33** | **N=38** | |
| Week 26 | 84.8 % | 65.8 % | 0.066 |
| Week 52 | 69.7 % | 60.5 % | 0.420 |
| **Discontinuation of Immunomodulators[2]** | **N=60** | **N=57** | |
| Week 52 | 30.0 % | 29.8 % | 0.983 |
| **Fistula remission[3]** | **N=15** | **N=21** | |
| Week 26 | 46.7 % | 38.1 % | 0.608 |
| Week 52 | 40.0 % | 23.8 % | 0.303 |

[1] p value for Standard Dose *versus* Low Dose comparison

[2] Immunosuppressant therapy could only be discontinued at or after week 26 at the investigator's discretion if the subject met the clinical response criterion

[3] Defined as a closure of all fistulas that were draining at Baseline for at least 2 consecutive post-Baseline visits

Statistically significant increases (improvement) from Baseline to week 26 and 52 in Body Mass Index and height velocity were observed for both treatment groups.

Statistically and clinically significant improvements from Baseline were also observed in both treatment groups for quality of life parameters (including IMPACT III).

One hundred patients (n=100) from the Paediatric CD study continued in an open-label long-term extension study. After 5 years of adalimumab therapy, 74.0 % (37/50) of the 50 patients remaining in the study continued to be in clinical remission, and 92.0 % (46/50) of patients continued to be in clinical response per PCDAI.

*Ulcerative Colitis*

The safety and efficacy of multiple doses of adalimumab were assessed in adult patients with moderately to severely active ulcerative colitis (Mayo score 6 to 12 with endoscopy subscore of 2 to 3) in randomised, double-blind, placebo-controlled studies.

In study UC-I, 390 TNF-antagonist naïve patients were randomised to receive either placebo at weeks 0 and 2, 160 mg adalimumab at week 0 followed by 80 mg at week 2, or 80 mg adalimumab at week 0 followed by 40 mg at week 2. After week 2, patients in both adalimumab arms received 40 mg eow. Clinical remission (defined as Mayo score ≤2 with no subscore >1) was assessed at week 8.

In study UC-II, 248 patients received 160 mg of adalimumab at week 0, 80 mg at week 2 and 40 mg eow thereafter, and 246 patients received placebo. Clinical results were assessed for induction of remission at week 8 and for maintenance of remission at week 52.

Patients induced with 160/80 mg adalimumab achieved clinical remission *versus* placebo at week 8 in statistically significantly greater percentages in study UC-I (18 % vs. 9 % respectively, p=0.031) and study UC-II (17 % vs. 9 % respectively, p=0.019). In study UC-II, among those treated with adalimumab who were in remission at week 8, 21/41 (51 %) were in remission at week 52.

Results from the overall UC-II study population are shown in Table 28.

**Table 28**

**Response, Remission and Mucosal Healing in Study UC-II**

**(Percent of Patients)**

| | Placebo | Adalimumab 40 mg eow |
|---|---|---|
| **Week 52** | **N=246** | **N=248** |
| Clinical Response | 18 % | 30 %* |
| Clinical Remission | 9 % | 17 %* |

| | | |
|---|---|---|
| Mucosal Healing | 15 % | 25 %* |
| Steroid-free remission for ≥ 90 days[a] | 6 %<br>(N=140) | 13 %*<br>(N=150) |
| **Week 8 and 52** | | |
| Sustained Response | 12 % | 24 %** |
| Sustained Remission | 4 % | 8 %* |
| Sustained Mucosal Healing | 11 % | 19 %* |

Clinical remission is Mayo score ≤2 with no subscore >1;

Clinical response is decrease from baseline in Mayo score ≥3 points and ≥30% plus a decrease in the rectal bleeding subscore [RBS] ≥1 or an absolute RBS of 0 or 1;

* p<0.05 for adalimumab vs. placebo pairwise comparison of proportions

** p<0.001 for adalimumab vs. placebo pairwise comparison of proportions

[a] Of those receiving corticosteroids at baseline

Of those patients who had a response at week 8, 47 % were in response, 29 % were in remission, 41 % had mucosal healing, and 20 % were in steroid-free remission for ≥90 days at week 52.

