1.0 Title Page

CLINICAL STUDY PROTOCOL M11-327 – VISUAL III

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

Incorporating Global Amendments 1, 2, 3, 4, 5, 6 and 7, Administrative Changes 1 and 2, Global Amendments 8 and 9, Administrative Changes 3, 4, 5, 6, 7 and 8, and Global Amendment 10

AbbVie Investigational Product:	Adalimumab
Date:	04 June 2015
Development Phase:	3
Study Design:	An open-label multicenter study designed to evaluate the long-term safety and efficacy of adalimumab in adult subjects with non-infectious intermediate-, posterior-, or pan-uveitis.
EudraCT Number:	2009-016196-29
Investigators:	Investigator information is on file at AbbVie.
Sponsor:	**Non-European Countries:** AbbVie Bldg. AP4-2 1 North Waukegan Road North Chicago, IL 60064, USA **Japan:** AbbVie GK 3-5-27, Mita, Minato-ku Tokyo, 108-6302, Japan **European Countries:** AbbVie Deutschland GmbH &Co KG Knollstrasse 50 67061 Ludwigshafen Germany

Sponsor/Emergency Contact:

US, Canada, Latin America:

Europe, Israel, and Australia:

Japan:

The specific contact details of the AbbVie legal/regulatory entity (person) within the relevant country are provided within the clinical trial agreement with the Investigator/Institution and in the Clinical Trial Application with the Competent Authority.

This study will be conducted in compliance with the protocol, Good Clinical Practice and all other applicable regulatory requirements, including the archiving of essential documents.

1.1 Protocol Amendment: Summary of Changes

The purpose of this amendment is to:

- Change the Sponsor/Emergency Contact to [redacted] Associate Medical Director for the United States (US), Canada and Latin America in Section 1.0, Title Page and Section 6.1.5, Adverse Event Reporting.

  Rationale: To inform the clinical sites of the change in contact for US, Canadian and Latin American subject safety concerns.
- Change the Sponsor/Emergency Contact information for Dr. [redacted] in Section 1.0, Title Page, and Section 6.1.5, Adverse Event Reporting **(new mobile phone number)**.

  Rationale: To inform the sites of the change in contact information for subject safety concerns.
- Update Study End date from March 2016 to March 2018 in Section 1.2, Synopsis, Section 5.1, Overall Study Design and Plan: Description, Section 5.4.1, Discontinuation of Individual Subjects.

  Rationale: To allow for extension of treatment for subjects that will complete the study prior to indication approval.
- Table 1, Study Activities, Section 5.3.1.1, Study Procedures.

  Description: Add visits every 12 weeks following Week 280 until the end of the study (not to exceed 15 March 2018).

  Rationale: To ensure appropriate follow up for subjects continuing in the study for the extension of treatment.
- Change the AbbVie Medical Monitor Contact for Japan to Dr. [redacted] in Section 6.1.5, Adverse Event Reporting, and add Dr. [redacted] as a secondary contact for Japan Section 1.0, Title Page, and Section 6.1.5, Adverse Event Reporting.

  Rationale: To inform the clinical sites of the change in contact for subject safety concerns in Japan.

- Change the fax number and email address of the Immunology Safety team in Section 6.1.5, Adverse Event Reporting.

  Rationale: To inform the clinical sites of the change in contact information for reporting serious adverse events and nonserious events of malignancy in subjects 30 years of age and younger.
- Change the Serious Adverse Event Reporting Contact from AbbVie Immunology Clinical Safety Management Team to Clinical Pharmacovigilance.

  Rationale: To comply with new AbbVie policy that all studies open beyond 2014 will transition to PV ownership in 2014.
- Add a back-up phone number for investigators to call in cases of subject safety concerns/medical emergencies that require immediate attention by the sponsor.

  Rationale: To ensure investigators reach the sponsor immediately in the event of a medical emergency.
- Add the Complaint and Product Complaint definition to Section 6.0, Complaints, Section 6.2.1, Definition, and Section 6.2.2, Reporting, as well as the reporting requirements for Product Complaints.

  Rationale: To implement a standard process for the collection of Product Quality Complaints in clinical trials for marketed combination products to be compliant with FDA regulation (21 CFR Part 4: Post-marketing Safety Reporting for Combination Products).
- Add AbbVie contacts and update site conduct directives relating to protocol deviations in Section 7.0, Protocol Deviations.

  Rationale: To comply with AbbVie procedures.
- Remove from Appendix F, AREDS 2008 Clinical Lens Opacity Grading Procedures, the website link of the AREDS 2008 Clinical Lens Opacity Grading Procedures.

  Rationale: Website no longer available.

An itemized list of all changes made to the protocol under this amendment can be found in Appendix L.

1.2 Synopsis

AbbVie	**Protocol Number:** M11-327
Name of Study Drug: Adalimumab	**Phase of Development:** 3
Name of Active Ingredient: Adalimumab	**Date of Protocol Synopsis:** 04 June 2015
Protocol Title: A Multicenter Open-Label Study of the Long-term Safety and Efficacy of the Human Anti-TNF Monoclonal Antibody Adalimumab in Subjects with Non-infectious Intermediate-, Posterior-, or Pan-uveitis – VISUAL III	
Objectives: The primary objective of this study is to evaluate the long-term safety of adalimumab 40 mg given every other week (eow) subcutaneously (SC) in subjects with non-infectious intermediate-, posterior-, or pan-uveitis who participated in Study M10-877 or Study M10-880. Long-term efficacy will also be assessed.	
Investigators: Investigator information on file at AbbVie.	
Study Sites: Up to 102 sites in the US, Canada, Europe, Israel, Australia, Latin America, and Japan.	
Study Population: Adults with non-infectious intermediate-, posterior-, or pan-uveitis who participated in Study M10-877 or Study M10-880 and who either discontinued from the study for having met the endpoint of Treatment Failure or remained in the study until its completion or remained in the study until the study was stopped.	
Number of Subjects to be Enrolled: Estimated 400 subjects who participated in one of the preceding Phase 3 studies, Study M10-877 or Study M10-880, and who are eligible for this study based on the inclusion/exclusion criteria.	
Methodology: This study is an open-label multicenter study designed to evaluate the long-term safety and efficacy of adalimumab in adult subjects with non-infectious intermediate-, posterior-, or pan-uveitis. All subjects will receive open-label adalimumab 40 mg dose eow SC regardless of treatment assignment in the randomized, double-masked studies. As subjects who discontinue from Study M10-877 or Study M10-880 due to "Treatment Failure" will have active disease at time of entry into Study M11-327, concomitant therapy with corticosteroids (oral or topical) and/or any one of the immunosuppressive therapies permitted in Study M10-877 and Study M10-880 will be allowed as necessary to control intraocular inflammation. Subjects who successfully complete Study M10-877 or Study M10-880 and have inactive disease at time of entry into Study M11-327 may continue, taper and/or discontinue concomitant corticosteroids and/or one immunosuppressive therapy based on the Investigator's clinical judgment. Study visits will occur at Week 0, 2, 4, 8, 12, 18 and every 12 weeks thereafter. Efficacy assessments will be performed at every visit. Subjects who enter the study due to Treatment Failure in Study M10-877 or Study M10-880 and fail to achieve adequate control of their disease flare within the first 8 weeks of Study M11-327 may discontinue from the study.	

Methodology (Continued): Any other subject experiencing a uveitis flare during the study as determined by the investigator may discontinue the study at any time. Subjects may continue in the study, if it is determined by the investigator that the flare was triggered by a reduction or discontinuation in concomitant corticosteroid or systemic immunosuppressive therapy where further adjustment to the concomitant therapy may be warranted. Any subject continuing to have an active uveitis flare in the opinion of the investigator for 4 weeks or more should be discontinued from the study. Safety data will be collected in the form of adverse events, physical examination, vital signs and laboratory tests throughout the treatment period and up to 70 days after the last dose of study drug. All subjects will have a 70-day follow-up phone call or visit to obtain follow-up information on any new or ongoing adverse events. The 70-day follow-up phone call or clinic visit will not be required for any subject that initiates commercial adalimumab.	
Diagnosis and Main Criteria for Inclusion/Exclusion: **Main Inclusion:** • Subject must have successfully enrolled in either Study M10-877 or Study M10-880 and either met the endpoint of "Treatment Failure" or completed the study.	
Main Exclusion: • A subject will be excluded from this study if the patient prematurely discontinued from Study M10-877 or Study M10-880 for any reason other than having a Treatment Failure event. • Subject with corneal or lens opacity that precludes visualization of the fundus or that likely requires cataract surgery during the duration of the trial. • Subjects with intraocular pressure of ≥ 25 mmHg and on ≥ 2 glaucoma medications or evidence of glaucomatous optic nerve injury. • Subject with proliferative or severe non-proliferative diabetic retinopathy or clinically significant macular edema due to diabetic retinopathy. • Subject with neovascular/wet age-related macular degeneration. • Subject with abnormality of vitreo-retinal interface (i.e., vitreomacular traction, epiretinal membranes, etc.) with the potential for macular structural damage independent of the inflammatory process. • Subject with a systemic inflammatory disease that requires therapy with a prohibited immunosuppressive agent at the time of study entry.	
Investigational Product:	Adalimumab
Doses:	40 mg eow dose
Mode of Administration:	SC (prefilled syringe)
Duration of Treatment:	The entire study will be terminated in March 2018.

Criteria for Evaluation:

Efficacy: Efficacy variables include:

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

Other efficacy variables include: Work Productivity and Activity Impairment Questionnaire: Specific Health Problem Questionnaire (WPAI-SHP), EuroQol-5D Questionnaire (EQ-5D) and Health Resource Utilization Questionnaire (HRU).

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

Statistical Methods:

Efficacy: Efficacy analyses will be based on the Intent to Treat (ITT) set which includes all subjects that received at least one dose of study drug in Study M11-327. All statistical analyses will be descriptive. Results will be stratified between subjects who entered into the study with active versus inactive uveitis. For subjects who had active uveitis when they entered the study, the efficacy analyses will start at Week 8. For subjects who had inactive uveitis when they entered the study, the efficacy analyses will start at Week 0. Continuous variables will be summarized by the number of non-missing observations, mean, standard deviation, median, quartiles, minimum and maximum. Categorical variables will be summarized by counts and percentages.

Safety: Safety analyses will be based on the safety set which includes all subjects that received at least one dose of study drug in Study M11-327. The number and percentage of subjects with treatment-emergent adverse events will be displayed with counts and percentages. The changes in laboratory data and vital signs will be summarized using descriptive statistics.

1.3 List of Abbreviations and Definition of Terms

AC	Anterior Chamber
AE	Adverse Event
ALT	Alanine Aminotransferase
ANA	Antinuclear Antibody
AREDS	Age-Related Eye Disease Study
AS	Ankylosing Spondylitis
AST	Aspartate Aminotransferase
ATEMS	Abbott Temperature Excursion Management System
BCG	Bacille Calmette-Guérin
BCVA	Best Corrected Visual Acuity
BUN	Blood Urea Nitrogen
CDM	Clinical Data Management
CME	Cystoid Macular Edema
CNS	Central Nervous System
CRA	Clinical Research Associate
CRP	C-reactive Protein
CXR	Chest X-ray
eCRF	Electronic Case Report Form
eow	Every Other Week
EAU	Experimental Autoimmune Uveoretinitis
EC	European Commission
ECG	Electrocardiogram
EDC	Electronic Data Capture
EMA	European Medicines Agency
EQ-5D	EuroQol-5D Questionnaire
ESR	Erythrocyte Sedimentation Rate
ETDRS	Early Treatment Diabetic Retinopathy Study
EU	European Union
FA	Fluorescein Angiography
FDA	US Food and Drug Administration
GCP	Good Clinical Practices
GPRD	Global Pharmaceutical Research and Development

HCG	Human Chorionic Gonadotropin
HIV	Human Immunodeficiency Virus
HRU	Health Resource Utilization Questionnaire
HSV	Herpes Simplex Virus
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
IGRA	Interferon-Gamma Release Assay
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
ITT	Intent to Treat
IUD	Intrauterine Device
IV	Intravenous
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
JIA	Juvenile Idiopathic Arthritis
MMR	Measles-Mumps-Rubella
MMRV	Measles-Mumps-Rubella-Varicella
MTX	Methotrexate
NEI	National Eye Institute
N_{nmiss}	Number of Non-Missing Observations
NYHA	New York Heart Association
OCT	Optical Coherence Tomography
OPV	Oral Polio Vaccine
PA	Posterior-Anterior
PMDA	Pharmaceuticals and Medical Devices Agency
POR	Proof of Receipt
PPD	Purified Protein Derivative
Ps	Psoriasis
PsA	Psoriatic Arthritis
PSC	Posterior Subcapsular
RA	Rheumatoid Arthritis
RBC	Red Blood Cell

SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SGOT	Serum Glutamic-Oxaloacetic Transaminase
SGPT	Serum Glutamic-Pyruvic Transaminase
SUN	Standardization of Uveitis Nomenclature
SUSAR	Suspected Unexpected Serious Adverse Reactions
TB	Tuberculosis
TNF	Tumor Necrosis Factor
US	United States
VEGF	Vascular Endothelial Growth Factor
VFQ-25	Visual Functioning Questionnaire
VKH	Vogt-Koyanagi-Harada disease
WBC	White Blood Cell
WPAI-SHP	Work Productivity and Activity Impairment, Questionnaire: Specific Health Problem Questionnaire V2.0

2.0 Table of Contents

1.0 Title Page 1
1.1 Protocol Amendment: Summary of Changes 3
1.2 Synopsis 5
1.3 List of Abbreviations and Definition of Terms 8
2.0 Table of Contents 11
3.0 Introduction 15
3.1 Uveitis Disease Overview 15
3.2 Epidemiology 15
3.3 Current Therapies for Non-Infectious Uveitis 16
3.4 Unmet Medical Need 16
3.5 Supporting Evidence for Anti-TNF Therapy as Potential Treatment Modality 18
3.5.1 Preclinical Evidence 18
3.5.2 Published Clinical Data 19
3.6 Adalimumab Overview 21
3.7 Benefits and Risks 22
4.0 Study Objectives 23
5.0 Investigational Plan 23
5.1 Overall Study Design and Plan: Description 23
5.2 Selection of Study Population 27
5.2.1 Inclusion Criteria 27
5.2.2 Exclusion Criteria 28
5.2.3 Prior and Concomitant Therapy 30
5.2.3.1 Prior Therapy 30
5.2.3.2 Concomitant Therapy 31
5.2.3.3 Prohibited Therapy 32
5.3 Efficacy, Pharmacokinetic and Safety Assessments/Variables 34
5.3.1 Efficacy and Safety Measurements Assessed and Flow Chart 34
5.3.1.1 Study Procedures 39
5.3.2 Drug Concentration Measurements 55
5.3.3 Efficacy Variables 55

5.3.3.1 Other Variables 56
5.3.4 Safety Variables 56
5.3.5 Pharmacokinetic Variables 56
5.4 Removal of Subjects from Therapy or Assessment 56
5.4.1 Discontinuation of Individual Subjects 56
5.4.2 Discontinuation of Entire Study 59
5.5 Treatments 59
5.5.1 Treatments Administered 59
5.5.2 Identity of Investigational Products 59
5.5.2.1 Packaging and Labeling 60
5.5.2.2 Storage and Disposition of Study Drugs 61
5.5.3 Method of Assigning Subjects to Treatment Groups 61
5.5.4 Selection and Timing of Dose for Each Subject 62
5.5.5 Masking 62
5.5.5.1 Data for Independent Data Monitoring Committee (IDMC) 63
5.5.6 Treatment Compliance 63
5.5.6.1 Drug Accountability 64
5.6 Discussion and Justification of Study Design 65
5.6.1 Discussion of Study Design and Choice of Control Groups 65
5.6.2 Appropriateness of Measurements 65
5.6.3 Suitability of Subject Population 65
5.6.4 Selection of Doses in the Study 65
6.0 Complaints 66
6.1 Medical Complaints 66
6.1.1 Definitions 67
6.1.1.1 Adverse Event 67
6.1.1.1.1 Uveitis-Related Events 68
6.1.1.2 Serious Adverse Events 68
6.1.2 Adverse Event Severity 70
6.1.3 Relationship to Study Drug 70
6.1.4 Adverse Event Collection Period 71
6.1.5 Adverse Event Reporting 72
6.1.6 Pregnancy 75

6.2 Product Complaint 75
6.2.1 Definition 75
6.2.2 Reporting 76
6.3 Toxicity Management 76
7.0 Protocol Deviations 77
8.0 Statistical Methods and Determination of Sample Size 78
8.1 Statistical Analysis Plans 78
8.1.1 Analysis Population 78
8.1.2 Planned Methods of Statistical Analysis 78
8.1.3 Analysis of Demographics and Baseline Characteristics 79
8.1.4 Analysis of Efficacy 79
8.1.5 Analysis of Safety 79
8.2 Determination of Sample Size 80
9.0 Ethics 80
9.1 Independent Ethics Committee (IEC) or Institutional Review Board (IRB) 80
9.2 Ethical Conduct of the Study 81
9.3 Subject Information and Consent 81
10.0 Source Documents and Case Report Form Completion 82
10.1 Source Documents 82
10.2 Case Report Forms 83
11.0 Data Quality Assurance 84
12.0 Use of Information and Publication 85
12.1 Use of Information 85
13.0 Completion of the Study 86
14.0 Investigator's Agreement 88
15.0 Reference List 89

List of Tables

Table 1. Study Activities 35

Table 2. Anterior Chamber Cells 42
Table 3. Lens Opacity Grading 43
Table 4. Vitreous Haze Grading 45
Table 5. Clinical Laboratory Tests 48
Table 6. Identity of Investigational Products 60

List of Figures

Figure 1. Study Schematic 24
Figure 2. Adverse Event Collection 72

List of Appendices

Appendix A. Responsibilities of the Clinical Investigator 93
Appendix B. List of Protocol Signatories 95
Appendix C. Non-Drug Materials Provided to the Study Sites 96
Appendix D. Day 70 Follow-up (Phone Call or Clinic Visit) 97
Appendix E. Subject Dosing Diary 98
Appendix F. AREDS 2008 Clinical Lens Opacity Grading Procedures 131
Appendix G. Visual Functioning Questionnaire (VFQ-25) 132
Appendix H. EuroQol-5D Questionnaire (EQ-5D) 143
Appendix I. Health Resource Utilization Questionnaire (HRU) 146
Appendix J. Work Productivity and Activity Impairment, Questionnaire: Specific Health Problem Questionnaire V2.0 (WPAI-SHP) 147
Appendix K. Japan Appendix 149
Appendix L. Protocol Amendment: List of Changes 158

3.0 Introduction

3.1 Uveitis Disease Overview

Uveitis refers to inflammation in the uveal tract of the eye which includes the iris, ciliary body, and choroid.[2] In addition, diseases in which the retina is affected are also often included under the term "uveitis." According to the Standardization of Uveitis Nomenclature (SUN) working group, uveitis can be classified according to the primary anatomical location of the inflammation – anterior-, intermediate-, posterior- or pan-uveitis (affecting all three areas).[3] The location of inflammation dictates the prognosis and recommended therapy for the disease. As an example, there is a higher risk for vision loss in subjects with panuveitis.[4] Uveitis can also be categorized by the etiology of the inflammatory process – infectious or non-infectious.[2] Non-infectious uveitis can then be further classified as to whether it is an isolated ocular syndrome (i.e., Birdshot choroidopathy) or if there is accompanying extra-ocular or systemic inflammation (i.e., sarcoidosis, Vogt-Koyanagi-Harada disease [VKH], Behcet's disease, Ankylosing spondylitis [AS], Juvenile idiopathic arthritis [JIA], Psoriatic arthritis [PsA], etc.). Patients with non-infectious uveitis but who do not have a characteristic disease pattern or systemic involvement that indicate a specific diagnosis are often labeled as having "idiopathic" uveitis.

3.2 Epidemiology

There are challenges in understanding the epidemiology of non-infectious uveitis due to the heterogeneity of the disease, variations in diagnostic work-up and availability of investigations or tests, lack of uniform classification systems or definitions of uveitis entities and referral or selection bias.[5] In addition, studies often combine both infectious and non-infectious types of uveitis.

In a review of the epidemiologic literature by Wakefield and Chang that covered various parts of the world, the annual incidence of uveitis was noted to be between 17 and 52 per 100,000 population.[5] Anterior uveitis is the most common type of uveitis in most regions of the world, though it is less common in Asian countries. Intermediate uveitis, on the

other hand, is universally the least common type of uveitis. Among those with posterior uveitis, toxoplasmic retinochoroiditis was the most commonly identified etiology, with the remaining cases being largely idiopathic. Most cases of panuveitis, in North America, Europe and Asia, are idiopathic. Other types of panuveitis are due to Sarcoid, Behcet's Disease, VKH or Toxoplasmosis.