Approximately 40% of patients in study UC-II had failed prior anti-TNF treatment with infliximab. The efficacy of adalimumab in those patients was reduced compared to that in anti-TNF naïve patients. Among patients who had failed prior anti-TNF treatment, week 52 remission was achieved by 3 % on placebo and 10 % on adalimumab.

Patients from studies UC-I and UC-II had the option to roll over into an open-label long-term extension study (UC III). Following 3 years of adalimumab therapy, 75 % (301/402) continued to be in clinical remission per partial Mayo score.

*Hospitalisation rates*

During 52 weeks of studies UC-I and UC-II, lower rates of all-cause hospitalisations and UC-related hospitalisations were observed for the adalimumab-treated arm compared to the placebo arm. The number of all cause hospitalisations in the adalimumab treatment group was 0.18 per patient year *vs*. 0.26 per patient year in the placebo group and the corresponding figures for UC-related hospitalisations were 0.12 per patient year *vs.* 0.22 per patient year.

*Quality of life*

In study UC-II, treatment with adalimumab resulted in improvements in the Inflammatory Bowel Disease Questionnaire (IBDQ) score.

*Uveitis*

The safety and efficacy of adalimumab were assessed in adult patients with non-infectious intermediate, posterior, and panuveitis, excluding patients with isolated anterior uveitis, in two randomised, double- masked, placebo-controlled studies (UV I and II). Patients received placebo or adalimumab at an initial dose of 80 mg followed by 40 mg every other week starting one week after the initial dose. Concomitant stable doses of one non-biologic immunosuppressant were permitted.

Study UV I evaluated 217 patients with active uveitis despite treatment with corticosteroids (oral prednisone at a dose of 10 to 60 mg/day). All patients received a 2-week standardised dose of prednisone 60 mg/day at study entry followed by a mandatory taper schedule, with complete corticosteroid discontinuation by week 15.

Study UV II evaluated 226 patients with inactive uveitis requiring chronic corticosteroid treatment (oral prednisone 10 to 35 mg/day) at baseline to control their disease. Patients subsequently underwent a mandatory taper schedule, with complete corticosteroid discontinuation by week 19.

The primary efficacy endpoint in both studies was ´time to treatment failure´. Treatment failure was defined by a multi-component outcome based on inflammatory chorioretinal and/or inflammatory retinal vascular lesions, anterior chamber (AC) cell grade, vitreous haze (VH) grade and best corrected visual acuity (BCVA).

*Clinical Response*

Results from both studies demonstrated statistically significant reduction of the risk of treatment failure in patients treated with adalimumab *versus* patients receiving placebo (See Table 29). Both studies demonstrated an early and sustained effect of adalimumab on the treatment failure rate *versus* placebo (see Figure 2).

**Table 29**

**Time to Treatment Failure in Studies UV I and UV II**

| Analysis Treatment | N | Failure N (%) | Median Time to Failure (months) | HR[a] | CI 95% for HR | *P* Value[b] |
|---|---|---|---|---|---|---|

| | | | | | | |
|---|---|---|---|---|---|---|
| **Time to Treatment Failure At or After Week 6 in study UV I**<br>Primary analysis (ITT) | | | | | | |
| Placebo | 107 | 84 (78.5) | 3.0 | - | - | - |
| Adalimumab | 110 | 60 (54.5) | 5.6 | 0.50 | 0.36,0.70 | <0.001 |
| **Time to Treatment Failure At or After Week 2 in study UV II**<br>Primary analysis (ITT) | | | | | | |
| Placebo | 111 | 61 (55.0) | 8.3 | - | - | - |
| Adalimumab | 115 | 45 (39.1) | NE[c] | 0.57 | 0.39,0.84 | 0.004 |

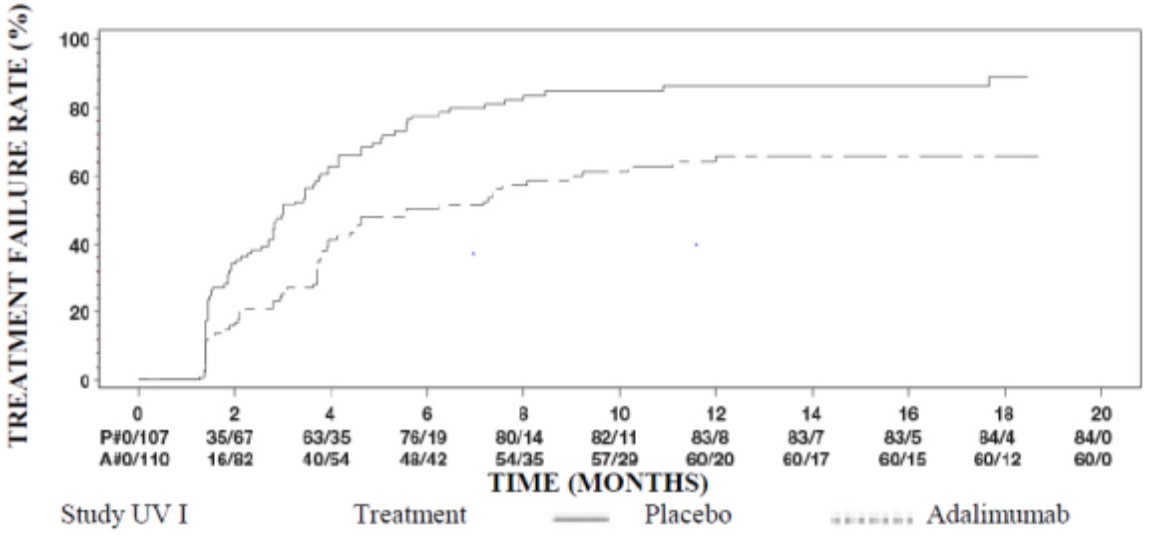
Note: Treatment failure at or after week 6 (study UV I), or at or after week 2 (study UV II), was counted as event. Drop outs due to reasons other than treatment failure were censored at the time of dropping out.

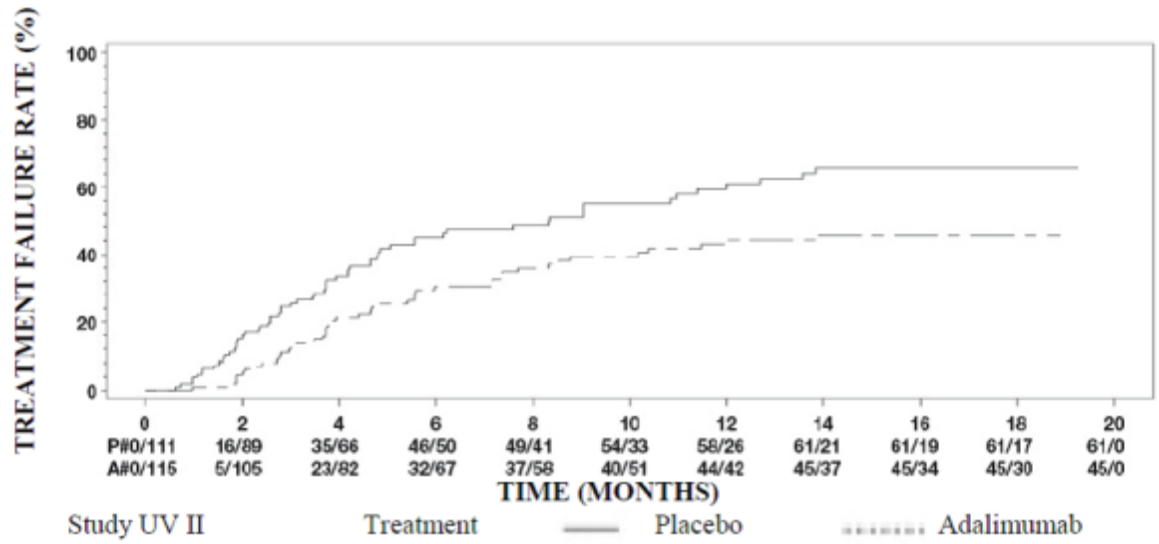
[a] HR of adalimumab vs placebo from proportional hazards regression with treatment as factor