3.3 Current Therapies for Non-Infectious Uveitis

Corticosteroids have been the mainstay of treatment for non-infectious uveitis because of their immediate efficacy. These can be administered either in a topical, oral or injectable form. However, ocular and/or systemic adverse effects of long-term corticosteroid therapy limit its use in the treatment of uveitis.[6-8] The type and severity of the disease dictate the route of administration of corticosteroids and the likelihood of requiring immunosuppressive therapy to control the uveitis.[6,9] Topical corticosteroid eye drops are often sufficient to successfully control anterior uveitis, while in inflammation involving the posterior segment of the eye, systemic or injectable corticosteroids are employed.

The most commonly used immunosuppressive agents are cyclosporine, mycophenolate mofetil, azathioprine and tacrolimus.[6-8] Based on the published recommendations of an expert panel, immunosuppressive agents should be considered for the management of ocular inflammatory disorders in the following situations: 1) the disease worsens on high-dose prednisone, 2) a response is not obtained after 2 to 4 weeks of high-dose prednisone, 3) the disease is not completely controlled after 4 weeks of high-dose prednisone, 4) chronic suppression of disease activity requires much more than 10 mg/day of prednisone (or its equivalent), 5) the type of uveitis requires immediate combination therapy with high-dose steroids and an immunosuppressive agent, 6) in the presence of corticosteroid side effects, or 7) requirement for doses of systemic corticosteroids that are highly likely to result in corticosteroid complications.[6]

3.4 Unmet Medical Need

In the US, it is estimated that about 10% of cases of blindness are due to uveitis.[10] In a retrospective Dutch study, all anatomical sites of inflammation of uveitis were shown to

have the potential to lead to visual impairment and blindness; however, the risks were highest for those with panuveitis and posterior uveitis.[4] Cystoid macular edema (CME) was identified as the leading cause of visual impairment (41%) and blindness (29%) in patients with uveitis. Therefore, there is a need to have adequate therapy in patients with all types of uveitis, particularly with posterior segment involvement given its higher risk for potential permanent disability.

The only drug class approved in the US by the Food and Drug Administration (FDA) for the treatment of uveitis is corticosteroids. An example is Retisert® (fluocinolone acetonide intravitreal implant), which is designed to release therapeutic levels of drug over approximately 30 months.[11] This is currently approved for the treatment of chronic non-infectious uveitis affecting the posterior segment of the eye. The 34-week interim results of a 3-year, prospective, randomized, dose-masked trial in subjects with unilateral or bilateral uveitis showed a significant reduction in flare rates in the implanted eye but a significant increase in flare rates in the contralateral, non-implanted eye.[12] More importantly, 3-year results showed statistically significantly higher incidence of chronic corticosteroid-associated effects in implanted versus non-implanted eyes such as need for glaucoma surgery (40% versus 2%, $P < 0.01$) and cataract extraction (93% versus 20%, $P < 0.01$).[13]

In the European Union, the only drug class widely approved for treatment of uveitis is likewise corticosteroids for systemic or local administration. In addition, the immunosuppressive agent cyclosporine holds national licenses for treatment of uveitis in some European countries. The registered indication of cyclosporine does differ between these countries and comprises the treatment of intermediate or posterior uveitis and Behcet's disease but partially restricts the usage to patients at risk of blindness, and when conventional (corticosteroid) therapy is not adequate or unjustifiable side effects occur.

In Japan, corticosteroids are also central to the treatment of uveitis. An example is Predonine® Tab (prednisolone), which is approved for the treatment of inflammatory diseases such as uveitis. The immunosuppressive agent, cyclosporine, is also used to treat uveitis, and has been approved for treatment of Behcet's with ocular involvement.

Remicade® (infliximab) has been approved in Japan for the treatment of refractory uveitis associated with Behcet's disease, but only in patients who have had an inadequate response to conventional therapy. Retisert® was designated as an orphan drug in Japan for posterior uveitis and is currently under Pharmaceuticals and Medical Devices Agency (PMDA) review.

Globally, there is a clear unmet medical need for additional effective therapies in patients with non-infectious intermediate-, posterior- and pan-uveitis who require chronic corticosteroid therapy and are at risk for the long-term side effects of corticosteroids. These include both ocular adverse effects – intraocular pressure elevation/glaucoma, cataracts – and systemic adverse effects – osteoporosis, hypertension, hyperlipidemia, diabetes mellitus and infections.[6,8] With the exception of some countries where cyclosporine and/or infliximab are approved under specific conditions, none of the immunosuppressive therapies that are currently part of standard of care to minimize chronic corticosteroid side effects and provide long-term control of uveitis have regulatory approval.

3.5 Supporting Evidence for Anti-TNF Therapy as Potential Treatment Modality

3.5.1 Preclinical Evidence

Much of the advances in the understanding of the pathophysiology of intermediate uveitis and other posterior segment intraocular inflammatory disorders are based on studies of the experimental autoimmune uveoretinitis (EAU) animal model. Various reports suggest that intermediate uveitis and posterior segment inflammation are mediated by T helper type1 CD4+ T cells.[14-16] Tumor necrosis factor (TNF)-α, a pro-inflammatory cytokine produced mainly by macrophages and T cells, has also been shown to play a role in the perpetuation of inflammation in uveitis by facilitating further leukocyte infiltration via adhesion molecule upregulation, macrophage activation and dendritic cell maturation/survival.[17] This has been supported by both laboratory and clinical studies showing elevated levels of TNF-α in peripheral CD4+ T cells of patients in both idiopathic and sarcoid intermediate uveitis and intraocularly in EAU rats.[15,18] In addition,

systemic blockade of TNF-α in EAU mice and rats ameliorated the manifestations of the disease.[19,20]

3.5.2 Published Clinical Data

There are numerous publications on the use of anti-TNF agents in the treatment of various types of anterior-, intermediate-, posterior- or pan-uveitis. Several of these publications demonstrate the effectiveness of infliximab and adalimumab although there have been reports on the lack of efficacy of etanercept in the treatment of uveitis.[21-32] Most of these are case reports/series or open-label studies. A few selected reports are described here. An adequate, well-controlled study of the efficacy and safety of anti-TNF therapy is lacking in the current literature.

It is well known that some of the diseases for which adalimumab is currently indicated, such as JIA, AS and PsA, can present with uveitis.[33] There have been reports of efficacy of adalimumab in pediatric patients with JIA-associated or idiopathic uveitis.[24,34] In the open-label uncontrolled RHAPSODY study of AS subjects, adalimumab decreased the rate of acute anterior uveitis flares by 51%.[35]

In an open-label study of Remicade® (infliximab) in 31 subjects with refractory autoimmune uveitis, 24 (77%) of these subjects achieved "clinical success" at Week 10.[29,30] Success was based on a composite clinical end point of visual acuity, control of intraocular inflammation, ability to taper concomitant medication therapy, and improvement in inflammatory signs on fluorescein angiography (FA) and/or Optical Coherence Tomography (OCT). Patient must have improvement in one of the four parameters without any worsening in the other three. Fifteen of the 24 subjects who achieved clinical success completed 1 year of therapy. Serious adverse events that were potentially related to infliximab included pulmonary embolus, congestive heart failure, lupus-like reaction and vitreous hemorrhage.

The same group of investigators did a similar open-label study of adalimumab in subjects with refractory/vision-threatening uveitis. Preliminary results in 16 of 22 subjects who

have reached Week 10 of the study showed "clinical success" in 10 of the 16 subjects.[36] Clinical success was also based on four parameters: visual acuity, control of intraocular inflammation, ability to taper concomitant corticosteroids/immunosuppressives and demonstration of clinical benefit by OCT or FA. There was no treatment-limiting toxicity noted in the interim report.

Likewise, in a Spanish prospective, uncontrolled study of 19 adult subjects with bilateral chronic non-infectious uveitis (1 anterior, 3 intermediate, 5 posterior and 10 panuveitis) or refractory uveitis who have failed or were intolerant to corticosteroid and immunosuppressive therapy, patients were treated with adalimumab 40 mg every other week (eow) subcutaneously for 1 year.[23] Twelve (63%) subjects achieved control of intraocular inflammation at the end of the follow-up period. All subjects were able to decrease concomitant immunosuppressives by at least 50%. Of the 33 eyes with CME at study start, 55% had complete resolution at Month 12. There was also statistically significant improvement in the mean visual acuity, anterior chamber (AC) and vitreous cavity inflammation. Only minor local adverse effects were noted.

Díaz-Llopis et al published in 2012 a prospective study on 131 subjects treated with adalimumab 40 mg eow and followed for 6 months. Anterior chamber inflammation and vitreous inflammation decreased significantly (*P* 0.001) from a mean of 1.51 and 1.03 at baseline to 0.25 and 0.14, respectively, at 6 months. Macular thickness was 296 (102) at baseline versus 240 (36) at the 6-month visit (*P* 0.001). Visual acuity improved by 0.3 logMAR in 32 of 150 eyes (21.3%) and worsened by 0.3 logMAR (15 letters) in 5 eyes (3.3%). The dose of corticosteroids decreased from 0.74 (3.50) to 0.20 (0.57) mg/kg/day (*P* 0.001). Cystoid macular edema, which was present in 40 eyes at baseline, showed complete resolution in 28 (70%) eyes at 6 months.
One hundred eleven (111) patients (85%) were able to reduce at least 50% of their baseline immunosuppression load.

Nine (9) patients (6.9%) had severe relapses during the 6 months of follow-up.[41]

3.6 Adalimumab Overview

Adalimumab is a recombinant human immunoglobulin (IgG1) monoclonal antibody containing only human peptide sequences. Adalimumab is produced by recombinant DNA technology in a mammalian cell expression system. It consists of 1330 amino acids and has a molecular weight of approximately 148 kilodaltons. Adalimumab is composed of fully human heavy and light chain variable regions, which confer specificity to human TNF, and human IgG1 heavy chain and kappa light chain sequences. Adalimumab binds with high affinity and specificity to soluble TNF-α but not to lymphotoxin-α (TNF-β).

TNF is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. Elevated levels of TNF play an important role in pathologic inflammation. Adalimumab binds specifically to TNF and neutralizes 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. After treatment with adalimumab, levels of acute phase reactants of inflammation (C-reactive protein [CRP] and erythrocyte sedimentation rate [ESR]) and serum cytokines rapidly decrease.

Adalimumab was first approved in US and EU for the treatment of RA in 2002 and 2003, respectively. Additional indications have been approved in the US and EU including Ps, PsA, AS, CD, UC and JIA. Additional updates regarding approved indications can be found in the current edition of the Humira® Investigational Drug Brochure.

Safety Information

Adalimumab therapy has a well established and well described safety profile based on extensive postmarketing experience and continued clinical trial subject exposure since the first approved indication in 2002 for rheumatoid arthritis. A detailed discussion of the pre-clinical toxicology, metabolism, pharmacology and safety experience with adalimumab can be found in the current Investigator's Brochure. AbbVie is committed to continue to collect safety information including those events that may occur in this trial in order to confirm this established safety profile and to identify any unknown potential

adverse reactions, rare events and those events with a long latency. AbbVie is participating in an FDA-requested, TNF inhibitor class wide exploration of the rare appearance of malignancy in subjects who are 30 years of age or younger at the time of diagnosis. The risk of malignancy in this age group has not been established and is difficult to study due to its rarity. AbbVie appreciates your attention to the additional reporting requirements needed in this unlikely event, outlined in Section 6.1.5 under Adverse Event Reporting.

AbbVie is planning to investigate the efficacy and safety of adalimumab in the treatment of patients with non-infectious uveitis.

3.7 Benefits and Risks

There is an unmet medical need for the treatment of non-infectious intermediate-, posterior- and pan uveitis and this represents the focus of the adalimumab clinical development plan. These types of uveitis are at a higher risk for vision loss compared to anterior uveitis. Disease management often requires chronic corticosteroid use, whether in an oral or injectable form, that presents with predictable long-term side effects; whereas anterior uveitis may be generally managed with topical corticosteroids.

Immunosuppressive agents have been used as corticosteroid-sparing or additive therapy in non-infectious intermediate-, posterior- or pan-uveitis but these have not been well studied, are not effective in all patients and also carry risk of certain adverse effects.

TNF-α has been shown to play a pivotal role in the inflammatory process in non infectious uveitis. The utility of TNF blockade has been supported by both pre-clinical experiments and positive results from open label prospective trials in particular with infliximab or adalimumab. Adalimumab can potentially offer a treatment option to patients with non-infectious uveitis in a clinical practice setting. Adalimumab has extensive clinical and post-marketing experience in a wide range of disease states. In the limited available information on patients with uveitis from the adalimumab clinical

trial database, there are no a priori additional risks that have been identified in the target uveitis patient population.

4.0 Study Objectives

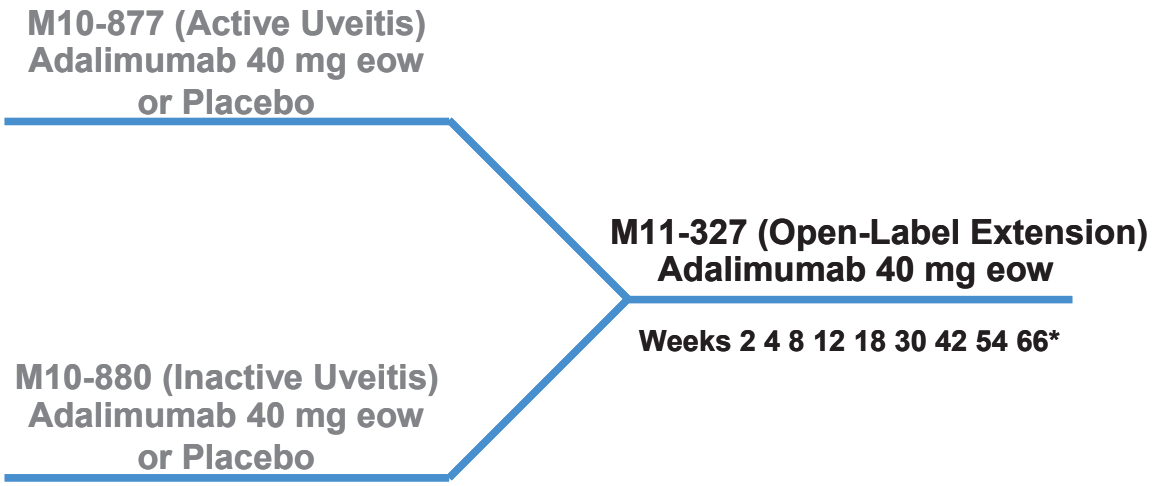
The primary objective of this study is to evaluate the long-term safety of adalimumab 40 mg dose given every other week (eow) subcutaneously (SC) in subjects with non-infectious intermediate-, posterior-, or pan-uveitis who participated in Protocol M10-877 or M10-880. Long-term efficacy will also be assessed.

5.0 Investigational Plan

5.1 Overall Study Design and Plan: Description

This study is a Phase 3, open-label multicenter study designed to evaluate long-term safety and efficacy of adalimumab in adult subjects with non-infectious intermediate-, posterior-, or pan-uveitis who have either discontinued from Study M10-877 or Study M10-880 for having met "Treatment Failure" criteria or have successfully completed Study M10-877 or Study M10-880. Subjects who prematurely discontinue from Study M10-877 or Study M10-880 for reasons other than for Treatment Failure as defined in the parent protocol, will not be eligible for this study.

Figure 1. Study Schematic



* Visits will occur every 12 weeks following Week 66 until the end of the study (not to exceed 15 March 2018).

Subjects rolling over from Study M10-877 and Study M10-880 will be evaluated for entry into this study at the final or last visit in the parent study. Therefore, Study M11-327 Baseline (Week 0) visit will be performed on the same day as the Final/Early Termination visit in the parent studies. At this visit, after administrating and obtaining the subject's consent, subjects will be evaluated to ensure they meet all inclusion criteria and none of the exclusion criteria listed in Section 5.2. If the Baseline visit occurs greater than (>) 14 days after the Final/Early Termination visit of the parent study, all procedures listed in the Baseline visit must be completed. The maximum amount of time allowed between the Final/Early Termination visit of the parent study and the Baseline visit of Study M11-327 is 28 days.

Starting at Baseline, all subjects will receive open-label adalimumab 40 mg dose eow SC regardless of treatment assignment in the randomized, double-masked Study M10-877 or Study M10-880.

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

Subjects who successfully complete Study M10-877 or Study M10-880 and have inactive disease at time of entry into Study M11-327 may continue, taper and/or discontinue concomitant corticosteroids and/or immunosuppressive therapy which were permitted in Study M10-877 and Study M10-880 based on the investigator's clinical judgment.

Subjects may be on only one of the allowed systemic immunosuppressants in addition to a systemic corticosteroid, at any timepoint.

Study visits will occur at Week 0, 2, 4, 8, 12, 18 and every 12 weeks thereafter. Efficacy assessments will be performed at every visit (Section 5.3.1). Both of the subject's eyes should be evaluated. **There will be no designated "study eye."**

Subjects who enter the study due to Treatment Failure in Study M10-877 or Study M10-880 and fail to achieve adequate control of their disease flare within the first 8 weeks may discontinue from the study.

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

The site research staff will instruct and supervise subjects or a designee on proper injection technique at the scheduled visits. Subjects or a trained designee will administer adalimumab outside of clinic visits according to the specified dosing schedule.

An Independent Data Monitoring Committee (IDMC) will be established to independently monitor and assess data for Study M10-877, Study M10-880 and Study M11-327. The IDMC will be in effect until the end of both Study M10-877 and Study M10-880. At each committee meeting, the IDMC will undertake a comprehensive review and assessment of the cumulative safety data, which will include M11-327 study data.

Subjects may discontinue adalimumab treatment at any time during study participation. Subjects that end study participation early will have an Early Termination Visit. No study drug will be administered or injected at the final visit.

Safety data will be collected in the form of adverse events, physical examination, vital signs and laboratory tests throughout the treatment period and up to 70 days after the last injection in this study. All subjects will have a 70-day follow-up phone call or clinic visit to obtain follow-up information on any new or ongoing adverse events. The 70-day follow-up phone call will not be required for any subject that initiates commercial adalimumab after the end of study participation.

Following country, local (if applicable) regulatory approval, and/or applicable local reimbursement approval of the study drug in a country, subjects should return to their next scheduled study visit as specified in the protocol. The termination visit should be conducted in place of their regular scheduled study visit. These subjects will be considered as having completed the study.

The entire study will be terminated in March 2018. Subjects who remain active in this clinical trial on 15 February 2018 should be contacted by the site to return for their study termination visit. Sites should complete the termination visit by 15 March 2018 for all of the remaining active subjects. These subjects will be considered as having completed the study.

5.2 Selection of Study Population

It is anticipated that approximately 400 adult subjects with non-infectious intermediate-, posterior-, or pan-uveitis will be enrolled at up to 102 investigational sites in the United States, Canada, Europe, Israel, Australia, Latin America and Japan.

A subject may be entered in this study provided that he/she has met all of the inclusion criteria specified in Section 5.2.1 and none of the exclusion criteria specified in Section 5.2.2 of this protocol.

5.2.1 Inclusion Criteria

A subject will be eligible for study participation if she/he meets the following criteria:

1. Subject must have successfully enrolled in either Study M10-877 or Study M10-880 and either met the endpoint of "Treatment Failure" or completed the study.
2. If female, subject is either not of childbearing potential, defined as postmenopausal for at least 1 year prior to entry or during participation in Study M10-877 or Study M10-880 or surgically sterile (bilateral tubal ligation, bilateral oophorectomy and/or hysterectomy) or is of childbearing potential and is practicing an approved method of birth control throughout the study and for 150 days after last dose of study drug.

   Examples of approved methods of birth control include the following (see local informed consent for more detail):

   - Condoms, sponge, foams, jellies, diaphragm or intrauterine device (IUD);
   - Hormonal contraceptives for 90 days prior to study drug administration;
   - A vasectomized partner.
3. Subject is judged to be in good health as determined by the Principal Investigator based upon the results of laboratory evaluations and physical examinations done throughout the preceding adalimumab uveitis Study M10-877 or Study M10-880.

4. Subjects must be able and willing to provide written informed consent and comply with the requirements of this study protocol.
5. Subjects must be able and willing to self-administer SC injections or have a qualified person available to administer SC injections.
6. This criterion has been removed.

Rationale for Inclusion Criteria:

a. The following criteria were implemented to select the appropriate subject population with sufficient disease activity for evaluation: 1 and 5.
b. The following criterion was implemented because the impact of adalimumab on pregnancy is unknown: 2.
c. The following criterion was implemented for safety of the subjects: 3.
d. The following criterion was implemented in accordance with harmonized good clinical practice: 4.

All laboratory results obtained during participation in Study M10-877 or Study M10-880 will be used to determine eligibility at Baseline.

5.2.2 Exclusion Criteria

1. A subject will be excluded from this study if the patient prematurely discontinued from Study M10-877 or Study M10-880 for any reason other than having a Treatment Failure event.
2. Subject with corneal or lens opacity that precludes visualization of the fundus or that likely requires cataract surgery during the duration of the trial.
3. Subjects with intraocular pressure of $\geq$ 25 mmHg and on $\geq$ 2 glaucoma medications or evidence of glaucomatous optic nerve injury.
4. This criterion has been removed.