[b] 2-sided *P* value from log rank test

[c] NE = not estimable. Fewer than half of at-risk subjects had an event

**Figure 2: Kaplan-Meier Curves Summarizing Time to Treatment Failure on or after Week 6 (Study UV I) or Week 2 (Study UV II)**




Note: P# = Placebo (Number of Events/Number at Risk); A# = Adalimumab (Number of Events/Number at Risk).

In study UV I statistically significant differences in favour of adalimumab *versus* placebo were observed for each component of treatment failure. In study UV II, statistically significant differences were observed for visual acuity only, but the other components were numerically in favour of adalimumab.

Of the 417 subjects included in the uncontrolled long-term extension of studies UV I and UV II, 46 subjects were regarded ineligible (e.g. developed complications secondary to diabetic retinopathy, due to cataract surgery or vitrectomy) and were excluded from the primary analysis of efficacy. Of the 371 remaining patients, 276 evaluable patients reached 78 weeks of open-label adalimumab treatment. Based on the observed data approach, 222 (80.4 %) were in quiescence (no active inflammatory lesions, AC cell grade ≤ 0.5+, VH grade ≤ 0.5+) with a concomitant steroid dose ≤ 7.5 mg per day, and 184 (66.7 %) were in steroid-free quiescence. BCVA was either improved or maintained (< 5 letters deterioration) in 88.4 % of the eyes at week 78. Among the patients who discontinued the study prior to week 78, 11% discontinued due to adverse events, and 5 % due to insufficient response to adalimumab treatment.

*Quality of Life*

Patient reported outcomes regarding vision-related functioning were measured in both clinical studies, using the NEI VFQ-25. Adalimumab was numerically favoured for the majority of subscores with statistically significant mean differences for general vision, ocular pain, near vision, mental health, and total score in study UV I, and for general vision and mental health in study UV II. Vision related effects were not numerically in favour of adalimumab for colour vision in study UVI and for colour vision, peripheral vision and near vision in study UV II.