5. Subject with proliferative or severe non-proliferative diabetic retinopathy or clinically significant macular edema due to diabetic retinopathy.
6. Subject with neovascular/wet age-related macular degeneration.
7. Subject with abnormality of vitreo-retinal interface (i.e., vitreomacular traction, epiretinal membranes, etc.) with the potential for macular structural damage independent of the inflammatory process.
8. Subject with a systemic inflammatory disease that requires therapy with a prohibited immunosuppressive agent at the time of study entry.
9. This criterion has been removed.
10. This criterion has been removed.
11. This criterion has been removed.
12. Female subjects who are pregnant or breast-feeding or considering becoming pregnant during the study.
13. Evidence of dysplasia or history of malignancy (including lymphoma and leukemia) other than a successfully treated non-metastatic cutaneous squamous cell, basal cell carcinoma or localized carcinoma in situ of the cervix.
14. Subject is considered by the Investigator, for any reason, to be an unsuitable candidate for the study (for example, abnormal laboratory results).
15. Subjects with infection(s) requiring treatment with intravenous (IV) anti-infectives within 30 days prior to the Baseline visit or oral anti-infectives within 14 days prior to the Baseline visit.
16. Subject with an active systemic viral infection or any active viral infection that based on the investigator's clinical assessment makes the subject an unsuitable candidate for the study.

Rationale for Exclusion Criteria:

a. The following criteria were implemented to select the appropriate subject population for evaluation: 1-8.
b. The following criterion was implemented because the impact of adalimumab on pregnancy is unknown: 12.
c. The following criteria were implemented for safety of the subjects: 13-16.

The Investigator should contact the AbbVie Medical Monitor identified in Section 6.1.5 if there are any questions regarding inclusion and exclusion criteria and eligibility.

5.2.3 Prior and Concomitant Therapy

Contact the AbbVie Medical Monitor identified in Section 6.1.5 if there are any questions regarding concomitant, prior or prohibited therapy(ies).

5.2.3.1 Prior Therapy

Any medications captured in the Study M10-877 eCRFs(s) or Study M10-880 eCRF(s) which are ongoing will be transcribed into the Study M11-327 source documents and automatically onto the eCRF(s).

In addition for subjects age ≤ 30 with a reported malignancy adverse event, prior exposure to, or current use of, antineoplastics, or other drugs which have a risk of malignancy as stated in their label and other relevant dosing information to estimate total exposure will be collected in the source documents and appropriate eCRF pages. At the time of the reported malignancy adverse event, sites will be asked if any of the prior and concomitant medications contributed to the event. Any medications used prior to the study will be captured on the appropriate eCRF. Information on the reason for use, date(s) of administration including start and end dates, highest maintained dose, dosage information including dose, route and frequency, and reason for stopping the medication will be collected in the source documents and appropriate eCRF pages.

The AbbVie study designated physician identified in Section 6.1.5 should be contacted if there are any questions regarding concomitant or prior therapies.

Medication categories:

- corticosteroids
- immunosuppressants
- anti-TNF drugs including commercial Humira
- other biologic agents
- antineoplastics
- other

5.2.3.2 Concomitant Therapy

All medications (including, but not limited to, prescription or over-the-counter medicines such as aspirin, antacids, vitamins, mineral supplements, and herbal preparations) that the subject is receiving from Baseline through the end of the study, must be recorded on the appropriate electronic Case Report Form (eCRF) along with the reason for use, dates of administration including start and end dates, and dosage including dose, frequency and route of administration.

Subjects will be allowed two periocular corticosteroid injections per eye per year during the duration of the study at the investigator's discretion. No intraocular or intravitreal injections will be allowed.

Subjects will be allowed to continue on one ongoing non-biologic protocol-permitted immunosuppressive therapy and one systemic corticosteroid at study entry. Alternatively, if the subject has not been on a non-biologic immunosuppressive previously, they can add one of the following at any time during the Study M11-327. In addition, doses must be within the acceptable limits listed below:

- Methotrexate (MTX) ≤ 25 mg per week

- Cyclosporine ≤ 4 mg/kg per day
- Mycophenolate mofetil ≤ 2 grams per day or an equivalent drug to mycophenolate mofetil (e.g., mycophenolic acid) at an equivalent dose approved by the Medical Monitor
- Azathioprine ≤ 175 mg per day
- Tacrolimus (oral formulation) ≤ 8 mg per day

The non-biologic immunosuppressive drug and/or corticosteroids can be initiated, changed or discontinued during the course of the study if it is considered appropriate for the subject in the investigator's expert opinion.

Dosage of topical eye drops (including topical corticosteroid eye drops) may be initiated or adjusted as medically necessary during the study.

The initiation, discontinuation and/or changes in dosing of these non-biologic immunosuppressive therapies and corticosteroids can have an impact on uveitis. However, the intent of allowing these to occur, is to reflect standard clinical practice in the management of uveitis.

Each vaccine administered to the subject should be listed as a concomitant medication on the Other Medications eCRF. Live vaccines may not be given concurrently while on study drug or for 70 days after the last dose of adalimumab.

5.2.3.3 Prohibited Therapy

With the exception of one allowed concomitant immunosuppressant, systemic/topical/periocular (per eye) corticosteroids as detailed in Section 5.2.3.2, the introduction of other medications for uveitis is prohibited during the study.

The following medications are prohibited during the study:

- All biologic therapies with a potential therapeutic impact on non-infectious uveitis, including but not limited to the following:
  - Enbrel® (etanercept);

- Remicade® (infliximab);
- Simponi® (golimumab);
- Orencia® (abatacept);
- Kineret® (anakinra);
- Rituxan®/MabThera® (rituximab);
- Tysabri® (natalizumab);
- Actemra®/RoActemra® (tocilizumab);
- Raptiva® (efalizumab);
- Cimzia® (certolizumab pegol);
- Stelara® (ustekinumab);
- Benlysta® (belimumab);

- Anti-VEGF therapy
- Live vaccines (during the study and for 70 days after the last dose of study drug) (including but not limited to the following: monovalent live attenuated influenza A (H1N1) [intranasal], seasonal trivalent live attenuated influenza (intranasal), herpes zoster, rotavirus, varicella (chicken pox), measles-mumps-rubella (MMR) or MMRV (measles-mumps-rubella-varicella), oral polio vaccine (OPV), smallpox, yellow fever, Bacillus Calmette-Guerin (BCG) and typhoid
- Rifampin/Pyrazinamide combination
- Anti-retroviral therapy
- All other immunosuppressive therapy other than MTX, cyclosporine, mycophenolate mofetil or an equivalent drug to mycophenolate mofetil (e.g., mycophenolic acid), azathioprine, and tacrolimus (oral formulation)
- Intraocular or intravitreal corticosteroid injections
- Ozurdex® (dexamethasone implant)
- Intravitreal MTX
- Medical or recreational marijuana
- Systemic carbonic anhydrase inhibitor

- Any TB-prophylaxis therapy (except for those subjects who entered the parent study prior to Study M10-877 Amendment 6 or Study M10-880 Amendment 7 and were still taking TB-prophylaxis when they entered Study M11-327)
- Retisert® (glucocorticosteroid implant)
- Cyclophosphamide
- Chlorambucil

5.3 Efficacy, Pharmacokinetic and Safety Assessments/Variables

5.3.1 Efficacy and Safety Measurements Assessed and Flow Chart

Safety data will be collected in the form of adverse events, physical examinations, vital signs and laboratory tests throughout the treatment period. Adverse events will also be collected up to 70 days after the last injection in this study.

The visit window for all scheduled visits is ±7 days for all visits. If a subject has an out of window visit, the next visit should occur as originally scheduled based on the first date of study drug administration (Baseline visit).

Study procedures will be performed as summarized in the visit schedule presented in Table 1.

Table 1. Study Activities

Activity	Baseline[a]	Week 2	Week 4	Week 8	Week 12	Week 18	Week 30	Week 42	Week 54	Week 66	Every 12 weeks following Week 66[r]	Final/ ET Visit	Unscheduled Visit[b]	70-Day Follow-up[c]
Informed Consent	X													
Inclusion/Exclusion Criteria	X													
VFQ-25[d]	X			X		X	X	X	X	X	X	X	X	
EuroQol Questionnaire (EQ-5D)[e]	X			X		X	X	X	X	X	X	X	X	
Work Productivity and Activity Impairment Questionnaire: Specific Health Problem Questionnaire (WPAI-SHP)[e]	X			X		X	X	X	X	X	X	X	X	
Health Resource Utilization Questionnaire (HRU)[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	
Vital Signs/Weight/Height[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	
Optical Coherence Tomography (OCT)	X	X	X	X	X	X	X	X	X	X	X	X	X	
Best Corrected Visual Acuity Testing (ETDRS)	X	X	X	X	X	X	X	X	X	X	X	X	X	
Slit Lamp Exam	X	X	X	X	X	X	X	X	X	X	X	X	X	
Tonometry	X	X	X	X	X	X	X	X	X	X	X	X	X	
Dilated Indirect Ophthalmoscopy	X	X	X	X	X	X	X	X	X	X	X	X	X	

Table 1. Study Activities

Activity	Baseline[a]	Week 2	Week 4	Week 8	Week 12	Week 18	Week 30	Week 42	Week 54	Week 66	Every 12 weeks following Week 66[r]	Final/ ET Visit	Unscheduled Visit[b]	70-Day Follow-up[c]
Informed Consent	X													
Inclusion/Exclusion Criteria	X													
VFQ-25[d]	X			X		X	X	X	X	X	X	X	X	
EuroQol Questionnaire (EQ-5D)[e]	X			X		X	X	X	X	X	X	X	X	
Work Productivity and Activity Impairment Questionnaire: Specific Health Problem Questionnaire (WPAI-SHP)[e]	X			X		X	X	X	X	X	X	X	X	
Health Resource Utilization Questionnaire (HRU)[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	
Vital Signs/Weight/Height[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	
Optical Coherence Tomography (OCT)	X	X	X	X	X	X	X	X	X	X	X	X	X	
Best Corrected Visual Acuity Testing (ETDRS)	X	X	X	X	X	X	X	X	X	X	X	X	X	
Slit Lamp Exam	X	X	X	X	X	X	X	X	X	X	X	X	X	
Tonometry	X	X	X	X	X	X	X	X	X	X	X	X	X	
Dilated Indirect Ophthalmoscopy	X	X	X	X	X	X	X	X	X	X	X	X	X	

Table 1. Study Activities

Activity	Baseline[a]	Week 2	Week 4	Week 8	Week 12	Week 18	Week 30	Week 42	Week 54	Week 66	Every 12 weeks following Week 66[r]	Final/ ET Visit	Unscheduled Visit[b]	70-Day Follow-up[c]
Informed Consent	X													
Inclusion/Exclusion Criteria	X													
VFQ-25[d]	X			X		X	X	X	X	X	X	X	X	
EuroQol Questionnaire (EQ-5D)[e]	X			X		X	X	X	X	X	X	X	X	
Work Productivity and Activity Impairment Questionnaire: Specific Health Problem Questionnaire (WPAI-SHP)[e]	X			X		X	X	X	X	X	X	X	X	
Health Resource Utilization Questionnaire (HRU)[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	
Vital Signs/Weight/Height[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	
Optical Coherence Tomography (OCT)	X	X	X	X	X	X	X	X	X	X	X	X	X	
Best Corrected Visual Acuity Testing (ETDRS)	X	X	X	X	X	X	X	X	X	X	X	X	X	
Slit Lamp Exam	X	X	X	X	X	X	X	X	X	X	X	X	X	
Tonometry	X	X	X	X	X	X	X	X	X	X	X	X	X	
Dilated Indirect Ophthalmoscopy	X	X	X	X	X	X	X	X	X	X	X	X	X	

Table 1. Study Activities (Continued)

Activity	Baseline[a]	Week 2	Week 4	Week 8	Week 12	Week 18	Week 30	Week 42	Week 54	Week 66	Every 12 weeks following Week 66[r]	Final/ ET Visit	Unscheduled Visit[b]	70-Day Follow-up[c]
Physical Exam[g]	X				X		X		X		X[g]	X	X	
Symptom Directed Physical Exam[g]		X	X	X		X		X		X	X[g]			
Urine Pregnancy Test[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	
Hematology/Chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X	
Urinalysis[i]	X		X		X		X		X		X	X	X	
TB Screening[j] (PPD Skin Test or QuantiFERON®-TB Gold or IGRA equivalent)	X							X[k]			X[j,k]			
Chest X-ray[l]	X[l]							X[l]			X[l]		X	
Antinuclear Antibody (ANA/Anti-dsDNA[m,n])													X	
Monitor Adverse Events[o]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Monitor Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	
Monitor Compliance		X	X	X	X	X	X	X	X	X	X	X	X	
Dispense Adalimumab Study Drug (Contact IXRS)	X		X	X	X[p]	X	X	X	X	X	X			
Perform Drug Accountability[q]		X	X	X	X	X	X	X	X	X	X	X		

Table 1. Study Activities (Continued)

a. All activities for Baseline except Informed Consent, Inclusion criteria, Exclusion criteria and Dispensing of Study Drug, will be completed as part of the Final/Early Termination visit in the parent study and will be used in analysis for Study M11-327. If the Baseline visit occurs greater than (>) 14 days after the Final/Early Termination visit of the parent study, all procedures listed in the Baseline visit must be completed. The maximum amount of time allowed between the Final/Early Termination visit of the parent study and the Baseline visit of Study M11-327 is 28 days.

b. If a subject presents at a site for an Unscheduled visit investigators should complete unscheduled visit procedures at their discretion.

c. The 70-day follow-up calculated from last dose of study drug should be conducted by telephone or at a routine clinic visit to collect any potential safety information.

d. Questionnaire will be administered by site staff (interview administered) prior to any study procedure or examination.

e. Questionnaire will be completed by the subject unless impaired vision prohibits. Site staff should complete the questionnaire with the subject, if the subject has impaired vision that precludes him/her from reading and completing the questionnaire.

f. Height used in analysis will be taken from the Screening visit of the parent study in which the subject enrolled. Weight will be measured at Baseline (measurement taken at the Final/Early Termination visit of the parent protocol), Unscheduled visit (if applicable) and Final/Early Termination visit. Vital sign determinations of sitting blood pressure, heart rate, respiratory rate and body temperature will be obtained at each visit.

g. A full physical exam will be performed at Baseline, Week 12, Week 30, Week 54, Unscheduled visit (if applicable), and every other visit (every 24 weeks) following Week 66 and Final/Early Termination Visit. An abbreviated symptom-directed physical exam will be completed at all other visits as warranted.

h. All females of childbearing potential will have a urine pregnancy test performed locally at the Baseline visit and all subsequently scheduled study visits. The frequency can be increased if local regulations require. Any subject with a positive urine pregnancy test result must have a negative serum test result performed at the central laboratory prior to enrollment or continuation in the study.

i. The central laboratory will perform the urine dipstick. If the urinalysis results are abnormal by dipstick, the central laboratory will perform a microscopic analysis.

j. An annual TB test must be completed at the Week 42, 90, 138, 186, 234, 282, or 330 visits for all subjects. Please reference Section 5.3.1.1 Study Procedures for further information.

k. If the TB test is missed at the Week 42, 90, 138, 186, 234, 282, or 330 visits, the subject must be brought in within 30 days of the visit to have the test completed.

l. Must include a PA and lateral view. The CXR is only required if a TB test result is positive. A CXR may be repeated at any time during the study as warranted based on the opinion of the Investigator and/or CXR is inconclusive. Other diagnostic imaging tests may be performed as needed if pulmonary involvement is suspected based on the investigator's clinical assessment. See Section 5.3.1.1 for details.

Table 1. Study Activities (Continued)

m. If a subject is enrolled in M11-327 prior to IEC/IRB approval of Global Protocol Amendment 4 of the parent study, the ANA/dsDNA sample will be collected at the subject's next scheduled visit following regulatory approval of M11-327 Global Amendment 4.

n. If a subject develops signs and symptoms of lupus, an ANA test may be repeated based on the investigator's clinical judgment.

o. All SAEs will be captured from the time that the subject signs the Informed Consent Form and all AEs reported from the time of study drug administration through study completion or Early Termination and at the 70-day follow up. Any adverse events experienced prior to first study drug administration in M11-327 will be reported in the parent protocol.

p. At the Week 12 clinic visit, the subject will be dispensed two kits that include a total of four syringes. One syringe should be removed from these kits and sent back to AbbVie per the Drug Destruction guidelines. If dosing at home, the remaining three syringes from these kits will be injected at home at Weeks 12, 14 and 16. At the Week 18 clinic visit, the subject will be dispensed three kits that include a total of six syringes which should be taken at Weeks 18, 20, 22, 24, 26 and 28.

q. Collect the packaging and any remaining drug from the last clinic visit.

r. Subjects will have study visits every 12 weeks following Week 66 until the end of study (not to exceed 15 March 2018).

5.3.1.1 Study Procedures

Subjects will have clinic visits at Baseline, Week 2, Week 4, Week 8, Week 12, Week 18 and every 12 weeks thereafter until the final visit which should occur no later than March 2018.

All activities for the Baseline visit except Informed Consent, Inclusion/Exclusion and Dispensing of Study Drug will be completed as part of the Final/Early Termination visit in the parent study and will be used in analysis for Study M11-327. If the Baseline visit occurs greater than (>) 14 days after the Final/Early Termination visit of the parent study, all procedures listed in the Baseline visit must be completed. The maximum amount of time allowed between the Final/Early Termination visit of the parent study and the Baseline visit of Study M11-327 is 28 days.

At Baseline (as part of the Final/Early Termination visit in the parent studies), Weeks 8, 18, 30, 42, 54, 66, every 12 weeks thereafter until the final visit which should occur no later than March 2018, and at the Final/Early Termination visit, the questionnaire assessments (to be completed in the following order: VFQ-25, EQ-5D, WPAI-SHP and the HRU) required for that visit should be completed first, followed by vital signs and eye exam assessments. The order of the eye examinations may occur according to established site procedures as long as the slit lamp examination for AC cells is performed prior to the application of mydriatic eye drops to dilate subject's pupils for further assessment.

Informed Consent

A signed informed consent will be obtained from the subject or their legally authorized representative before any study-related procedures are undertaken. Details about how informed consent will be obtained and documented are provided in Section 9.3.

If the parent studies are prematurely stopped based upon the recommendation of the IDMC, and this recommendation is based on safety concerns, subjects will be required to return for their Final/Early Termination visit in Study M11-327.

Inclusion/Exclusion Criteria

Subjects will be eligible for study participation if he/she meets all inclusion criteria and none of the exclusion criteria at the Baseline visit.

Assignment of Subject Numbers

Subjects will keep the same subject number that they were assigned in the parent study (Study M10-877 or Study M10-880).

Visual Functioning Questionnaire (VFQ-25)

The VFQ-25 will be completed at the Baseline visit (or as part of the Final/Early Termination visit of Study M10-877 or Study M10-880), Week 8, Week 18 and every visit thereafter prior to any study procedure or examination. A copy of the questionnaire is located in Appendix G.

The questionnaire will be interview administered. The site will complete this questionnaire directly onto the CRFs and will be considered source documents.

EuroQol-5D Questionnaire (EQ-5D)

Subjects will complete the EQ-5D questionnaire at the Baseline visit (or as part of the Final/Early Termination visit of Study M10-877 or Study M10-880), Week 8, Week 18 and every visit thereafter prior to any study procedure or examination. A copy of the questionnaire is located in Appendix H. The subject will complete this questionnaire directly onto the CRFs and will be considered source documents.

Site staff should complete the questionnaire with the subject, if the subject has impaired vision that precludes him/her from reading and completing the questionnaire.

Work Productivity and Activity Impairment, Questionnaire: Specific Health Problem Questionnaire (WPAI-SHP)

Subjects will complete the WPAI-SHP questionnaire at the Baseline visit (or as part of the Final/Early Termination visit of Study M10-877 or Study M10-880), Week 8, Week 18

and every visit thereafter prior to any study procedure or examination. A copy of the questionnaire is located in Appendix J. The subject will complete this questionnaire directly onto the CRFs and will be considered source documents.

Site staff should complete the questionnaire with the subject, if the subject has impaired vision that precludes him/her from reading and completing the questionnaire.

Health Resource Utilization Questionnaire (HRU)

Sites will complete the HRU questionnaire at the Baseline visit (or as part of the Final/Early Termination visit of Study M10-877 or Study M10-880), and at all subsequent visits in the study. A copy of the questionnaire is located in Appendix I.

The questionnaire will be interview administered by the site. The answers will be documented on the source worksheet provided by the sponsor and entered in the eCRF.

Vital Signs/Weight/Height

Vital signs will be obtained at each visit. This includes sitting blood pressure, heart rate, respiratory rate and body temperature. Each subject's height used in the analysis will be taken from the Screening visit of the parent study (Study M10-877 or Study M10-880). For this study, Baseline weight and vital signs measurements will be taken from the final visit of the parent study for the purposes of analysis if Study M11-327 Baseline visit occurs ≤ 14 days since the last visit from the parent study (Study M10-877 or Study M10-880). If the Baseline visit occurs greater than (>) 14 days after the last visit from the parent study, baseline weight and vital signs measurements will be taken at that Baseline visit. Weight will be measured at the Unscheduled visit (if applicable) and Final/Early Termination visit.

Best Corrected Visual Acuity Testing

Refraction and assessment of best corrected visual acuity (BCVA) will be assessed at every visit.

At each visit, subjects should undergo refraction and the result of refraction for each eye will be recorded on the eCRF.

Using the appropriate corrective lenses based on that visit's refraction, subject's BCVA is measured using an ETDRS chart which will be specified and provided if necessary by the sponsor. Please refer to the Visual Acuity Manual provided by the sponsor for instructions.

A qualified and trained health care professional must perform the refraction and BCVA testing. Specific training and instructions will be provided by the sponsor.

Slit Lamp Exam

The slit lamp exam will be conducted at each study visit to assess the following findings: Anterior chamber cell count and Age-Related Eye Disease Study (AREDS) lens opacity grading.[3,37,38] Slit lamp examination for AC cells is performed prior to application of mydriatic eyedrops to dilate subject's pupils for further assessment.

The AREDS classification does not apply to a subject, if he/she has pseudophakia.

The number of AC cells observed within a 1 mm × 1 mm slit beam will be recorded for each eye. The reported number will be used to determine the grade according to the SUN criteria[3] (Table 2).

Table 2. Anterior Chamber Cells

Grade	Cells in Field
0	< 1
0.5 +	1 – 5
1 +	6 – 15
2 +	16 – 25
3 +	26 – 50
4 +	> 50

Using the AREDS standard photographs as reference, the degree of lens opacity will be graded for each type: nuclear, cortical, and posterior subcapsular (PSC) (Table 3).[37,38] See Appendix F for further instructions regarding lens opacity grading procedures.

Table 3. Lens Opacity Grading

Grading for Nuclear Lens Opacity	
< 1.0	no nuclear opacity, or less than NS Std. No. 1
1.0	opacity similar to NS No. 1
1.5	opacity between NS No. 1 and NS Std. No. 2
2.0	opacity similar to NS No. 2
2.5	opacity between NS No. 2 and NS Std. No. 3
3.0	opacity similar to NS No. 3
> 3.0	opacity greater than NS No. 3
8.0	cannot evaluate
Grading for Cortical Lens Opacity	
< 1.0	no cortical opacity, or opacity obviously less than CO Std. No. 1
1.0	opacity similar to cortical opacity Std. No. 1
1.5	opacity between CO Std. No. 1 and Std. No. 2
2.0	opacity similar to CO Std. No. 2
2.5	opacity between CO Std. No. 2 and Std. No. 3
3.0	opacity similar to CO No. 3
> 3.0	cortical opacity obviously greater than Std. No. 3
8.0	cannot evaluate
Grading for Posterior Subcapsular (PSC) Opacity	
< 1.0	no PSC opacity, or opacity obviously < PSC Std. No. 1
1.0	opacity similar to PSC No. 1
1.5	opacity between PSC No. 1 and Std. No. 2
2.0	opacity similar to PSC No. 2
2.5	opacity between PSC No. 2 and Std. No. 3
3.0	opacity similar to PSC No. 3
> 3.0	PSC obviously greater than PSC No. 3
8.0	cannot evaluate

Optical Coherence Tomography

Optical Coherence Tomography will be performed at every visit. Sites must use one of three OCT machines for this clinical trial to determine central retinal thickness and the presence of macular edema:

- Stratus OCT (Carl Zeiss Meditec, Inc.)
- Cirrus HD-OCT (Carl Zeiss Meditec, Inc.)
- Spectralis (Heidelberg Engineering)

Each subject will undergo OCT measurements of the central retinal thickness (1 mm subfield) to evaluate for macular edema at every visit using the same protocol approved machine throughout the study. The same OCT machine that was used in Study M10-877 or Study M10-880 should be used in Study M11-327. OCT images will be sent to the Central Reader for transmission to AbbVie. Although it is preferred to complete the OCT measurements following pupil dilation, it is important that the site conducts the scans consistently across each subject (using the same model of OCT device for each patient) throughout the study.

Tonometry

Tonometry will be performed at every visit to measure the intraocular pressure for both eyes. Applanation tonometry is preferred but non-contact tonometry can also be used if the site does not have the equipment to perform applanation tonometry. However, the same technique should be used for all visits for an individual patient.

Dilated Indirect Ophthalmoscopy

Subject's eyes should be dilated in preparation for indirect ophthalmoscopy. The examination technique and instrument used should remain consistent for each subject throughout the study.

Dilated indirect ophthalmoscopy is performed to determine both vitreous haze grading and the absence/presence of inflammatory chorioretinal and/or inflammatory retinal vascular lesions.

Lesion location(s), number, size(s) and whether the lesions are active or inactive should be documented with a retinal drawing in the subject's source documentation, if a lesion is identified.

Grading of vitreous haze (Table 4) will be based on the publication from the National Eye Institute (NEI) which has also been adapted by the SUN working group.[3,39]

Sites will use the standard photographs given to them by the sponsor and the description in Table 4 when determining the grade for vitreous haze.

Table 4. Vitreous Haze Grading

Grade	Description
0	No evident vitreal haze
0.5 +	Slight blurring of the optic disc margin because of the haze; normal striations and reflex of the nerve fiber layer cannot be visualized
1 +	Permits a better definition of both the optic nerve head and the retinal vessels (compared to higher grades)
2 +	Permits better visualization of the retinal vessels (compared to higher grades)
3 +	Permits the observer to see the optic nerve head, but the borders are quite blurry
4 +	Optic nerve head is obscured

At all visits dilated indirect ophthalmoscopy will be performed to determine the presence/absence of new inflammatory chorioretinal and/or inflammatory retinal vascular lesions compared to the findings from the final visit of the parent study (Study M10-877 or Study M10-880) based on the Investigators' clinical judgment.

Physical Examination

Medically qualified personnel who routinely do a complete physical exam should perform this assessment at the designated study visits listed in Table 1. At all other visits, a symptom directed physical exam will be performed either by the investigator or the medically qualified personnel who performed the complete physical exam. Abnormalities noted after the Baseline visit of the parent study should be evaluated and documented by the Investigator as to whether or not these are adverse events.

Pregnancy Tests

At the Baseline visit and all subsequent visits thereafter, subjects of childbearing potential will have a urine pregnancy test (provided by the central laboratory) performed locally by designated study personnel. The frequency can be increased if local regulations require. Subjects of non-childbearing potential are defined as postmenopausal for at least 1 year or surgically sterile (bilateral tubal ligation, bilateral oophorectomy and/or hysterectomy).

If any urine pregnancy test is positive, a serum pregnancy test must be requested on the central laboratory requisition form and performed by the central laboratory prior to enrollment or continuation in the study. A lactating or pregnant female will not be eligible for participation or continuation in this study.

Clinical Laboratory Tests

Lab evaluations will be performed according to the schedule outlined in Table 1.

Blood draws should be performed after completion of questionnaires (i.e., VFQ-25, EQ-5D, WPAI-SHP, HRU) and vital sign determinations during a study visit, but before study drug administration, if applicable.

A certified central laboratory will be utilized to process and provide results for the general laboratory tests. The investigator will review all laboratory test results. All laboratory test results that are considered clinically significant by the investigator will be followed to a satisfactory conclusion. Laboratory abnormalities are considered to be adverse events only if these result in discontinuation from the study, necessitate therapeutic intervention, and/or the investigator considers them to be adverse events.

In cases where laboratory tests are performed locally for specific study purposes, certifications and laboratory reference ranges will be collected for the tests which are performed.

The central laboratory chosen for this study (ICON Laboratory Services) will provide instructions regarding the collection, processing and shipping of these samples.

Table 5. Clinical Laboratory Tests

Hematology[a]	Clinical Chemistry	Urinalysis[b]	Serology	Other[e]
Hematocrit Hemoglobin Red Blood Cell (RBC) count White Blood Cell (WBC) count Neutrophils Bands Lymphocytes Monocytes Basophils Eosinophils Platelet count (estimate not acceptable)	Blood Urea Nitrogen (BUN) Creatinine Total bilirubin Serum glutamic-pyruvic transaminase (SGPT/ALT) Serum glutamic-oxaloacetic transaminase (SGOT/AST) Alkaline phosphatase Sodium Potassium Calcium Inorganic phosphorus Uric acid Cholesterol Total protein Glucose Triglycerides Albumin	Specific gravity Ketones[c] pH Protein Blood Glucose	Antinuclear Antibody (ANA)/Anti-dsDNA[d] QuantiFERON®-TB Gold test[f]	Human Chorionic Gonadotropin (HCG)

a. Automated basic hematology testing does not include band reporting. If a manual differential is required, only band results over 5 are reported.

b. Microscopic urinalysis performed by the central laboratory at all visits if dipstick UA is abnormal.

c. The result should be interpreted in the context of additional clinical and test information.

d. If a subject enrolls in Study M11-327 prior to IEC/IRB approval of Global Amendment 4 in either parent study, an antinuclear antibody (ANA)/Anti-dsDNA sample will be collected at the subject's next scheduled visit. However, if a subject develops signs and symptoms of lupus, an ANA/Anti-dsDNA test may be repeated based on the investigator's clinical judgment.

e. Urine pregnancy test is performed on all female subjects of child bearing potential at the Baseline visit (Final visit of parent protocol), and all subsequent visits thereafter. A serum HCG test must be requested on the central laboratory requisition if urine HCG is positive. Any subject with a positive urine pregnancy test must have a negative serum test result at the central laboratory prior to enrollment or continuation in the study.

f. If TB screening tests are not available locally, the central laboratory can be used to perform the QuantiFERON®-TB Gold test. For countries that ship to ICON New York, the estimated turnaround time is 5 to 8 days. For countries that ship to ICON Dublin, the estimated turnaround time is 9 to 12 days. For ICON Singapore, the estimated turnaround time is 11 to 14 days.

Note: Baseline laboratory values will be taken from the parent study (Study M10-877 or Study M10-880) unless the Baseline visit occurs greater than (>) 14 days since the last visit in the parent study (Study M10-877 or Study M10-880).

Urinalysis

Urine samples will be obtained for urinalysis testing as noted in Table 1. The central laboratory will perform a urine dipstick analysis and if the results are abnormal, the central laboratory will perform a microscopic urinalysis.

TB Screening

The TB screening tests are diagnostic test results to be interpreted in the context of the patient's epidemiology, history, exam findings, etc. and it is the responsibility of the investigator to determine if a patient has previous, active or latent tuberculosis or not in conjunction with a negative TB Screening test.

Under no circumstances can a patient with a positive PPD result or positive QuantiFERON®-TB Gold test (or IGRA equivalent) continue in the study.

For the TB Screening, either a PPD skin test (alternatively, also known as tuberculin skin test) must be placed or the QuantiFERON®-TB Gold test (or IGRA equivalent) must be performed during the Baseline visit and Week 42, 90, 138, 186, 234, 282, and 330 visits for all subjects. The same type of TB test should be done at Weeks 42, 90, 138, 186, 234, 282 and 330 that was done at Baseline. For subjects with a positive PPD skin test in the parent protocol, a QuantiFERON®-TB Gold test (or IGRA equivalent) must be performed at the Baseline and Week 42, 90, 138, 186, 234, 282, and 330 visits. For subjects with a negative TB test in the parent protocol, the same type of test that was used in the parent protocol (either PPD or QuantiFERON®-TB Gold [or IGRA equivalent]) must be used for every TB test in Study M11-327. If a subject had a negative PPD test or negative QuantiFERON®-TB Gold test (or IGRA equivalent) within 90 days prior to Baseline, and all protocol required documentation is available, the test does not need to be repeated, provided nothing has changed in the subject's medical history to warrant a repeat test.

If the subject has a positive TB Screening test (either positive PPD test or positive QuantiFERON®-TB Gold test [or IGRA equivalent]), the subject must be discontinued. If the subject has a repeat indeterminate QuantiFERON®-TB Gold test (or IGRA

equivalent), the subject must be discontinued. The subject should be brought back in immediately for an Early Termination visit. For subjects with a prior history of Bacille Calmette-Guérin (BCG) administration, the QuantiFERON®-TB Gold test (or IGRA equivalent) test is recommended.

The TB screening tests are preferably performed locally. If TB screening tests (PPD test and/or QuantiFERON®-TB Gold test) are not available locally, the central laboratory can be used to perform the QuantiFERON®-TB Gold test. Sites utilizing the central lab for the QuantiFERON®-TB Gold test should be aware the results for samples sent to ICON New York require an estimated turnaround time of 5 to 8 days, samples sent to ICON Dublin require an estimated turnaround time of 9 to 12 days and samples sent to ICON Singapore require an estimated turnaround time of 11 to 14 days. It is also required to incubate samples for 16 to 24 hours at 37°C prior to shipping, frozen, to the central lab for processing.

For the PPD test:

> The subject will be required to have the PPD test read by a licensed healthcare professional 48 to 72 hours after placement (or as per local guidelines), when the induration is maximal. An induration (not erythema) of 5 mm or greater will be considered as PPD positive. The absence of induration should be recorded, as "0 mm," not "negative."
>
> Subjects who have had an ulcerating reaction to a PPD skin test in the past should not be re-exposed. Therefore, they should not be tested with PPD and instead must have a QuantiFERON®-TB Gold test (or IGRA equivalent) performed to rule out active or latent TB. If the subject has a history of an ulcerative reaction and has a positive or repeat indeterminate QuantiFERON®-TB Gold test (or IGRA equivalent) the subject cannot continue in the study.

If there are sites where the available testing materials are not accepted, an alternative tuberculin skin test may be substituted, but the method must be submitted and approved by AbbVie prior to use with study subjects.

If QuantiFERON®-TB Gold test (or IGRA equivalent) result is indeterminate, the test should be repeated with a fresh blood sample. If a repeat QuantiFERON®-TB Gold (or IGRA equivalent) result is indeterminate, this should be considered a positive test result and the subject should be discontinued.

A corresponding adverse event should be captured on the adverse event page in the eCRF and in the source documents in the case of a positive test result.

For sites participating in the Czech Republic, the following local requirements will also be applicable:

- A pulmonologist will be responsible to obtain a detailed medical history with respect to Tuberculosis exposure. This information needs to include Bacillus Calmette Guérin (BCG) vaccination, cohabitation with individuals who have had TB, and/or who reside or work in TB endemic locations. The information obtained by the pulmonologist must be documented in the patient's source note, dated and signed by the pulmonologist.
- A pulmonologist must review the results of TB Screening Test (PPD skin test or QuantiFERON®-TB Gold test [or IGRA equivalent]) and the chest x-ray and has to give his/her opinion about the continuation of each patient in the study. This opinion must be documented in writing in the patient's source documents.
- All patients with a positive TB Screening test (PPD or QuantiFERON®-TB Gold [or IGRA equivalent]) must be discontinued from the study. Under no circumstances can a patient with a positive TB test result or a prior history of treatment for active or latent tuberculosis be allowed to remain in this trial.

Chest X-ray (CXR)

If a subject has a positive TB test at Baseline or Weeks 42, 90, 138, 186, 234, 282, or 330, subjects will undergo a standard CXR (posterior anterior [PA] and lateral views) to rule out the presence of TB or other clinically relevant findings.

In the assessment of the CXR, a radiologist must specifically note the presence or absence of (1) calcified granulomas, (2) pleural scarring/thickening, and (3) signs of active TB. The Principal Investigator will indicate the clinical significance of any findings and will sign and date the report. In the absence of abnormal findings the Principal Investigator should sign and date the report to indicate review of the report.

Subjects can have a repeat CXR at any time during the study as warranted based on the opinion of the Investigator and/or the CXR is inconclusive.

In addition, other diagnostic imaging tests may be performed as needed if pulmonary involvement is suspected based on the Investigator's clinical assessment.

Antinuclear Antibody (ANA)/Anti-dsDNA Testing

If a subject is enrolled in Study M11-327 prior to the IEC/IRB approval of Global Protocol Amendment 4 in either parent study, the ANA/Anti-ds-DNA sample will be collected at the subject's next scheduled visit following regulatory approval of Study M11-327 Global Protocol Amendment 4.

A repeat ANA/Anti-ds-DNA would be warranted if a subject has clinical signs and symptoms suggestive of lupus. The Anti-ds-DNA antibody testing will be performed in case of a positive ANA result.

All samples will be sent to the central laboratory for processing.

Adverse Events

Adverse events will be assessed at every study visit from Baseline through the Final/Early Termination visit, and during the 70-day phone call or clinic visit (if applicable). A phone

call or routine clinic visit should occur approximately 70 days after last dose of study medication to obtain follow-up information on any ongoing or new adverse events (Section 6.0 and Appendix D).

Any ongoing adverse events at the time of the Termination visit in the previous Study M10-877 or Study M10-880 will be automatically transferred onto the Study M11-327 eCRF.

Concomitant Medication

All medications (including, but not limited to, prescription or over-the-counter medicines such as aspirin, antacids, vitamins, mineral supplements, and herbal preparations) used from the Baseline visit through the end of the study must be recorded on the appropriate eCRF. Any ongoing systemic or local therapy at the time of Termination visit in the previous study M10-877 or M10-880 will be automatically transferred onto the M11-327 eCRF.

Contact the AbbVie Medical Monitor identified in Section 6.1.5, if there are any questions regarding concomitant or prior therapy(ies).

Each vaccine administered to the subject should be listed as a concomitant medication on the Other Medications eCRF. Live vaccines may not be given concurrently while on study drug or for 70 days after the last dose of adalimumab.

Concomitant use of nutritional supplements should be recorded as concomitant medications (generic and/or brand name, dose [if known], frequency) on the Other Medications eCRF.

Dispense Study Drug

Study drug will be administered to subjects by study site medical staff, by himself/herself or by a designee (friend, family member or health care professional) throughout the study.

Subjects, a designated family member or friend, will be trained to administer study medication during the first visit or several times, if appropriate. This training must be documented in the subject's source document.

Subjects or a trained designated family member or friend or a health care professional will administer the injections of the study medication in the subject's home or in the clinic during the weeks the subjects are not in the office for scheduled study visits.

Subjects will maintain a Subject Dosing Diary for all study medication administered outside of the study visit (i.e., at home). The Subject Dosing Diary will be reviewed and verified for compliance at each clinic visit. All relevant dosing information will be retained by study personnel. Additionally, any discernible departure from the protocol regarding study drug administration will be documented appropriately. A sample of the Subject Dosing Diary is presented in Appendix E.

For subjects that cannot/will not self-administer study drug or do not have adequate support (friend, family member or healthcare professional) at home, administration will occur in the clinic.

At all office visits, subjects should be observed after study drug administration until judged clinically stable by the study personnel. If an anaphylactic reaction or other serious allergic reaction occurs, administration of study medication should be discontinued immediately and appropriate therapy initiated. When dosing at home, subjects should be instructed to contact the site immediately with any signs or symptoms of a reaction.

For subjects who deviate from the dosing schedule, every effort should be made to bring the subject back to the original dosing schedule as soon as possible.

The subject must be instructed to return study drug at each clinic visit for the purpose of compliance assessment and drug accountability as detailed in Section 5.5.6.1.

5.3.2 Drug Concentration Measurements

There will be no drug concentration measurements in this protocol.

5.3.3 Efficacy Variables

Efficacy will be determined at each visit by the following criteria. Both of the subjects' eyes will be assessed. The following endpoints will be used to evaluate the long-term efficacy of adalimumab to treat subjects with non-infectious intermediate-, posterior-, or pan-uveitis.

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

uveitis when they entered the study and to Week 8 for subjects who had active uveitis when they entered the study.[40]

5.3.3.1 Other Variables

Other variables for which data will be collected and analyzed include:

- Work Productivity and Activity Impairment, Questionnaire: Specific Health Problem Questionnaire (WPAI-SHP)
- EuroQol-5D Questionnaire (EQ-5D)
- Health Resource Utilization Questionnaire (HRU)

5.3.4 Safety Variables

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

5.3.5 Pharmacokinetic Variables

There will be no pharmacokinetics performed as part of this study.

5.4 Removal of Subjects from Therapy or Assessment

5.4.1 Discontinuation of Individual Subjects

A subject may withdraw from the study at any time. The Investigator may discontinue any subject's participation for any reason, including an adverse event, safety concerns or failure to comply with the protocol. Please refer to Section 6.3, Toxicity Management, for more information regarding the type and duration of follow-up of subjects after adverse events.

Subjects will be withdrawn from the study immediately if any one of the following occurs:

- Clinically significant abnormal laboratory result(s) or adverse event(s), as determined by the Investigator in consultation with the AbbVie Medical Monitor.
- The Investigator believes it is in the best interest of the subject.
- The subject requests withdrawal from the study.
- Inclusion and exclusion criteria violation was noted after the subject started study drug, when continuation of the study drug would place the subject at risk as determined by the AbbVie Medical Monitor.
- Introduction of prohibited medications or dosages when continuation of the study drug would place the subject at risk as determined by the AbbVie Medical Monitor.
- Subject has positive PPD test or positive (or indeterminate re-test) QuantiFERON®-TB Gold test (or IGRA equivalent) result at Baseline, Week 42, 90, 138, 186, 234, 282, or 330.
- Subject is non-compliant with TB prophylaxis (for those subjects who entered the parent study prior to Study M10-877 Amendment 6 or Study M10-880 Amendment 7 and were still taking TB Prophylaxis when they entered Study M11-327).
- Subject becomes pregnant while on study medication.
- Subject has known dysplasia of the gastrointestinal tract (a colonoscopy is not required to enter the study) or a malignancy, except for localized non-melanoma skin cancer. Discontinuation for carcinoma in-situ of the cervix is at the discretion of the Investigator.
- Subject is diagnosed with lupus-like syndrome, multiple sclerosis or demyelinating disease.
- Subject is significantly non-compliant with study procedures which would put the subject at risk for continued participation in the trial as determined by the Investigator, in consultation with the AbbVie Medical Monitor.