*Paediatric Uveitis*

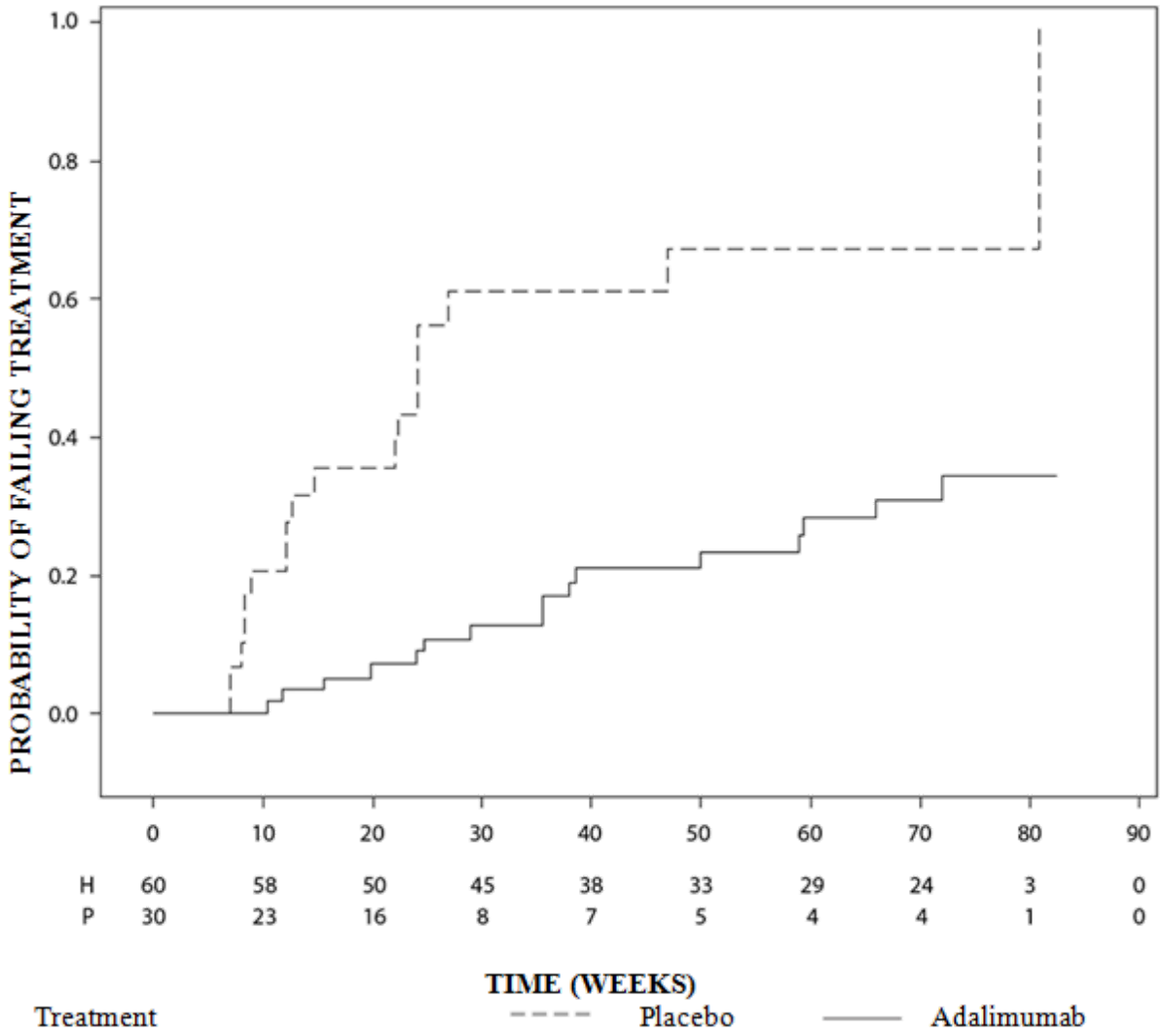
The safety and efficacy of adalimumab was assessed in a randomized, double-masked, controlled study of 90 paediatric patients from 2 to < 18 years of age with active JIA-associated noninfectious anterior uveitis who were refractory to at least 12 weeks of methotrexate treatment. Patients received either placebo or 20 mg adalimumab (if < 30 kg) or 40 mg adalimumab (if ≥ 30 kg) every other week in combination with their baseline dose of methotrexate.

The primary endpoint was 'time to treatment failure'. The criteria determining treatment failure were worsening or sustained non-improvement in ocular inflammation, partial improvement with development of sustained ocular co-morbidities or worsening of ocular co-morbidities, non-permitted use of concomitant medications, and suspension of treatment for an extended period of time.

*Clinical Response*

Adalimumab significantly delayed the time to treatment failure, as compared to placebo (See Figure 3, P < 0.0001 from log rank test). The median time to treatment failure was 24.1 weeks for subjects treated with placebo, whereas the median time to treatment failure was not estimable for subjects treated with adalimumab because less than one-half of these subjects experienced treatment failure. Adalimumab significantly decreased the risk of treatment failure by 75 % relative to placebo, as shown by the hazard ratio (HR = 0.25 [95 % CI: 0.12, 0.49]).

**Figure 3: Kaplan-Meier Curves Summarizing Time to Treatment Failure in the Paediatric Uveitis Study**




Note: P = Placebo (Number at Risk); H = Adalimumab (Number at Risk).

Immunogenicity

Anti-adalimumab antibodies may develop during adalimumab treatment. Formation of anti-adalimumab antibodies is associated with increased clearance and reduced efficacy of adalimumab. There is no apparent correlation between the presence of anti-adalimumab antibodies and the occurrence of adverse events.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of the studies with the reference medicinal product containing adalimumab in one or more subsets of the paediatric population in ulcerative colitis, see section 4.2 for information on paediatric use.

**5.2 Pharmacokinetic properties**

Absorption and distribution

After subcutaneous administration of a single 40 mg dose, absorption and distribution of adalimumab was slow, with peak serum concentrations being reached about 5 days after administration. The average absolute bioavailability of adalimumab estimated from three studies following a single 40 mg subcutaneous dose was 64 %. After single intravenous doses ranging from 0.25 to 10 mg/kg, concentrations were dose proportional. After doses of 0.5 mg/kg (~40 mg), clearances ranged from 11 to 15 ml/hour, the distribution volume (Vss) ranged from 5 to 6 litres and the mean terminal phase half-life was approximately two weeks. Adalimumab concentrations in the synovial fluid from several rheumatoid arthritis patients ranged from 31-96 % of those in serum.

Following subcutaneous administration of 40 mg of adalimumab every other week in adult rheumatoid arthritis (RA) patients the mean steady-state trough concentrations were approximately 5 µg/ml (without concomitant methotrexate) and 8 to 9 µg/ml (with concomitant methotrexate), respectively. The serum adalimumab trough levels at steady-state increased roughly proportionally with dose following 20, 40 and 80 mg subcutaneous dosing every other week and every week.

Following the administration of 24 mg/m$^2$ (up to a maximum of 40 mg) subcutaneously every other week to patients with polyarticular juvenile idiopathic arthritis (JIA) who were 4 to 17 years the mean trough steady-state (values measured from week 20 to 48) serum adalimumab concentration was 5.6 ± 5.6 µg/ml (102 % CV) for adalimumab without concomitant methotrexate and 10.9 ± 5.2 µg/ml (47.7 % CV) with concomitant methotrexate.

In patients with polyarticular JIA who were 2 to <4 years old or aged 4 and above weighing <15 kg dosed with adalimumab 24 mg/$m^2$ , the mean trough steady-state serum adalimumab concentrations was 6.0 ± 6.1 µg/ml (101% CV) for adalimumab without concomitant methotrexate and 7.9 ± 5.6 µg/ml (71.2% CV) with concomitant methotrexate.

Following the administration of 24 mg/$m^2$ (up to a maximum of 40 mg) subcutaneously every other week to patients with enthesitis-related arthritis who were 6 to 17 years, the mean trough steady-state (values measured at week 24) serum adalimumab concentrations were 8.8 ± 6.6 µg/ml for adalimumab without concomitant methotrexate and 11.8 ± 4.3 µg/ml with concomitant methotrexate.

Following subcutaneous administration of 40 mg of adalimumab every other week in adult non-radiographic axial spondyloarthritis patients, the mean (±SD) trough steady-state concentration at Week 68 was 8.0 ± 4.6 µg/ml.

In adult patients with psoriasis, the mean steady-state trough concentration was 5 µg/ml during adalimumab 40 mg every other week monotherapy treatment.

Following the administration of 0.8 mg/kg (up to a maximum of 40 mg) subcutaneously every other week to paediatric patients with chronic plaque psoriasis, the mean ± SD steady-state adalimumab trough concentration was approximately 7.4 ± 5.8 µg/ml (79% CV).

In adult patients with hidradenitis suppurativa, a dose of 160 mg adalimumab on week 0 followed by 80 mg on week 2 achieved serum adalimumab trough concentrations of approximately 7 to 8 µg/ml at week 2 and week 4. The mean steady-state trough concentration at week 12 through week 36 were approximately 8 to 10 µg/ml during adalimumab 40 mg every week treatment.

Adalimumab exposure in adolescent HS patients was predicted using population pharmacokinetic modelling and simulation based on cross-indication pharmacokinetics in other paediatric patients (paediatric psoriasis, juvenile idiopathic arthritis, paediatric Crohn's disease, and enthesitis-related arthritis). The recommended adolescent HS dosing schedule is 40 mg every other week. Since exposure to adalimumab can be affected by body size, adolescents with higher body weight and inadequate response may benefit from receiving the recommended adult dose of 40 mg every week.