If, during the course of study drug administration, the subject prematurely discontinues study drug use, the procedures outlined for the Final/Early Termination Visit must be completed within 2 weeks of the last dose of study drug, and preferably prior to the

initiation of another therapy. However, these procedures should not interfere with the initiation of any new treatments or therapeutic modalities that the Investigator feels are necessary to treat the subject's condition. Following discontinuation of the study drug, the subject will be treated in accordance with the Investigator's best clinical judgment.

All attempts must be made to determine the date of the last dose of study drug and the primary reason for premature discontinuation. The information will be recorded on the appropriate eCRF page. Subjects who prematurely discontinue will not be replaced.

A final phone call or clinic visit will be completed approximately 70 days after the last dose of study drug to determine the status of any ongoing adverse events/serious adverse events or the occurrence of any new adverse events/serious adverse events. The call/visit information should be documented in the subject's source documents per Appendix D, Day 70 Follow-up (Phone Call or Clinic Visit). The 70-day follow-up phone call or clinic visit will not be required for any subject that initiates adalimumab therapy not supplied in the context of the clinical trial after the end of study participation.

For subjects that are considered lost to follow-up, reasonable attempts must be made to obtain information on the final status of the subject. At a minimum, two phone calls must be made and one certified letter must be sent.

Following country and local (if applicable) regulatory approval and/or applicable local reimbursement approval of the study drug in a country, subjects should return to their next scheduled study visit as specified in the protocol. The termination visit should be conducted in place of their regular scheduled study visit. These subjects will be considered as having completed the study.

The entire study will be terminated in March 2018. Subjects who remain active in this clinical trial on 15 February 2018 should be contacted by the site to return for their study termination visit. Sites should complete the termination visit by 15 March 2018 for all of the remaining active subjects. These subjects will be considered as having completed the study.

5.4.2 Discontinuation of Entire Study

AbbVie reserves the right to discontinue a site's participation in the study at any time and to remove all study materials. Possible reasons for termination of the study at a site include, but are not limited to:

- Safety concerns based on reported data
- Unsatisfactory enrollment with respect to quantity or quality
- Inaccurate or incomplete data collection
- Falsification of records
- Significant non-compliance with protocol requirements
- Recommendation by the IDMC to discontinue the uveitis investigational program due to safety concerns.

AbbVie may terminate this study prematurely, either in its entirety or at any study site, for reasonable cause provided that written notice is submitted in advance of the intended termination. The Investigator may also terminate the study at their site for reasonable cause, after providing written notice to AbbVie in advance of the intended termination. Advance notice is not required by either party if the study is stopped due to safety concerns.

5.5 Treatments

5.5.1 Treatments Administered

Study drug will be provided as a sterile, preservative-free solution for injection contained in 1 mL prefilled syringes containing adalimumab 40 mg/0.8 mL. Drug will be subcutaneously administered as a 40 mg dose every other week at approximately the same time of day starting at Baseline.

5.5.2 Identity of Investigational Products

The individual study drug information is presented in Table 6.

Table 6. Identity of Investigational Products

Drug	Dosage Form	Device	Formulation	Manufacturer
Adalimumab	Parenteral	Prefilled syringe	40 mg/0.8 mL solution for injection Adalimumab/Mannitol, Citric acid monohydrate, Sodium citrate, Disodium phosphate dihydrate, Sodium dihydrogen phosphate dihydrate, Sodium chloride, Polysorbate 80, Water for injections, Sodium hydroxide added as necessary to adjust pH	AbbVie/Abbott

5.5.2.1 Packaging and Labeling

Adalimumab 40 mg/0.8 mL Prefilled Syringes:

Subject cartons will contain two prefilled syringes of adalimumab 40 mg/0.8 mL. The number of kits dispensed will be managed by the IVR/IWR system. At a minimum, the following information will appear on either the syringe and/or carton labels:

- Caution statement(s)
- Sponsor identification
- Protocol number
- Drug identification
- Quantity of contents
- Storage conditions
- Dosing instructions
- Kit number
- Route of administration
- Excipients (as required)
- Blank spaces to write the subject's identification number, and date dispensed (as required)
- Finishing lot number

- Expiry date (as required)

Each drug will be labeled as required per country requirements. Labels must remain affixed to study drug as applicable.

5.5.2.2 Storage and Disposition of Study Drugs

Adalimumab prefilled syringes are to be stored protected from light at 2° to 8°C/36° to 46°F. Study drug **must not be frozen** at any time. A storage temperature log is to be maintained to document proper storage conditions. The refrigerator temperature must be recorded each business day to document proper function. The maximum, minimum and current temperature for refrigerator temperature must be documented and reviewed for temperature excursions. Malfunctions or any temperature excursion must be reported to AbbVie immediately. Study medication should be quarantined and not dispensed until AbbVie Global Pharmaceutical Research and Development (GPRD) or Abbott Temperature Excursion Management System (ATEMS) deems the medication as acceptable.

All clinical supplies must be stored and locked in a secure place until they are dispensed for subject use or are returned to AbbVie.

Investigational products are for investigational use only and are to be used only within the context of this study. The clinical supplies for this study must be maintained under adequate security and stored under conditions specified on the label.

5.5.3 Method of Assigning Subjects to Treatment Groups

All subjects will be centrally registered by the Interactive Voice Response System, (IVRS)/Interactive Web Response System (IWRS) at the Baseline study visit. This study is open-label therefore all subjects will be assigned to active treatment. The sites will be provided with appropriate kit number(s) for drug-dispensing purpose for each subject by the IVRS/IWRS. Before the study is initiated, the telephone number and call-in directions

for the IVRS/IWRS will be provided to each site. Study drug will be dispensed at the study visits summarized in Table 1.

The IVRS/IWRS will be maintained by Bracket (formerly United BioSource Corporation):

Bracket
303 Second Street, Suite 700
7th Floor South Tower
San Francisco, CA 94107 USA

5.5.4 Selection and Timing of Dose for Each Subject

Subjects should take study medication as outlined in Section 5.5.1.

Each subject will be assigned to open-label eow adalimumab dosing. If a subject should forget to administer the injection of study medication on their regularly scheduled dosing date, they should take the forgotten injection as soon as they remember the dose was missed up to the day of their next scheduled dose. The subject should not administer two doses on the same day.

In the event the incorrect dose is taken or a dose is missed, the subject should be instructed to contact the site to determine how to proceed with dosing. The subject must record all dosing information on the Subject Dosing Diary (Appendix E).

Doses not administered (e.g., not taken before next dose is scheduled), should be recorded as not taken in the source. The extra dose should be returned to the study site full. The subject should resume their regular dosing schedule based on the date of first dose at Baseline.

5.5.5 Masking

This study is open-label. There is no masking of treatment assignment.

5.5.5.1 Data for Independent Data Monitoring Committee (IDMC)

An Independent Data Monitoring Committee (IDMC) will be established to independently monitor and assess data from Study M10-877 (active uveitis), Study M10-880 (inactive uveitis) and Study M11-327 (open-label long-term extension). The IDMC will be in effect until the end of both Study M10-877 and Study M10-880. At each committee meeting, the IDMC will undertake a comprehensive review and assessment of the cumulative safety data. The IDMC will meet every 6 months or at a frequency determined by the IDMC and render their recommendation for either the termination or continuation of the study or an amendment to the study. The IDMC analysis will be conducted by a statistics vendor external to AbbVie in order for the sponsor to remain masked to the results of the study.

If the parent studies are prematurely stopped based upon the recommendation of the IDMC, and this recommendation is based on safety concerns, subjects will be required to return for their Final/Early Termination visit in Study M11-327.

5.5.6 Treatment Compliance

The Investigator or his/her designated representatives will dispense study drug only for use by subjects enrolled in the study in accordance with the protocol. The study drug must not be used for reasons other than that described in the protocol.

The subject or their qualified designee will administer all doses of study drug when not at the site. Appropriate site staff will supervise the subject's administration of the study drug at the Baseline office study visit to ensure proper injection technique. In order to document compliance with the treatment regimen, the subject will be given a Subject Dosing Diary (Appendix E) to record all injection dates and times. Compliance information will be documented on the appropriate eCRF. Subjects will be counseled on missed doses of medication. If the subject does not return the Subject Dosing Diary, IP cartons and sharp containers (when applicable), the site should question the subject and obtain as much information as possible as to the dosing of the study drug.

The information should be documented on the source documents as per "best recollection" and when possible, re-verified when the Subject Dosing Diary is returned before completing on the applicable eCRF page.

5.5.6.1 Drug Accountability

The Investigator or designee will verify that study drug supplies are received intact, at the appropriate temperature, (in the US adequate temperature is cool to the touch, outside of the US temperature recording devices [TempTale®] are provided in the shipments), and in the correct amounts from the drug depot. This will be accomplished by documenting the condition of the shipment, verifying the kit numbers in the package against the Proof of Receipt (POR) or similar document included with each drug shipment, and documenting this verification by signing and dating the POR or similar document. The original POR Note or similar document will be kept in the site files as a record of what was received.

In addition, an interactive web response system (IWRS) will be used to document Investigational Product Accountability including but not limited to date received, the lot number, kit number(s), date dispensed, subject number and the identification with date of person dispensing the drug.

All empty pre-filled syringe cartons and used prefilled syringes will be inventoried by the site. Each subject will be given their own sharps disposal container to store used pre-filled syringes. Empty IP cartons and Sharps containers should be returned by the subject at each visit for accountability and compliance purposes and new containers issued as necessary. Empty cartons and returned Sharps containers will be retained (unless prohibited by local law) until the CRA is on site to confirm the returned medication. CRAs and site staff will complete study medication accountability via IVRS/IWRS, source documents, Subject Dosing Diaries, empty IP cartons and by visually inspecting the syringes in the Sharps container whenever possible. Used Sharps containers should never be opened. Once the CRA has verified drug accountability at the site, the site staff and CRA will document that the used prefilled syringes have been destroyed, using appropriate biohazard precautions, when appropriate. A copy of the

destruction methodology should be maintained at the site's facility. Unused medication will be returned by the CRA after drug accountability has been completed at the site.

An overall accountability of the study drug will be performed and verified by the CRA throughout the study and at the site closeout visit.

The investigator and/or named the sub-investigators agree not to supply study medication to any persons not enrolled in the study.

5.6 Discussion and Justification of Study Design

5.6.1 Discussion of Study Design and Choice of Control Groups

The design of this clinical trial was chosen to gather long-term safety and tolerability data for adalimumab in this subject population and to further evaluate the long-term effectiveness of adalimumab in the treatment of non-infectious uveitis.

5.6.2 Appropriateness of Measurements

Standard statistical, clinical, and laboratory procedures will be utilized in this study. All efficacy measurements in this study are standard for assessing disease activity in subjects with uveitis. All clinical and laboratory procedures in this study are standard and generally accepted.

5.6.3 Suitability of Subject Population

Subjects with uveitis who met the endpoint treatment failures or have successfully completed Study M10-877 or Study M10-880 may be eligible for this study. These subjects are candidates for systemic immunosuppressive therapy to allow reduction and/or discontinuation of corticosteroid therapy.

5.6.4 Selection of Doses in the Study

Dosing of adalimumab in this study is the same as that proposed in the parent Phase 3 Study M10-877 and Study M10-880. Since it will be unknown whether a subject entering

this study was randomized to adalimumab or placebo in the parent study, no loading dose will be given in this study.

In total, adalimumab has now been tested in clinical studies in over 29,000 subjects representing more than 56,000 patient years.

6.0 Complaints

A Complaint is any written, electronic, or oral communication that alleges deficiencies related to the physical characteristics, identity, quality, purity, potency, durability, reliability, safety, effectiveness, or performance of a product/device after it is released for distribution.

The investigational product in this trial contains both:

- Biologic compound(s) and
- Device component(s) (pre-filled syringe).

Complaints associated with any component of this investigational product must be reported to the Sponsor (Section 6.2.2). For adverse events, please refer to Sections 6.1 through 6.1.6. For product complaints, please refer to Section 6.2.

6.1 Medical Complaints

The Investigator will monitor each subject for clinical and laboratory evidence of adverse events on a routine basis throughout the study. The Investigator will assess and record any adverse event in detail including the date of onset, event diagnosis (if known) or sign/symptom, severity, time course, duration and outcome, relationship of the adverse event to study drug and any action(s) taken. For serious adverse events, if the investigator's opinion of possibly, probably not, or not related to study drug is given, an 'Other' cause of event must be provided by the investigator for the adverse event. For adverse events to be considered intermittent, the events must be of similar nature and

severity. Adverse events, whether in response to a query, observed by site personnel, or reported spontaneously by the subject will be recorded.

All adverse events will be followed to a satisfactory conclusion.

6.1.1 Definitions

6.1.1.1 Adverse Event

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not the event is considered causally related to the use of the product.

Such an event can result from use of the drug as stipulated in the protocol or labeling, as well as from accidental or intentional overdose, drug abuse, or drug withdrawal. Any worsening of a pre-existing condition or illness is considered an adverse event. Worsening in severity of a reported adverse event should be reported as a new adverse event. Laboratory abnormalities and changes in vital signs are considered to be adverse events only if they result in discontinuation from the study, necessitate therapeutic medical intervention, (meets protocol specific criteria [refer to Section 6.3 regarding toxicity management]) and/or if the Investigator considers them to be adverse events.

An elective surgery/procedure scheduled to occur during a study will not be considered an adverse event if the surgery/procedure is being performed for a pre-existing condition and the surgery/procedure has been preplanned prior to study entry. However, if the pre-existing condition deteriorates unexpectedly during the study (e.g., surgery performed earlier than planned), then, the deterioration of the condition for which the elective surgery/procedure is being done will be considered an adverse event.

6.1.1.1.1 Uveitis-Related Events

The following events are known complications related to the condition being treated and will be classified as uveitis-related events. These events will be analyzed separately from other adverse events in the final study report.

The following events are not a complete list of all potential uveitis-related events (e.g., choroidal thickening, choroidal detachment, retinal effusion, are not included but could possibly be events related to uveitis). The investigator must determine if a specific event is uveitis-related.

- Loss of transparency of the cornea
- Band keratopathy
- Synechiae
- Cataracts
- Glaucoma/increased intraocular pressure
- Vitreous hemorrhage
- Macular edema
- Retinal detachment
- Epiretinal membrane
- Vitreo-macular traction
- Retinal ischemia
- Vision loss
- Hypotony

6.1.1.2 Serious Adverse Events

If an adverse event meets any of the following criteria, it is to be reported to AbbVie as a serious adverse event (SAE) within 24 hours of the site being made aware of the serious adverse event.

Death of Subject	An event that results in the death of a subject.
Life-Threatening	An event that, in the opinion of the Investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
Hospitalization or Prolongation of Hospitalization	An event that results in an admission to the hospital for any length of time or prolongs the subject's hospital stay. This does not include an emergency room visit or admission to an outpatient facility.
Congenital Anomaly	An anomaly detected at or after birth, or any anomaly that results in fetal loss.
Persistent or Significant Disability/Incapacity	An event that results in a condition that substantially interferes with the activities of daily living of a study subject. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle).
Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome	An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of subject, life-threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Additionally, any elective or spontaneous abortion or stillbirth is considered an important medical event. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.
Spontaneous Abortion	Miscarriage experienced by study subject.

Elective Abortion	Elective abortion performed on study subject.

6.1.2 Adverse Event Severity

The Investigator will use the following definitions to rate the severity of each adverse event:

Mild	The adverse event is transient and easily tolerated by the subject.
Moderate	The adverse event causes the subject discomfort and interrupts the subject's usual activities.
Severe	The adverse event causes considerable interference with the subject's usual activities and may be incapacitating or life-threatening.

6.1.3 Relationship to Study Drug

The Investigator will use the following definitions to assess the relationship of the adverse event to the use of study drug:

Probably Related	An adverse event has a strong temporal relationship to study drug or recurs on re-challenge and an Other cause of event is unlikely or significantly less likely.
Possibly Related	An adverse event has a strong temporal relationship to the study drug and an Other cause of event is equally or less likely compared to the potential relationship to study drug.
Probably Not Related	An adverse event has little or no temporal relationship to the study drug and/or a more likely Other cause of event exists.
Not Related	An adverse event is due to an underlying or concurrent illness or effect of another drug and is not related to the study drug (e.g., has no temporal relationship to study drug or has a much more likely Other cause of event).

For causality assessments, events meeting the categories of probably or possibly related will be considered "associated." Events that are probably not or not related will be

considered "not associated." In addition, when the Investigator has not reported a causality or deemed it not assessable, AbbVie will consider the event associated.

If an Investigator's opinion of possibly, probably not, or not related to study drug is given, an 'Other' cause of event must be provided by the Investigator for the serious adverse event.

6.1.4 Adverse Event Collection Period

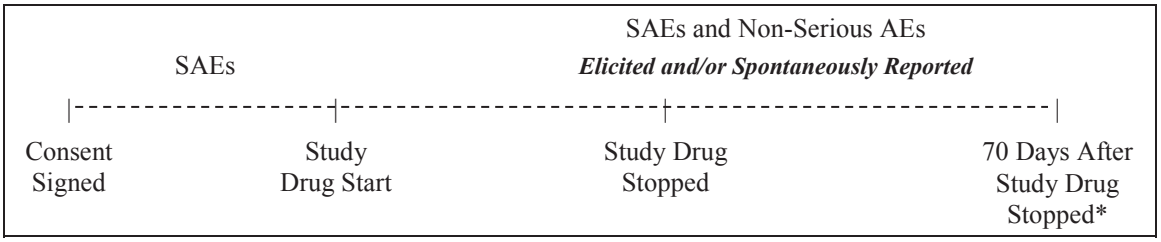
All adverse events reported from the time of study drug administration until 70 days, following discontinuation of study drug administration have elapsed will be collected, whether solicited or spontaneously reported by the subject. In addition, serious adverse events will be collected from the time the subject signs the study-specific informed consent if the subject does not have the Baseline visit on the same day. Any adverse events experienced prior to first study drug administration in M11-327 will be reported in the parent protocol. Adverse event information will be collected and recorded on the appropriate eCRFs. In the event of a death, the date and reason for death should be collected.

Subjects will be contacted approximately 70 days following study drug discontinuation for an assessment of any new or ongoing AEs except those subjects who continue on adalimumab therapy after the end of study participation. These subjects are not required to complete the 70-day follow-up and any new Adverse Events should be reported through the mechanism used for all post marketing adverse experiences.

There may be instances where a 70-day follow-up phone call or clinic visit occurs after the locking of the clinical database. In this situation, any adverse events reported to AbbVie from this 70-day follow-up phone call or clinic visit will be evaluated for inclusion in the clinical database. All SAEs or Adverse Events of Special Interest, as defined by AbbVie, reported during the 70-day follow-up phone call or clinic visit must be captured in the clinical database. The 70-day follow-up phone call will not be required for any subject that initiates commercial adalimumab after the end of study participation.

Adverse event information will be collected as shown in Figure 2.

Figure 2. Adverse Event Collection



* Except for subjects who continue on adalimumab therapy after the end of study participation.

6.1.5 Adverse Event Reporting

In the event of a serious adverse event, and additionally, any nonserious event of malignancy in subjects 30 years of age and younger, whether related to study drug or not, the investigator will notify Clinical Pharmacovigilance within 24 hours of the site being aware of the event by entering the serious adverse event or nonserious event of malignancy in subjects 30 years of age and younger data into the electronic data capture (EDC) system. Serious adverse events and nonserious events of malignancy in subjects 30 years of age and younger, that occur prior to the site having access to the RAVE system or if RAVE is not operable should be sent to Clinical Pharmacovigilance within 24 hours of site being made aware of the adverse event.

FAX to:	[redacted]
Email:	

For serious adverse event concerns, contact the Immunology Safety Team at:

Immunology Safety Team
Immunology Development
[redacted]
AbbVie
1 North Waukegan Road
North Chicago, IL 60064
USA

Fax:
Safety Hotline:
Email:
[redacted]

For any subject safety concerns, please contact the AbbVie Medical Monitors listed below:

For US, Canada, and Latin America:

[redacted]

For Europe, Israel, Australia and Japan:

[redacted]

Secondary Contact for Japan (Regional Medical Monitor):

[redacted]

[redacted] and [redacted] cover for each other. For any subject safety concerns or medical emergencies in which both medical monitors are unavailable, please call the following central back-up number:

Phone: [redacted]

In the EU, the sponsor will be responsible for Suspected Unexpected Serious Adverse Reactions (SUSAR) reporting for the Investigational Medicinal Product (IMP) in

accordance with Directive 2001/20/EC. The reference document used for SUSAR reporting in EU countries for adalimumab will be the most current version of the Investigator's Brochure.