In patients with Crohn's disease, the loading dose of 80 mg adalimumab on week 0 followed by 40 mg adalimumab on week 2 achieves serum adalimumab trough concentrations of approximately 5.5 µg/ml during the induction period. A loading dose of 160 mg adalimumab on week 0 followed by 80 mg adalimumab on week 2 achieves serum adalimumab trough concentrations of approximately 12 µg/ml during the induction period. Mean steady-state trough levels of approximately 7 µg/ml were observed in Crohn's disease patients who received a maintenance dose of 40 mg adalimumab every other week.

In paediatric patients with moderate to severe CD, the open-label adalimumab induction dose was 160/80 mg or 80/40 mg at weeks 0 and 2, respectively, dependent on a body weight cut-off of 40 kg. At week 4, patients were randomised 1:1 to either the Standard Dose (40/20 mg eow) or Low Dose (20/10 mg eow) maintenance treatment groups based on their body weight. The mean (±SD) serum adalimumab trough concentrations achieved at week 4 were 15.7±6.6 µg/ml for patients ≥40 kg (160/80 mg) and 10.6±6.1 µg/ml for patients <40 kg (80/40 mg).

For patients who stayed on their randomised therapy, the mean (±SD) adalimumab trough concentrations at week 52 were 9.5±5.6 µg/ml for the Standard Dose group and 3.5±2.2 µg/ml for the Low Dose group. The mean trough concentrations were maintained in patients who continued to receive adalimumab treatment eow for 52 weeks. For patients who dose escalated from eow to weekly regimen, the mean (±SD) serum concentrations of adalimumab at week 52 were 15.3±11.4 µg/ml (40/20 mg, weekly) and 6.7±3.5 µg/ml (20/10 mg, weekly).

In patients with ulcerative colitis, a loading dose of 160 mg adalimumab on week 0 followed by 80 mg adalimumab on week 2 achieves serum adalimumab trough concentrations of approximately 12 µg/ml during the induction period. Mean steady-state trough levels of approximately 8 µg/ml were observed in ulcerative colitis patients who received a maintenance dose of 40 mg adalimumab every other week.

In adult patients with uveitis, a loading dose of 80 mg adalimumab on week 0 followed by 40 mg adalimumab every other week starting at week 1, resulted in mean steady-state concentrations of approximately 8 to 10 µg/mL.

Adalimumab exposure in paediatric uveitis patients was predicted using population pharmacokinetic modelling and simulation based on cross-indication pharmacokinetics in other paediatric patients (paediatric psoriasis, juvenile idiopathic arthritis, paediatric Crohn's disease, and enthesitis-related arthritis). No clinical exposure data are available on the use of a loading dose in children < 6 years. The predicted exposures indicate that in the absence of methotrexate, a loading dose may lead to an initial increase in systemic exposure.

Population pharmacokinetic and pharmacokinetic/pharmacodynamic modelling and simulation predicted comparable adalimumab exposure and efficacy in patients treated with 80 mg every other week when compared with 40 mg every week (including adult patients with RA, HS, UC, CD or Ps, patients with adolescent HS, and paediatric patients ≥ 40 kg with CD).

Exposure-response relationship in paediatric population

On the basis of clinical trial data in patients with JIA (pJIA and ERA), an exposure-response relationship was established between plasma concentrations and PedACR 50 response. The apparent adalimumab plasma concentration that produces half the maximum probability of PedACR 50 response (EC50) was 3 µg/ml (95% CI: 1-6 µg/ml).

Exposure-response relationships between adalimumab concentration and efficacy in paediatric patients with severe chronic plaque psoriasis were established for PASI 75 and PGA clear or minimal, respectively. PASI 75 and PGA clear or minimal increased with increasing adalimumab concentrations, both with a similar apparent EC50 of approximately 4.5 µg/mL (95% CI 0.4-47.6 and 1.9-10.5, respectively).

Elimination

Population pharmacokinetic analyses with data from over 1,300 RA patients revealed a trend toward higher apparent clearance of adalimumab with increasing body weight. After adjustment for weight differences, gender and age appeared to have a minimal effect on adalimumab clearance. The serum levels of free adalimumab (not bound to anti-adalimumab antibodies, AAA) were observed to be lower in patients with measurable AAA.

Hepatic or renal impairment

Adalimumab has not been studied in patients with hepatic or renal impairment.

### 5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on studies of single dose toxicity, repeated dose toxicity, and genotoxicity.

An embryo-foetal developmental toxicity/perinatal developmental study has been performed in cynomolgus monkeys at 0, 30 and 100 mg/kg (9-17 monkeys/group) and has revealed no evidence of harm to the foetuses due to adalimumab. Neither carcinogenicity studies, nor a standard assessment of fertility and postnatal toxicity, were performed with adalimumab due to the lack of appropriate models for an antibody with limited cross-reactivity to rodent TNF and to the development of neutralising antibodies in rodents.

## 6. Pharmaceutical particulars

### 6.1 List of excipients

Sodium citrate

Citric acid monohydrate

Histidine

Histidine hydrochloride monohydrate

Sorbitol

Polysorbate 20

Water for injections

### 6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

### 6.3 Shelf life

3 years

### 6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C). Do not freeze. Keep the pre-filled syringe or pre-filled pen in outer carton in order to protect from light.

A single Imraldi pre-filled syringe or pre-filled pen may be stored at temperatures up to a maximum of 25°C for a period of up to 28 days. The syringe or pen must be protected from light, and discarded if not used within the 28-day period.

### 6.5 Nature and contents of container

Imraldi 40 mg solution for injection in pre-filled syringe

0.8 ml solution for injection in single-use pre-filled syringe (type I glass) with a stainless steel needle, a rigid needle shield, a rubber plunger (bromobutyl), a plunger rod, a safe-shield body and a finger flange for patient use.

Packs of:

• 1 pre-filled syringe, with 2 alcohol pads

• 2 pre-filled syringes, each with 1 alcohol pad

• 4 pre-filled syringes, each with 1 alcohol pad

• 6 pre-filled syringes, each with 1 alcohol pad

Imraldi 40 mg solution for injection in pre-filled pen

0.8 ml solution for injection in single-use pre-filled pen for patient use containing a pre-filled syringe. The syringe inside the pen is made from type I glass with a stainless steel needle, a rigid needle shield, a rubber plunger (bromobutyl).

Packs of:

• 1 pre-filled pen, with 2 alcohol pads

• 2 pre-filled pens, each with 1 alcohol pad

• 4 pre-filled pens, each with 1 alcohol pad

• 6 pre-filled pens, each with 1 alcohol pad

Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

## 7. Marketing authorisation holder

Samsung Bioepis NL B.V.

Olof Palmestraat 10

2616 LR Delft

The Netherlands

## 8. Marketing authorisation number(s)

Imraldi 40 mg solution for injection in pre-filled syringe

EU/1/17/1216/001

EU/1/17/1216/002

EU/1/17/1216/003

EU/1/17/1216/004

Imraldi 40 mg solution for injection in pre-filled pen

EU/1/17/1216/005

EU/1/17/1216/006

EU/1/17/1216/007

EU/1/17/1216/008

## 9. Date of first authorisation/renewal of the authorisation

Date of first authorisation: 24 August 2017

## 10. Date of revision of the text

**08/2019**

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

## Company Contact Details

Biogen Biosimilars

**Address**

Innovation House, 70 Norden Road, Maidenhead, Berkshire, SL6 4AY

**Telephone**

+44 (0) 203 608 8622

**Medical Information e-mail**

Medinfo_biogen@quintiles.com

**WWW**

https://www.biogen.uk.com

**Medical Information Direct Line**

+44 (0) 203 608 8622