6.1.6 Pregnancy

Pregnancy in a study subject must be reported to AbbVie within 1 working day of the site becoming aware of the pregnancy. Subjects who become pregnant during the study must be discontinued (Section 5.4.1). Pregnancies will be collected from the date of the first dose through 150 days following the last dose of study medication.

Information regarding a pregnancy occurrence in a study subject and the outcome of the pregnancy will be collected. Pregnancy in a study subject is not considered an AE. However, the medical outcome of an elective or spontaneous abortion, stillbirth or congenital anomaly is considered a SAE and must be reported to AbbVie within 24 hours of the site becoming aware of the event.

6.2 Product Complaint

6.2.1 Definition

A Product Complaint is any Complaint (see Section 6.0 for the definition) related to the biologic or drug component of the product or to the medical device component(s).

For a product this may include, but is not limited to, damaged/broken product or packaging, product appearance whose color/markings do not match the labeling, labeling discrepancies/inadequacies in the labeling/instructions (example: printing illegible), missing components/product, device not working properly, or packaging issues.

For medical devices, a product complaint also includes all deaths of a patient using the device, any illness, injury, or adverse event in the proximity of the device, an adverse event that could be a result of using the device, any event needing medical or surgical intervention including hospitalization while using the device and use errors.

Any information available to help in the determination of causality by the device to the events outlined directly above should be captured.

6.2.2 Reporting

Product Complaints concerning the investigational product and/or device must be reported to the Sponsor within 24 hours of the study site's knowledge of the event via the Product Complaint form. Product Complaints occurring during the study will be followed-up to a satisfactory conclusion. All follow-up information is to be reported to the Sponsor (or an authorized representative) and documented in source as required by the Sponsor. Product Complaints associated with adverse events will be reported in the study summary. All other complaints will be monitored on an ongoing basis.

Product Complaints may require return of the product with the alleged complaint condition (syringe). In instances where a return is requested, every effort should be made by the investigator to return the product within 30 days. If returns cannot be accommodated within 30 days, the site will need to provide justification and an estimated date of return.

The description of the complaint is important for AbbVie in order to enable AbbVie to investigate and determine if any corrective actions are required.

6.3 Toxicity Management

For the purpose of medical management, all adverse events and laboratory abnormalities that occur during the study must be evaluated by the Investigator. Subjects who develop a new infection while receiving study drug should be monitored closely. Administration of study injections should be interrupted if a subject develops an infection requiring IV anti-infective treatment or if an infection meets the definition of "serious" (refer to Section 6.1.1.2 for definitions). Study medication may be restarted once the physician determines that the infection has been successfully treated. Otherwise prohibited concomitant medications may be given if medically necessary. Prior to use, every attempt

should be made to contact the AbbVie Study Physician for direction on re-introduction of study drug after prohibited medication administration.

If the subject must undergo elective surgery, the study injections must be interrupted 2 weeks prior to the surgery. If the subject must undergo emergency surgery, the study injections must be interrupted at the time of the surgery. The injectable study medication can recommence at least 2 weeks after surgery once the physician has examined the surgical site and determined that it has healed and there is no sign of infection.

7.0 Protocol Deviations

AbbVie does not allow intentional/prospective deviations from the protocol. The Principal Investigator is responsible for complying with all protocol requirements, and applicable global and local laws regarding protocol deviations. If a protocol deviation occurs (or is identified) after a subject has been enrolled, the Principal Investigator is responsible for notifying Independent Ethics Committee (IEC)/Independent Review Board (IRB) regulatory authorities (as applicable), and the AbbVie Clinical Monitor(s) assigned to your site. Alternative contacts are as follows:

Alternate Contacts

North America, Latin America, and Japan	Europe, Israel, and Australia
[redacted]	

Such contact must be made as soon as possible to permit a review by AbbVie to determine the impact of the deviation on the subject and/or the study.

For purposes of this protocol, reportable deviations are defined as:

- Subject entered into the study even though they did not satisfy entry criteria
- Subject who developed withdrawal criteria during the study and was not withdrawn
- Subject who received wrong treatment or incorrect dose
- Subject who received excluded or prohibited concomitant treatment

8.0 Statistical Methods and Determination of Sample Size

8.1 Statistical Analysis Plans

The primary objective of the statistical analysis is to evaluate the long-term safety and efficacy of adalimumab 40 mg given every other week (eow) subcutaneously (SC) in subjects with non-infectious intermediate-, posterior-, or pan-uveitis who participated in Study M10-877 or Study M10-880. The following statistical analysis will be done in the total set of subjects. Efficacy analysis will be performed in the Intent to Treat (ITT) set. The safety analysis will be conducted in the Safety set.

The analysis strategy described below will be supplemented by a detailed statistical analysis plan (SAP) which will be completed prior to database lock.

8.1.1 Analysis Population

Both, the ITT set and the safety set include all subjects who received at least one dose of study medication.

No per protocol analysis will be done.

8.1.2 Planned Methods of Statistical Analysis

Descriptive statistics will be provided. These include the number of observations, means, standard deviation, minimum, 1st quartile, median, 3rd quartile, and maximum for

continuous variables; and counts and percentages for discrete variables. The analyses will be performed using SAS (SAS Institute Inc., Cary, NC, USA).

8.1.3 Analysis of Demographics and Baseline Characteristics

Demographics and Baseline characteristics of the study subjects will be summarized using descriptive statistics.

8.1.4 Analysis of Efficacy

All statistical analyses will be descriptive. Results will be stratified between subjects who entered into the study with active versus inactive uveitis. For subjects who had active uveitis when they entered the study, the efficacy analyses will start at Week 8. For subjects who had inactive uveitis when they entered the study, the efficacy analyses will start at Week 0. Continuous variables will be summarized by the number of non-missing observations, mean, standard deviation, median, quartiles, minimum and maximum. Categorical variables will be summarized by counts and percentages.

8.1.5 Analysis of Safety

Treatment-emergent AEs will be summarized using descriptive statistics. Treatment-emergent AEs are defined as events with an onset date on or after the first study drug administration until 70 days following the last study drug administration. In case of increasing severity of an existing AE, the worsening will be considered as a new AE with a new onset date.

AEs will be tabulated by system organ class and preferred term whereby the most current implemented MedDRA dictionary will be used. Also, summaries by severity and relationship to study drug will be done. Certain AEs, like serious or severe, leading to premature withdrawal, will be listed and described in detail. AEs of special interest for treatment with biologics will be defined in the SAP and analyzed separately.

Other safety variables like laboratory data and vital signs will be described by descriptive statistics as mentioned before. In addition, shift tables and listings will be provided for abnormal values whereby the normal range of the analyzing laboratory will be used.

The IDMC will undertake a comprehensive review and assessment of the cumulative safety data until the completion of Study M10-877 and Study M10-880. Please refer to Section 5.5.5.1 for additional information regarding IDMC review.

8.2 Determination of Sample Size

The sample size of this study will depend on how many subjects rollover into the extension study, who have either discontinued from M10-877 or M10-880 due to a "Treatment Failure" or have successfully completed M10-877 or M10-880.

9.0 Ethics

9.1 Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

Good Clinical Practice (GCP) requires that the clinical protocol, any protocol amendments, the Investigator's Brochure, the informed consent and all other forms of subject information related to the study (e.g., advertisements used to recruit subjects) and any other necessary documents be reviewed by an IEC/IRB. The IEC/IRB will review the ethical, scientific and medical appropriateness of the study before it is conducted. IEC/IRB approval of the protocol, informed consent and subject information and/or advertising, as relevant, will be obtained prior to the authorization of drug shipment to a study site.

Any amendments to the protocol will require IEC/IRB approval prior to implementation of any changes made to the study design. The Investigator will be required to submit, maintain and archive study essential documents according to ICH GCP.

Any serious adverse events that meet the reporting criteria, as dictated by local regulations, will be reported to both responsible Ethics Committees and Regulatory

Agencies, as required by local regulations. During the conduct of the study, the Investigator should promptly provide written reports (e.g., ICH Expedited Reports, and any additional reports required by local regulations) to the IEC/IRB of any changes that affect the conduct of the study and/or increase the risk to subjects. Written documentation of the submission to the IEC/IRB should also be provided to AbbVie.

9.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, ICH guidelines, applicable regulations and guidelines governing clinical study conduct and the ethical principles that have their origin in the Declaration of Helsinki, and all applicable local regulations. Responsibilities of the clinical investigator are specified in Appendix A.

9.3 Subject Information and Consent

The Investigator or his/her representative will explain the nature of the study to the subject, and answer all questions regarding this study. Prior to any study-related Baseline procedures being performed on the subject, the informed consent statement will be reviewed and signed and dated by the subject, the person who administered the informed consent, and any other signatories according to local requirements. A copy of the signed and dated informed consent form will be given to the subject and the original will be placed in the subject's medical record. An entry must also be made in the subject's dated source documents to confirm that informed consent was obtained prior to any study-related procedures and that the subject received a signed copy.

For subjects that complete or terminate early from the study, but are within the 70-day follow-up window: if an updated informed consent form is approved these subjects will not be required to return to the study site for the purposes of signing the updated informed consent form, provided the subject is contacted regarding the changes and there is documentation of the contact in the subject's source documents.

If the parent studies are prematurely stopped based upon the recommendation of the IDMC, and this recommendation is based on safety concerns, subjects will be required to return for their Final/Early Termination visit in Study M11-327.

10.0 Source Documents and Case Report Form Completion

10.1 Source Documents

Source documents are defined as original documents, data and records. This may include hospital records, clinical and office charts, laboratory data/information, subjects' diaries or evaluation checklists, pharmacy dispensing and other records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, and/or x-rays. Data collected during this study must be recorded on the appropriate source documents.

The investigator(s)/institution(s) will permit study-related monitoring, audits, IEC/IRB review, and regulatory inspection(s), providing direct access to source data documents.

The following assessments that will be completed by the subject or physician will be considered source documentation:

- NEI Visual Functioning Questionnaire (VFQ-25)
- EuroQol-5D Questionnaire (EQ-5D)
- Health Resource Utilization Questionnaire (HRU)
- Work Productivity and Activity Impairment, Questionnaire: Specific Health Problem Questionnaire (WPAI-SHP)

The adverse event eCRF data segments of: alternate etiology, severity, frequency and relationship to study drug, may also be used as source and will require an Investigator approval on the eCRF as verification of the accuracy of the information.

10.2 Case Report Forms

Electronic case report forms (eCRF) must be completed for each subject screened/enrolled in this study. These forms will be used to transmit information collected during the study to AbbVie and regulatory authorities, as applicable. The eCRF data for this study are being collected with an electronic data capture (EDC) system called Rave® provided by the technology vendor Medidata Solutions Incorporated, NY, USA. The EDC system and the study-specific electronic Case Report Forms (eCRFs) will comply with Title 21 CFR Part 11. The documentation related to the validation of the EDC system is available through the vendor, Medidata, while the validation of the study-specific eCRFs will be conducted by AbbVie and will be maintained in the Trial Master File at AbbVie.

The Investigator will document subject data in his/her own subject files. These subject files will serve as source data for the study. All eCRF data required by this protocol will be recorded by investigative site personnel in the EDC system. All data entered into the eCRF will be supported by source documentation. The central laboratory will send hard copies of laboratory results to sites which must be reviewed by the Investigator and filed as source data.

The Investigator or an authorized member of the Investigator's staff will make any necessary corrections to the eCRF. All change information, including the date and person performing the corrections, will be available via the audit trail, which is part of the EDC system. For any correction, a reason for the alteration will be provided. The eCRFs will be reviewed periodically for completeness, legibility, and acceptability by AbbVie personnel (or their representatives). AbbVie (or their representatives) will also be allowed access to all source documents pertinent to the study in order to verify eCRF entries. The Principal Investigator will review the eCRFs for completeness and accuracy and provide his or her electronic signature and date to eCRFs as evidence thereof.

Medidata will provide access to the EDC system for the duration of the trial through a password-protected method of internet access. Such access will be removed from investigator sites at the end of the site's participation in the study. Data from the EDC

system will be archived on appropriate data media (CD-ROM, etc.) and provided to the Investigator at that time as a durable record of the site's eCRF data. It will be possible for the Investigator to make paper printouts from that media.

The site will complete the VFQ-25 and HRU questionnaires via interview. The remaining questionnaires listed below will be completed by the subject, except when subjects with impaired vision cannot complete the questionnaires on their own, the site may administer the questionnaire. Except for the HRU which will be entered into EDC by the site, the subjects and site will enter responses on paper Case Report Forms provided by AbbVie and forwarded to AbbVie CDM for double data entry.

Any corrections to the questionnaires can only be made by the original respondent. All changed information, including the date and person performing the corrections, will be available via the audit trail.

- NEI Visual Functioning Questionnaire (VFQ-25)
- EuroQol-5D Questionnaire (EQ-5D)
- Health Resource Utilization Questionnaire (HRU)
- Work Productivity and Activity Impairment, Questionnaire: Specific Health Problem Questionnaire (WPAI-SHP)

11.0 Data Quality Assurance

Prior to the initiation of the study, a meeting will be held with AbbVie personnel, the Investigators and appropriate site personnel. This meeting will include a detailed discussion of the protocol, performance of study procedures, eCRF, Subject Questionnaires and Subject Diary completion, and specimen collection methods.

The AbbVie CRA will monitor each site throughout the study.

Source document verification will be performed.

All data entered in the database will be verified at AbbVie. Any discrepancies will be reviewed. The data will be reviewed and computer logic checks will be run to identify items such as inconsistent study dates. A manual review of selected line listings also will be performed at the end of the study. Queries will be generated in the EDC system. Any necessary corrections will be made to the eCRF.

The data from the central laboratory analyses will be electronically transferred from the central laboratory to the study database. A final review of all laboratory results will be conducted by a physician and clinical review team at AbbVie.

12.0 Use of Information and Publication

12.1 Use of Information

All information concerning adalimumab and AbbVie operations, such as AbbVie patent applications, formulas, manufacturing processes, basic scientific data, or formulation information, supplied by AbbVie and not previously published is considered confidential information.

The information developed during the conduct of this clinical trial is also considered confidential and will be used by AbbVie in connection with the development of adalimumab. This information may be disclosed as deemed necessary by AbbVie to other clinical Investigators, other pharmaceutical companies, to the FDA and to other government agencies. To allow for the use of the information derived from this clinical trial and to ensure complete and thorough analysis, the Investigator is obligated to provide AbbVie with complete test results and all data developed in this study and to provide direct access to source data/documents for trial-related monitoring, audits, IEC/IRB review, and regulatory inspection.

This confidential information shall remain the sole property of AbbVie, shall not be disclosed to others without the written consent of AbbVie, and shall not be used except in the performance of this study.

The Investigator will maintain a confidential subject identification code list of all subjects enrolled in the study (by name and subject number). This list will be maintained at the site and will not be retrieved by AbbVie.

Information regarding this study may be posted on various internet web sites and will maximally include study name, number, general population to be enrolled, entrance qualifications, brief description of the study, study objectives, doses, accruing Investigators (upon their approval) and number of subjects to be enrolled.

Please refer to your Investigator site contract for information related to publication practices.

13.0 Completion of the Study

The investigator will conduct the study in compliance with the protocol and complete the study within the timeframe specified in the contract between the investigator (Director of the Site in Japan) and AbbVie. Continuation of this study beyond this date must be mutually agreed upon in writing by both the investigator (Director of the Site in Japan) and AbbVie. The investigator will provide a final report to the IEC/IRB following conclusion of the study, and will forward a copy of this report to AbbVie or their representative.

The investigator (Director of the Site in Japan) must retain any records related to the study according to local requirements. If the investigator (Director of the Site in Japan) is not able to retain the records, he/she must notify AbbVie to arrange alternative archiving options.

AbbVie will select the signatory investigator from the investigators who participate in the study. Selection criteria for this investigator will include level of participation as well as significant knowledge of the clinical research, investigational drug and study protocol. The signatory investigator for the study will review and sign the final study report in accordance with the European Medicines Agency (EMA) Guidance on Investigator's Signature for Study Reports.

The end-of-study is defined as the date of the last subject's last scheduled visit or the actual date of follow-up contact, whichever is later.

AbbVie may terminate this study prematurely, for reasonable cause, provided that written notice is submitted a reasonable time in advance of the intended termination. Advance notice is not required if the study is stopped due to safety concerns.

14.0 Investigator's Agreement

1. I have received and reviewed the Investigator's Brochure for adalimumab.
2. I have read this protocol and agree that the study is ethical.
3. I agree to conduct the study as outlined and in accordance with all applicable regulations and guidelines.
4. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.
5. I agree that all electronic signatures will be considered the equivalent of a handwritten signature and will be legally binding.

Protocol Title:	A Multicenter Open-Label Study of the Long-term Safety and Efficacy of the Human Anti-TNF Monoclonal Antibody Adalimumab in Subjects with Non-infectious Intermediate-, Posterior-, or Pan-uveitis – VISUAL III
Protocol Date:	04 June 2015

Signature of Principal Investigator	Date
Name of Principal Investigator (printed or typed)	

15.0 Reference List

1. Mazurek GH, Jereb J, Vernon A, et al. Updated guidelines for using Interferon Gamma Release Assays to detect Mycobacterium tuberculosis infection – United States, 2010. MMWR Recomm Rep. 2010 Jun 25;59(RR-5):1-25.
2. Yanoff M, Duker JS, editors. Yanoff and Duker: Ophthalmology, 3rd ed. Elsevier Health Sciences; 2009.
3. Jabs DA, Nussenblatt RB, Rosenbaum JT. The standardization of uveitis nomenclature (SUN) working group. Standardization of uveitis nomenclature for reporting clinical data. Results of the First International Workshop. Am J Ophthalmol. 2005;140(3):509-16.
4. Rothova A, Suttorp-van Schulten MS,Treffers WF, Kijlstra A. Causes and frequency of blindness in patients with intraocular inflammatory disease. Br J Ophthalmol. 1996;80(4):332-6.
5. Wakefield D, Chang JH. International Ophthalmology Clinics. 2005 Spring 45(2):1-13.
6. Jabs DA, Rosenbaum JT, Foster CS, Holland GN, Jaffe GJ, Louie JS, 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):492-513.
7. Cervantes-Castaneda RA, Jawed N, Foster CS. Immunosuppressive therapy for noninfectious uveitis. Retinal Physician. 2007;March:30-8.
8. Becker MD, Smith JR, Max R, Fiehn C. Management of sight-threatening uveitis: new therapeutic options. Drugs. 2005;65(4):497-519.
9. Smith JR, Rosenbaum JT. Management of Uveitis: A rheumatologic perspective. Arthritis Rheum. 2002;46(2):309-18.
10. Nussenblatt R. The natural history of uveitis. Int Ophthalmology. 1990;14:303-8.
11. Retisert (fluocinolone acetonide intravitreal implant [Package Insert]. Rochester, NY: Bausch & Lomb; 2007.

12. Jaffe GJ, Martin D, Callanan D, Pearson PA, Levy B. Fluocinolone acetonide implant (Retisert) for noninfectious posterior uveitis: Thirty-four-week results of a multicenter randomized clinical study. Ophthalmology. 2006;113:1020-7.
13. Callanan DG, Jaffe GJ, Martin DF, Pearson PA, Comstock TL. Treatment of posterior uveitis with a fluocinolone acetonide implant: Three-year clinical trial results. Arch Ophthalmol. 2008;126(9):1191-1201.
14. Caspi RR, Sun B, Agarwal RK. T cell mechanisms in experimental autoimmune uveoretinitis: susceptibility is a function of the cytokine response profile. Eye. 1997;11:209-12.
15. Murphy CC, Duncan L, Forrester JV, Dick AD. Systemic CD4+ T cell phenotype and activation status in intermediate uveitis. Br J Ophthalmol. 2004;88:412-6.
16. Deschenes J, Char DH, Kaleta S. Activated T lymphocytes in uveitis. Br J Ophthalmol. 1988;72:83-7.
17. Dick AD, Forrester JV, Liversidge J, Cope AP. The role of tumour necrosis factor (TNF-a) in experimental autoimmune uveoretinitis (EAU). Progress in Retinal and Eye Research. 2004;23:617-37.
18. Okada AA, Sakai J, Usui M, Mizuguchi J. Intraocular cytokine quantification of experimental autoimmune uveoretinitis in rats. Ocular Immunology and Inflammation. 1998;6(2):111-20.
19. Sartani G, Silver PB, Rizzo LV, Chan C, Wiggert B, Mastorakos G, et al. Anti-tumor necrosis factor alpha therapy suppresses the induction of experimental autoimmune uveoretinitis in mice by inhibiting antigen priming. Invest Ophthalmol Vis Sci. 1996;37:2211-8.
20. Dick AD, Duncan L, Hale G, Waldmann H, Isaacs J. Neutralizing TNF-alpha activity modulates T-cell phenotype and function in experimental autoimmune uveoretinitis. J of Autoimmunity. 1998;11:255-64.
21. Callejas-Rubio JL, Sánchez-Cano D, García Serrano JL, Ortego-Centeno N. Letter to the Editor: Adalimumab therapy for refractory uveitis: A pilot study. J Ocul Pharmac Ther. 2008;24(6):613-4.

22. Mushtaq B, Saeed T, Situnayake RD, Murray PI. Adalimumab for sight-threatening uveitis in Behcet's disease. Eye. 2007;21:824-5.

23. Diaz-Llopis M, Garcia-Delpech S, Salom D, Udaondo P, Hernandez-Garfella M, Bosch-Morell F, et al. Adalimumab therapy for refractory uveitis: A pilot study. J Ocul Pharmacol Ther. 2008;24:351-61.

24. Vazquez-Cobian LB, Flynn T, Lehman TJA. Adalimumab therapy for childhood uveitis. J Pediatr. 2006;149:572-5.

25. Tognon S, Graziani G, Marcolongo R. Anti-TNF-Therapy in seven patients with Behcet's uveitis: advantages and controversial aspects. Ann. N.Y. Acad. Sci. 2007;1110:474-84.

26. Saurenmann RK, Levin AV, Rose JB, Parker S, Rabinovitch T. Tumour necrosis factor a inhibitors in the treatment of childhood uveitis. Rheumatology. 2006;45:982-9.

27. Niccoli L, Nannini C, Benucci M, Chindamo C, Cassara E. Long-term efficacy of infliximab in refractory posterior uveitis of Behcet's disease: a 24-month follow-up study. Rheumatology. 2007;46:1161-4.

28. Lindstedt EW, Baarsma GS, Kuijpers RWAM, van Hagen PM. Anti-TNF-a therapy for sight threatening uveitis. Br J Ophthalmol. 2005;89:533-6.

29. Suhler EB, Smith JR, Wertheim MS, Lauer AK, Kurz DE. A prospective trial of infliximab therapy for refractory uveitis. Arch Ophthalmol. 2005;123:903-12.

30. Suhler EB, Smith JR, Giles TR, Lauer AK, Wertheim MS. Infliximab therapy for refractory uveitis: 2-year results of a prospective trial. Arch Ophthalmol. 2009;127(6):819-22.

31. Schmeling H, Horneff G. Etanercept and uveitis in patients with juvenile idiopathic arthritis. Rheumatology. 2005;44:1008-11.

32. Foster CS, Tufail F, Waheed NK, Chu D, Miserocchi E. Efficacy of etanercept in preventing relapse of uveitis controlled by methotrexate. Arch Ophthalmol. 2003;121(4):437-40.

33. Jakob E, Reuland MS, Mackensen F, Harsch N, Fleckenstein M, Lorenz HM, et al. Uveitis subtypes in a german interdisciplinary uveitis center – analysis of 1916 patients. J Rheumatol. 2009;36(1):127-36.

34. Biester S, Deuter C, Michels H, Haefner R, Kuemmerle-Deschner J, Doycheva D, et al. Adalimumab in the therapy of uveitis in childhood. Br J Ophthalmol. 2007;91:319-24.

35. Rudwaleit M, Rodevand E, Holck P, Vanhoof J, Kron M, Kary S, et al. Adalimumab effectively reduces the rate of anterior uveitis flares in patients with active ankylosing spondylitis. Ann Rheum Dis. 2009;68:696-701.

36. Suhler EB, Goldstein DA, Lowder CY, Giles TR, Liesegang TL. Adalimumab (Humira) for the treatment of refractory uveitis: preliminary results of a multicenter prospective phase II clinical trial. Oral Presentation, Association of Research in Vision and Ophthalmology annual meeting. Fort Lauderdale, FL. 2009.

37. The Age-Related Eye Diseases Study Group. The age-related eye disease study (AREDS) system for classifying cataracts from photographs: AREDS report no. 4. Am J Ophthalmol. 2001 Feb;131(2):167-75.

38. Chew EY, Kim J, Sperduto R, Datiles MB III, Coleman H, Smith J, et al. Evaluation of the Age-Related Eye Disease Study (AREDS) Clinical Lens Grading System. Accepted for publication in Ophthalmology.

39. Nussenblatt RB, Palestine AG, Chan C, Roberge F. Standardization of vitreal inflammatory activity in intermediate and posterior uveitis. Ophthalmology. 1985;92:467-71.

40. Nussenblatt RB, Peterson JS, Foster CS, Rao NA, See RF. Initial Evaluation of Subcutaneous Daclizumab Treatments for Noninfectious Uveitis. Ophthalmology. 2005;112:764-770.

41. Díaz-Llopis M, Salom D, Garcia-de-Vicuña C, et al. Treatment of refractory uveitis with adalimumab: a prospective multicenter study of 131 patients. Ophthalmology. 2012;119(8):1575-81.

Appendix A. Responsibilities of the Clinical Investigator

Clinical research studies sponsored by AbbVie are subject to the Good Clinical Practices (GCP) and local regulations and guidelines governing the study at the site location. In signing the Investigator Agreement in Section 14.0 of this protocol, the Investigator is agreeing to the following:

1. Conducting the study in accordance with the relevant, current protocol, making changes in a protocol only after notifying AbbVie, except when necessary to protect the safety, rights or welfare of subjects.
2. Personally conducting or supervising the described investigation(s).
3. Informing all subjects, or persons used as controls, that the drugs are being used for investigational purposes and complying with the requirements relating to informed consent and ethics committees [e.g., independent ethics committee (IEC) or institutional review board (IRB)] review and approval of the protocol and amendments.
4. Reporting adverse experiences that occur in the course of the investigation(s) to AbbVie and the site director.
5. Reading the information in the Investigator's Brochure/safety material provided, including the instructions for use and the potential risks and side effects of the investigational product(s).
6. Informing all associates, colleagues, and employees assisting in the conduct of the study about their obligations in meeting the above commitments.
7. Maintaining adequate and accurate records of the conduct of the study, making those records available for inspection by representatives of AbbVie and/or the appropriate regulatory agency, and retaining all study-related documents until notification from AbbVie.
8. Maintaining records demonstrating that an ethics committee reviewed and approved the initial clinical investigation and all amendments.

9. Reporting promptly, all changes in the research activity and all unanticipated problems involving risks to human subjects or others, to the appropriate individuals (e.g., coordinating Investigator, institution Director) and/or directly to the ethics committees and AbbVie.

10. Following the protocol and not making any changes in the research without ethics committee approval, except where necessary to eliminate apparent immediate hazards to human subjects.

Appendix B. List of Protocol Signatories

Name	Title	Functional Area
[redacted]		Clinical
		Clinical
		Statistics
		Clinical

Appendix C. Non-Drug Materials Provided to the Study Sites

Study sites will receive the following supplies prior to or during the study:

- Tote Bags
- Coolers
- Sharps Containers
- Ice Packs
- Subject Dosing Diary

Appendix D. Day 70 Follow-up (Phone Call or Clinic Visit)

Site Name/Number: _____/_____

Subject Number: _____

Please contact all subjects approximately 70 days following last study drug administration.

Date of Call/Visit: _____

☐ Lost to Follow-up (Please check this box if subject was not willing to provide any follow-up information or you were unable to speak to the subject following at least two phone call attempts and one certified letter).

☐ No Events Reported

List any Adverse Events (AE) and/or Serious Adverse Events (SAE) that occurred since the subject's last study drug administration. Please document all adverse events on a 500 AE CRF in the EDC system. (Please report all SAEs to AbbVie within 24 hours of being made aware of the event). **In addition, please note stop dates to any adverse events that were ongoing at the last study visit. If an adverse event is determined to be ongoing at the 70 day call/visit, please note in source documents and in EDC.**

_____	_____
_____	_____
_____	_____
_____	_____

Name of person completing form (printed): _____

Signature of person completing form: _____

Date: _____

Please fax this form to AbbVie at [redacted]

Appendix E. Subject Dosing Diary

M11 – 327
Subject Diary

Subject Number: _____

Subject Injection Instructions

0.8 mL dose

(Administered as a single dose-pre-filled syringe)

Protocol M11-327

Table of Contents

Dosing Schedule

General Information and Supplies

Injection Procedures

Study Drug Dosing Schedule

Subject Number: _____

You will require subcutaneous (SC) injections throughout the study.

At the Baseline visit and at Week 4 and Week 8 you will be dispensed 1 kit that includes 2 syringes. All of these syringes will be injected on the appropriate dosing weeks as instructed by the investigator.

At Week 12 you will be dispensed 2 kits that include 2 syringes each. The clinic will remove one syringe for return to Abbott and administer one injection for your Week 12 dose. You will take home 2 syringes for dosing at Weeks 14 and 16.

Starting at Week 18 and throughout the remainder of the study you will be dispensed 3 kits that include 2 syringes each. These are all the injections you will need until your next study visit 12 weeks later. All of these syringes are to be injected at the appropriate dosing weeks.

You will be supplied with a tote bag in which to carry your syringes home. Please return all used and unused syringes and empty boxes to the clinic on your next visit. Used syringes should be placed in the special sharps container provided. All unused syringes should be returned in the original box.

If an injection is missed or something occurs where the full dose cannot be injected, contact your study center immediately for further instructions. Please record any missed doses on your Subject Dosing Diary.

Remember to complete your dosing sheet after each injection and to call the doctor's office if you are having problems administering your study medication.

General Information

- Pre-filled syringes will be labeled "Adalimumab 40mg /0.8mL Solution for Injection".
- Store all adalimumab pre-filled syringes in your refrigerator NOT in the freezer. Should the syringes accidentally become frozen, call your study doctor's office.
- Study medication should be taken at about the same time of day, on the same day of the week as directed by your study doctor.

- **USE A NEW SYRINGE EVERY INJECTION DAY.** There may be medication left in the syringe. **DO NOT RE-USE.**
- Save all study medications. ***Pre-filled syringes (used and unused) & empty boxes must be returned to the study center at each visit.*** Used syringes will be disposed of in a sharps container provided to you.
- Call your doctor IMMEDIATELY if you experience any itching, hives, shortness of breath, or any symptom that has you concerned. If you are unable to reach your doctor or if you experience life-threatening symptoms **call**, _____ or proceed to your nearest emergency room.

Injection Procedures (PFS)

1. Setting up for an injection

- Find a clean flat surface.
- Do not use if the seals on the carton are broken or missing. Contact your study doctor's office if the seals are broken.
- Take one kit with the prefilled syringe(s) of adalimumab from the refrigerator. Do not use a prefilled syringe that has been frozen or if it has been left in direct sunlight.
- Return any unused syringe(s) to the refrigerator.

You will need the following items for each dose:

- study medication in pre-filled syringe(s)
- alcohol prep(s)
- cotton ball or gauze pad(s)

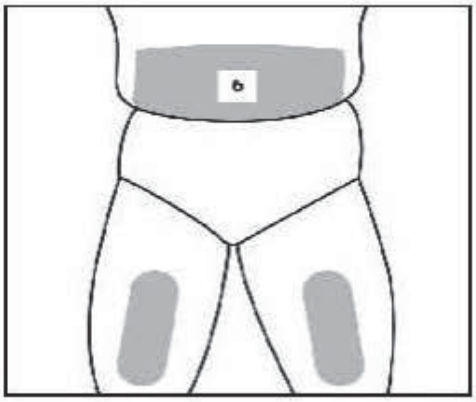
If you do not have all of the items you need to give yourself an injection, call your study physician. Use only the items provided in the box your adalimumab comes in.

- Make sure the liquid in the prefilled syringe is clear and colorless. Do not use a prefilled syringe if the liquid is cloudy or discolored or has flakes or particles in it.

- Have a special sharps (puncture proof) container nearby for disposing of used needles and syringes.

For your protection, it is important that you follow these instructions.

2. Choosing and preparing an injection site



- Wash your hands well.
- Choose a site on the front of your thighs or your stomach area (abdomen). If you choose your abdomen, you should avoid the area 5 cm (2 in) around your belly button (navel).
- Choose a different site each time you give yourself an injection. Each new injection should be given at least 2.5 cm (1 in) from a site you used before. Never inject into areas where the skin is tender, bruised, red or hard or where you have scars or stretch marks.
- If you have psoriasis, you should try not to inject directly into any raised, thick, red or scaly skin patches or lesions.
- You may find it helpful to keep notes on the location of your injection sites.
- Wipe the site where adalimumab is to be injected with an alcohol prep (swab), using a circular motion. Do not touch this area again until you are ready to inject.

3. How to prepare your adalimumab dose for injection with a Prefilled Syringe

- Hold the syringe upright with the needle facing down. Check to make sure that the amount of liquid in the syringe is the same or close to the 0.8 mL line for the 40 mg prefilled syringe. The top of the liquid may be curved. If the syringe does not have the correct amount of liquid, do not use that syringe. Call your study doctor.
- Remove the needle cover taking care not to touch the needle with your fingers or allow it to touch any surface.
- Turn the syringe so the needle is facing up and slowly push the plunger in to push the air in the syringe out through the needle. If a small drop of liquid comes out of the needle that is okay.
- Do not shake the syringe.

4. Injecting Adalimumab

- With your other hand, gently squeeze an area of the cleaned area of skin and hold it firmly.
- You will inject into this raised area of skin. Hold the syringe like a pencil at about a 45° angle (see picture) to the skin.
- With a quick, short, "dart-like" motion, push the needle into the skin.
- After the needle is in, let go of the skin. Pull back slightly on the plunger. If blood appears in the syringe it means that you have entered a blood vessel. Do not inject adalimumab. Pull the needle out of the skin and repeat the steps to choose and clean a new injection site. Do not use the same syringe. Dispose of it in your special sharps container. If no blood appears, slowly push the plunger all the way in until all of the adalimumab is injected.
- When the syringe is empty, remove the needle from the skin keeping it at the same angle it was when it was pushed into the skin.
- Press a cotton ball or gauze pad over the injection site and hold it for 10 seconds. Do not rub the injection site. You may have slight bleeding. This is normal.
- Dispose of the syringe right away into your special sharps container.

Dosing Diary
Adalimumab

Instructions: To be completed for every study dose. Study medication should be taken at about the same time of day, on the same day of the week as directed by your study doctor. Please refer to the Self Injection Instructions provided to you for additional dosing information. Call the doctor's office if you are having problems administering your study medication.

M11-327

___-___ ___-___ ___-___ ___
Subject Identification Number

Adalimumab Dosing Diary

Date	Week #	Kit Number	Time of Study Drug Administration	Was the entire volume injected? (Y/N)	Initials of Person Administering Study Medication	Comments
19-Mar-13	EXAMPLE	101010	9:35	Y	MM	none
	Study Entry					
	Week 2					
	Week 4					
	Week 6					
	Week 8					

20120312 Dosing Diary Uveitis
White Copy (site)

Abbott Laboratories

Adalimumab Dosing
Yellow Copy (diary)

M11-327

___-___ ___-___ ___-___ ___
Subject Identification Number

Adalimumab Dosing Diary

Date	Week #	Kit Number	Time of Study Drug Administration	Was the entire volume injected? (Y/N)	Initials of Person Administering Study Medication	Comments
19-Mar-13	EXAMPLE	101010	9:35	Y	MM	none
	Week 10					
	Week 12					
	Week 14					
	Week 16					
	Week 18					

20120312 Dosing Diary Uveitis
White Copy (site)

Abbott Laboratories

Adalimumab Dosing
Yellow Copy (diary)

M11-327

___-___ ___-___ ___-___ ___-___
Subject Identification Number

Adalimumab Dosing Diary

Date	Week #	Kit Number	Time of Study Drug Administration	Was the entire volume injected? (Y/N)	Initials of Person Administering Study Medication	Comments
19-Mar-13	EXAMPLE	101010	9:35	Y	MM	none
	Week 20					
	Week 22					
	Week 24					
	Week 26					
	Week 28					
	Week 30					

20120312 Dosing Diary Uveitis
White Copy (site)

Abbott Laboratories

Adalimumab Dosing
Yellow Copy (diary)

M11-327

___-___ ___-___ ___-___ ___-___
Subject Identification Number

Adalimumab Dosing Diary

Date	Week #	Kit Number	Time of Study Drug Administration	Was the entire volume injected? (Y/N)	Initials of Person Administering Study Medication	Comments
19-Mar-13	EXAMPLE	101010	9:35	Y	MM	none
	Week 32					
	Week 34					
	Week 36					
	Week 38					
	Week 40					
	Week 42					

20120312 Dosing Diary Uveitis
White Copy (site)

Abbott Laboratories

Adalimumab Dosing
Yellow Copy (diary)

M11-327

___-___ ___-___ ___-___ ___-___
Subject Identification Number

Adalimumab Dosing Diary

Date	Week #	Kit Number	Time of Study Drug Administration	Was the entire volume injected? (Y/N)	Initials of Person Administering Study Medication	Comments
19-Mar-13	EXAMPLE	101010	9:35	Y	MM	none
	Week 44					
	Week 46					
	Week 48					
	Week 50					
	Week 52					
	Week 54					

20120312 Dosing Diary Uveitis
White Copy (site)

Abbott Laboratories

Adalimumab Dosing
Yellow Copy (diary)

M11-327

___-___ ___-___ ___-___ ___-___
Subject Identification Number

Adalimumab Dosing Diary

Date	Week #	Kit Number	Time of Study Drug Administration	Was the entire volume injected? (Y/N)	Initials of Person Administering Study Medication	Comments
19-Mar-13	EXAMPLE	101010	9:35	Y	MM	none
	Week 56					
	Week 58					
	Week 60					
	Week 62					
	Week 64					
	Week 66					

20120312 Dosing Diary Uveitis
White Copy (site)

Abbott Laboratories

Adalimumab Dosing
Yellow Copy (diary)

M11-327

___-___ ___-___ ___-___ ___-___
Subject Identification Number

Adalimumab Dosing Diary

Date	Week #	Kit Number	Time of Study Drug Administration	Was the entire volume injected? (Y/N)	Initials of Person Administering Study Medication	Comments
19-Mar-13	EXAMPLE	101010	9:35	Y	MM	none
	Week 68					
	Week 70					
	Week 72					
	Week 74					
	Week 76					
	Week 78					
	Week 80					
	Week 82					

20120312 Dosing Diary Uveitis
White Copy (site)

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Adalimumab Dosing
Yellow Copy (diary)

M11-327

___-___ ___-___ ___-___ ___-___
Subject Identification Number

Adalimumab Dosing Diary

Date	Week #	Kit Number	Time of Study Drug Administration	Was the entire volume injected? (Y/N)	Initials of Person Administering Study Medication	Comments
19-Mar-13	EXAMPLE	101010	9:35	Y	MM	none
	Week 84					
	Week 86					
	Week 88					
	Week 90					
	Week 92					
	Week 94					
	Week 96					
	Week 98					

20120312 Dosing Diary Uveitis
White Copy (site)

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Adalimumab Dosing
Yellow Copy (diary)

M11-327

___-___ ___-___ ___-___ ___
Subject Identification Number

Adalimumab Dosing Diary

Date	Week #	Kit Number	Time of Study Drug Administration	Was the entire volume injected? (Y/N)	Initials of Person Administering Study Medication	Comments
19-Mar-13	EXAMPLE	101010	9:35	Y	MM	none
	Week 100					
	Week 102					
	Week 104					
	Week 106					
	Week 108					
	Week 110					
	Week 112					
	Week 114					

20120312 Dosing Diary Uveitis
White Copy (site)

Abbott Laboratories

Adalimumab Dosing
Yellow Copy (diary)

M11-327

___-___ ___-___ ___-___ ___-___
Subject Identification Number

Adalimumab Dosing Diary

Date	Week #	Kit Number	Time of Study Drug Administration	Was the entire volume injected? (Y/N)	Initials of Person Administering Study Medication	Comments
19-Mar-13	EXAMPLE	101010	9:35	Y	MM	none
	Week 116					
	Week 118					
	Week 120					
	Week 122					
	Week 124					
	Week 126					
	Week 128					
	Week 130					

20120312 Dosing Diary Uveitis
White Copy (site)

Abbott Laboratories

Adalimumab Dosing
Yellow Copy (diary)

M11-327

___-___ ___-___ ___-___ ___-___
Subject Identification Number

Adalimumab Dosing Diary

Date	Week #	Kit Number	Time of Study Drug Administration	Was the entire volume injected? (Y/N)	Initials of Person Administering Study Medication	Comments
19-Mar-13	EXAMPLE	101010	9:35	Y	MM	none
	Week 132					
	Week 134					
	Week 136					
	Week 138					
	Week 140					
	Week 142					
	Week 144					
	Week 146					

20120312 Dosing Diary Uveitis
White Copy (site)

Abbott Laboratories

Adalimumab Dosing
Yellow Copy (diary)

M11-327

___-___ ___-___ ___-___ ___-___
Subject Identification Number

Adalimumab Dosing Diary

Date	Week #	Kit Number	Time of Study Drug Administration	Was the entire volume injected? (Y/N)	Initials of Person Administering Study Medication	Comments
19-Mar-13	EXAMPLE	101010	9:35	Y	MM	none
	Week 148					
	Week 150					
	Week 152					
	Week 154					
	Week 156					
	Week 158					
	Week 160					
	Week 162					

20120312 Dosing Diary Uveitis
White Copy (site)

Abbott Laboratories

Adalimumab Dosing
Yellow Copy (diary)

M11-327

___-___ ___-___ ___-___ ___-___
Subject Identification Number

Adalimumab Dosing Diary

Date	Week #	Kit Number	Time of Study Drug Administration	Was the entire volume injected? (Y/N)	Initials of Person Administering Study Medication	Comments
19-Mar-13	EXAMPLE	101010	9:35	Y	MM	none
	Week 164					
	Week 166					
	Week 168					
	Week 170					
	Week 172					
	Week 174					
	Week 176					
	Week 178					

20120312 Dosing Diary Uveitis
White Copy (site)

Abbott Laboratories

Adalimumab Dosing
Yellow Copy (diary)

M11-327

___-___ ___-___ ___-___ ___-___
Subject Identification Number

Adalimumab Dosing Diary

Date	Week #	Kit Number	Time of Study Drug Administration	Was the entire volume injected? (Y/N)	Initials of Person Administering Study Medication	Comments
19-Mar-13	EXAMPLE	101010	9:35	Y	MM	none
	Week 180					
	Week 182					
	Week 184					
	Week 186					
	Week 188					
	Week 190					
	Week 192					
	Week 194					

20120312 Dosing Diary Uveitis
White Copy (site)

Abbott Laboratories

Adalimumab Dosing
Yellow Copy (diary)

M11-327

___-___ ___-___ ___-___ ___-___
Subject Identification Number

Adalimumab Dosing Diary

Date	Week #	Kit Number	Time of Study Drug Administration	Was the entire volume injected? (Y/N)	Initials of Person Administering Study Medication	Comments
19-Mar-13	EXAMPLE	101010	9:35	Y	MM	none
	Week 196					
	Week 198					
	Week 200					
	Week 202					
	Week 204					
	Week 206					
	Week 208					
	Week 210					

20120312 Dosing Diary Uveitis
White Copy (site)

Abbott Laboratories

Adalimumab Dosing
Yellow Copy (diary)

M11-327

___-___ ___-___ ___-___ ___-___
Subject Identification Number

Adalimumab Dosing Diary

Date	Week #	Kit Number	Time of Study Drug Administration	Was the entire volume injected? (Y/N)	Initials of Person Administering Study Medication	Comments
19-Mar-13	EXAMPLE	101010	9:35	Y	MM	none
	Week 212					
	Week 214					
	Week 216					
	Week 218					
	Week 220					
	Week 222					
	Week 224					
	Week 226					

20120312 Dosing Diary Uveitis
White Copy (site)

Abbott Laboratories

Adalimumab Dosing
Yellow Copy (diary)

M11-327

___-___ ___-___ ___-___ ___-___
Subject Identification Number

Adalimumab Dosing Diary

Date	Week #	Kit Number	Time of Study Drug Administration	Was the entire volume injected? (Y/N)	Initials of Person Administering Study Medication	Comments
19-Mar-13	EXAMPLE	101010	9:35	Y	MM	none
	Week 228					
	Week 230					
	Week 232					
	Week 234					
	Week 236					
	Week 238					
	Week 240					
	Week 242					

20120312 Dosing Diary Uveitis
White Copy (site)

Abbott Laboratories

Adalimumab Dosing
Yellow Copy (diary)

M11-327

___-___ ___-___ ___-___ ___-___
Subject Identification Number

Adalimumab Dosing Diary

Date	Week #	Kit Number	Time of Study Drug Administration	Was the entire volume injected? (Y/N)	Initials of Person Administering Study Medication	Comments
19-Mar-13	EXAMPLE	101010	9:35	Y	MM	none
	Week 244					
	Week 246					
	Week 248					
	Week 250					
	Week 252					
	Week 254					
	Week 256					
	Week 258					

20120312 Dosing Diary Uveitis
White Copy (site)

Abbott Laboratories

Adalimumab Dosing
Yellow Copy (diary)

M11-327

___-___ ___-___ ___-___ ___-___ ___-___ ___-___
Subject Identification Number

Adalimumab Dosing Diary

Date	Week #	Kit Number	Time of Study Drug Administration	Was the entire volume injected? (Y/N)	Initials of Person Administering Study Medication	Comments
19-Mar-13	EXAMPLE	101010	9:35	Y	MM	none
	Week 260					
	Week 262					
	Week 264					
	Week 266					
	Week 268					
	Week 270					
	Week 272					
	Week 274					

20120312 Dosing Diary Uveitis
White Copy (site)

Abbott Laboratories

Adalimumab Dosing
Yellow Copy (diary)

M11-327

___-___ ___-___ ___-___ ___
Subject Identification Number

Adalimumab Dosing Diary

Date	Week #	Kit Number	Time of Study Drug Administration	Was the entire volume injected? (Y/N)	Initials of Person Administering Study Medication	Comments
19-Mar-13	EXAMPLE	101010	9:35	Y	MM	none
	Week 276					
	Week 278					
	Week 280					
	Week 282					
	Week 284					
	Week 286					
	Week 288					
	Week 290					

20120312 Dosing Diary Uveitis
White Copy (site)

Abbott Laboratories

Adalimumab Dosing
Yellow Copy (diary)

M11-327

___-___ ___-___ ___-___ ___
Subject Identification Number

Adalimumab Dosing Diary

Date	Week #	Kit Number	Time of Study Drug Administration	Was the entire volume injected? (Y/N)	Initials of Person Administering Study Medication	Comments
19-Mar-13	EXAMPLE	101010	9:35	Y	MM	none
	Week 292					
	Week 294					
	Week 296					
	Week 298					
	Week 300					
	Week 302					
	Week 304					
	Week 306					

20120312 Dosing Diary Uveitis
White Copy (site)

Abbott Laboratories

Adalimumab Dosing
Yellow Copy (diary)

M11-327

___-___ ___-___ ___-___ ___
Subject Identification Number

Adalimumab Dosing Diary

Date	Week #	Kit Number	Time of Study Drug Administration	Was the entire volume injected? (Y/N)	Initials of Person Administering Study Medication	Comments
19-Mar-13	EXAMPLE	101010	9:35	Y	MM	none
	Week 308					
	Week 310					
	Week 312					
	Week 314					
	Week 316					
	Week 318					
	Week 320					
	Week 322					

20120312 Dosing Diary Uveitis
White Copy (site)

Abbott Laboratories

Adalimumab Dosing
Yellow Copy (diary)

M11-327

___-___ ___-___ ___-___ ___
Subject Identification Number

Adalimumab Dosing Diary

Date	Week #	Kit Number	Time of Study Drug Administration	Was the entire volume injected? (Y/N)	Initials of Person Administering Study Medication	Comments
19-Mar-13	EXAMPLE	101010	9:35	Y	MM	none
	Week 324					
	Week 326					
	Week 328					
	Week 330					
	Week 332					
	Week 334					
	Week 336					
	Week 338					

20120312 Dosing Diary Uveitis
White Copy (site)

Abbott Laboratories

Adalimumab Dosing
Yellow Copy (diary)

M11-327

___-___ ___-___ ___-___ ___
Subject Identification Number

Adalimumab Dosing Diary

Date	Week #	Kit Number	Time of Study Drug Administration	Was the entire volume injected? (Y/N)	Initials of Person Administering Study Medication	Comments
19-Mar-13	EXAMPLE	101010	9:35	Y	MM	none
	Week 340					
	Week 342					
	Week 344					
	Week 346					
	Week 348					
	Week 350					
	Week 352					
	Week 354					

20120312 Dosing Diary Uveitis
White Copy (site)

Abbott Laboratories

Adalimumab Dosing
Yellow Copy (diary)

M11-327

___-___ ___-___ ___-___ ___
Subject Identification Number

Adalimumab Dosing Diary

Date	Week #	Kit Number	Time of Study Drug Administration	Was the entire volume injected? (Y/N)	Initials of Person Administering Study Medication	Comments
19-Mar-13	EXAMPLE	101010	9:35	Y	MM	none
	Week 356					
	Week 358					
	Week 360					
	Week 362					
	Week 364					
	Week 366					
	Week 368					
	Week 370					

20120312 Dosing Diary Uveitis
White Copy (site)

Abbott Laboratories

Adalimumab Dosing
Yellow Copy (diary)

M11-327

___-___ ___-___ ___-___ ___
Subject Identification Number

Adalimumab Dosing Diary

Date	Week #	Kit Number	Time of Study Drug Administration	Was the entire volume injected? (Y/N)	Initials of Person Administering Study Medication	Comments
19-Mar-13	EXAMPLE	101010	9:35	Y	MM	none
	Week 372					
	Week 374					
	Week 376					
	Week 378					
	Week ___					
	Week ___					

20120312 Dosing Diary Uveitis
White Copy (site)

Abbott Laboratories

Adalimumab Dosing
Yellow Copy (diary)

Appendix F. AREDS 2008 Clinical Lens Opacity Grading Procedures

AREDS Study Group

- Dilate pupils to at least 5 mm diameter
- Use slit lamp with ~10× magnification
- Use brightest beam intensity
- Nuclear opacity
  - Orient beam at 45° to viewing axis
  - Adjust slit beam to standard parameters: 8 mm height and 0.3 mm width
  - Compare opalescence of nucleus with that in standard photos
- Cortical and PSC opacities
  - Select wide slit beam setting optimum for retro-illumination of lens
  - Visualize lens opacities against red fundus reflex background
  - Count only opacities definitely visible against red reflex
  - Mentally combine all cortical opacities into one contiguous area
  - Compare total opacity area with that in standard photos
- Classify each opacity with scale defined by 3 standard photos
- Select nearest half-step
  - Similar to standard or between two standards
  - Obviously less than mildest standard or greater than most severe

Appendix G. Visual Functioning Questionnaire (VFQ-25)

PB/IA

National Eye Institute
Visual Functioning Questionnaire - 25
(VFQ-25)

version 2000

(INTERVIEWER ADMINISTERED FORMAT)

January 2000

Instructions:

I'm going to read you some statements about problems which involve your vision or feelings that you have about your vision condition. After each question I will read you a list of possible answers. Please choose the response that best describes your situation.

Please answer all the questions as if you were wearing your glasses or contact lenses (if any).

Please take as much time as you need to answer each question. All your answers are confidential. In order for this survey to improve our knowledge about vision problems and how they affect your quality of life, your answers must be as accurate as possible. Remember, if you wear glasses or contact lenses for a particular activity, please answer all of the following questions as though you were wearing them.

Visual Functioning Questionnaire - 25

PART 1 - GENERAL HEALTH AND VISION

1. **In general, would you say your overall health is*:**

	(Circle One)	
READ CATEGORIES:	**Excellent**	**1**
	Very Good	**2**
	Good	**3**
	Fair	**4**
	Poor	**5**

2. **At the present time, would you say your eyesight using both eyes (with glasses or contact lenses, if you wear them) is excellent, good, fair, poor, or very poor or are you completely blind?**

	(Circle One)	
READ CATEGORIES:	**Excellent**	**1**
	Good	**2**
	Fair	**3**
	Poor	**4**
	Very Poor	**5**
	Completely Blind	**6**

3. How much of the time do you worry about your eyesight?
(Circle One)

READ CATEGORIES:

None of the time	1
A little of the time	2
Some of the time	3
Most of the time	4
All of the time?	5

4. How much pain or discomfort have you had in and around your eyes (for example, burning, itching, or aching)? Would you say it is:
(Circle One)

READ CATEGORIES:

None	1
Mild	2
Moderate	3
Severe, or	4
Very severe?	5

PART 2 - DIFFICULTY WITH ACTIVITIES

The next questions are about how much difficulty, if any, you have doing certain activities wearing your glasses or contact lenses if you use them for that activity.

5. How much difficulty do you have reading ordinary print in newspapers? Would you say you have:
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

6. How much difficulty do you have doing work or hobbies that require you to see well up close, such as cooking, sewing, fixing things around the house, or using hand tools? Would you say:
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

7. Because of your eyesight, how much difficulty do you have finding something on a crowded shelf?
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

8. How much difficulty do you have reading street signs or the names of stores?
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

9. Because of your eyesight, how much difficulty do you have going down steps, stairs, or curbs in dim light or at night?

(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

10. Because of your eyesight, how much difficulty do you have noticing objects off to the side while you are walking along?
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

11. Because of your eyesight, how much difficulty do you have seeing how people react to things you say?
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

12. **Because of your eyesight, how much difficulty do you have picking out and matching your own clothes?**
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

13. **Because of your eyesight, how much difficulty do you have visiting with people in their homes, at parties, or in restaurants?**
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

14. **Because of your eyesight, how much difficulty do you have going out to see movies, plays, or sports events?**
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

15. Now, I'd like to ask about driving a car. Are you currently driving, at least once in a while?

(Circle One)

Yes..... 1 *Skip To Q 15c*

No 2

15a. IF NO, ASK: Have you never driven a car or have you given up driving?

(Circle One)

Never drove..... 1 *Skip To Part 3, Q 17*

Gave up..... 2

15b. IF GAVE UP DRIVING: Was that mainly because of your eyesight, mainly for some other reason, or because of both your eyesight and other reasons?

(Circle One)

Mainly eyesight..... 1 *Skip To Part 3, Q 17*

Mainly other reasons..... 2 *Skip To Part 3, Q 17*

Both eyesight and other reasons .... 3 *Skip To Part 3, Q 17*

15c. IF CURRENTLY DRIVING: How much difficulty do you have driving during the daytime in familiar places? Would you say you have:

(Circle One)

No difficulty at all 1

A little difficulty..... 2

Moderate difficulty 3

Extreme difficulty 4

16. How much difficulty do you have <u>driving at night</u>? Would you say you have: (READ CATEGORIES AS NEEDED)

	(Circle One)
No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Have you stopped doing this because of your eyesight	5
Have you stopped doing this for other reasons or are you not interested in doing this	6

16a. How much difficulty do you have <u>driving in difficult conditions, such as in bad weather, during rush hour, on the freeway, or in city traffic</u>? Would you say you have:
(READ CATEGORIES AS NEEDED)

	(Circle One)
No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Have you stopped doing this because of your eyesight	5
Have you stopped doing this for other reasons or are you not interested in doing this	6

PART 3: RESPONSES TO VISION PROBLEMS

The next questions are about how things you do may be affected by your vision. For each one, I'd like you to tell me if this is true for you all, most, some, a little, or none of the time.

READ CATEGORIES:	All of the time	Most of the time	Some of the time	A little of the time	None of the time
	(Circle One On Each Line)				
17. Do you accomplish less than you would like because of your vision?	1	2	3	4	5
18. Are you limited in how long you can work or do other activities because of your vision?.....	1	2	3	4	5
19. How much does pain or discomfort in or around your eyes, for example, burning, itching, or aching, keep you from doing what you'd like to be doing? Would you say:	1	2	3	4	5

For each of the following statements, please tell me if it is definitely true, mostly true, mostly false, or definitely false for you or you are not sure.

(Circle One On Each Line)

	Definitely True	Mostly True	Not Sure	Mostly False	Definitely False
20. I stay home most of the time because of my eyesight.	1	2	3	4	5
21. I feel frustrated a lot of the time because of my eyesight.	1	2	3	4	5
22. I have much less control over what I do, because of my eyesight.	1	2	3	4	5
23. Because of my eyesight, I have to rely too much on what other people tell me...	1	2	3	4	5
24. I need a lot of help from others because of my eyesight.	1	2	3	4	5
25. I worry about doing things that will embarrass myself or others, because of my eyesight.	1	2	3	4	5

That's the end of the interview. Thank you very much for your time and your help.

Appendix H. EuroQol-5D Questionnaire (EQ-5D)

EQ-5D

Health Questionnaire

(English version for the US)

By placing a checkmark in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about	☐
I have some problems in walking about	☐
I am confined to bed	☐

Self-Care

I have no problems with self-care	☐
I have some problems washing or dressing myself	☐
I am unable to wash or dress myself	☐

Usual Activities (*e.g., work, study, housework, family or leisure activities*)

I have no problems with performing my usual activities	☐
I have some problems with performing my usual activities	☐
I am unable to perform my usual activities	☐

Pain/Discomfort

I have no pain or discomfort	☐
I have moderate pain or discomfort	☐
I have extreme pain or discomfort	☐

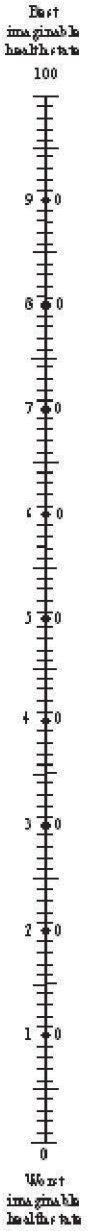
Anxiety/Depression

I am not anxious or depressed	☐
I am moderately anxious or depressed	☐
I am extremely anxious or depressed	☐

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



Appendix I. Health Resource Utilization Questionnaire (HRU)

Since the last study visit has the subject had any visits for their uveitis other than the protocol required visit?

YES: ____
NO: ____
If YES, please provide the following:

1. Since the last protocol required visit, has the subject been seen by a health care professional for their uveitis?

   YES: ____
   NO: ____
   If YES, how many times: ____

2. Since the last protocol required visit, has the subject been seen in the Emergency Room for their uveitis?

   YES: ____
   NO: ____
   If YES, how many times: ____

3. Since the last protocol required visit, has the subject been admitted to the hospital due to their uveitis?

   YES: ____
   NO: ____

   If YES, please list the ADMISSION DATE: __ __/___ ___ ___/ ___ ___ ___ __
   DD MMM YYYY

   DISCHARGE DATE: __ __/___ ___ ___/ ___ ___ ___ __
   DD MMM YYYY

Appendix J. Work Productivity and Activity Impairment, Questionnaire: Specific Health Problem Questionnaire V2.0 (WPAI-SHP)

The following questions ask about the effect of your UVEITIS on your ability to work and perform regular activities. *Please fill in the blanks or circle a number, as indicated.*

1. Are you currently employed (working for pay)? _____ NO ___ YES
   If NO, check "NO" and skip to question 6.

The next questions are about the **past 7 days**, not including today.

2. During the past 7 days, how many hours did you miss from work because of problems associated with your UVEITIS? Include hours you missed on sick days, times you went in late, left early, etc., because of your UVEITIS. Do not include time you missed to participate in this study.

   _____HOURS

3. During the past seven days, how many hours did you miss from work because of any other reason, such as vacation, holidays, time off to participate in this study?

   _____HOURS

4. During the past seven days, how many hours did you actually work?
   _____HOURS *(If "0," skip to question 6.)*

5. During the past 7 days, how much did your UVEITIS affect your productivity <u>while you were working</u>?

Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as usual. If UVEITIS affected your work only a little, choose a low number. Choose a high number if UVEITIS affected your work a great deal.

Consider only how much UVEITIS affected productivity while you were working.

UVEITIS had no effect on my work	0	1	2	3	4	5	6	7	8	9	10	UVEITIS completely prevented me from working

CIRCLE A NUMBER

6. During the past 7 days, how much did your UVEITIS affect your ability to do your regular daily activities, other than work at a job?

By regular activities, we mean the usual activities you do, such as work around the house, shopping, childcare, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could do and times you accomplished less than you would like. If UVEITIS affected your activities only a little, choose a low number. Choose a high number if UVEITIS affected your activities a great deal.

Consider only how much UVEITIS affected your ability to do your regular daily activities, other than work at a job.

UVEITIS had no effect on my daily activities	0	1	2	3	4	5	6	7	8	9	10	UVEITIS completely prevented me from doing my daily activities

CIRCLE A NUMBER

WPAI:SHP V2.0 (US English)

Appendix K. Japan Appendix

In Japan only, the above protocol is to be followed except where indicated in the sections below. It is anticipated that approximately 400 adult subjects with non-infectious intermediate-, posterior-, or pan-uveitis will be enrolled at up to 102 investigational sites in the United States, Canada, Europe, Israel, Latin America, Japan and Australia.

5.3.1 Efficacy and Safety Measurements Assessed and Flow Chart

Safety data will be collected in the form of adverse events, physical examinations, vital signs and laboratory tests throughout the treatment period. Adverse events will also be collected up to 70 days after the last injection in this study. The 70-day follow-up phone call will not be required for any subject that initiates commercial adalimumab after the end of study participation.

The visit window for all scheduled visits is ±7 days for all visits. If a subject has an out of window visit, the next visit should occur as originally scheduled based on the first date of study drug administration (Baseline visit).

Study procedures will be performed per the main protocol as summarized in the visit schedule presented in Table 1 except where indicated in the sections below.

Table 1. Study Activities - Japan Only

Activity	Baseline[J1]	Week 2	Week 4	Week 8	Week 12	Week 18	Week 30	Week 42	Week 54	Week 66	Every 12 Weeks Following Week 66[r]	Final/Early Termination Visit	Unscheduled Visit	70-Day Follow-up
Chest X-ray	X							X				X	X	

These footnotes only pertain to the Japan portion of the study and do not replace any procedures in the main protocol.

J1. The chest x-ray does not need to be repeated even if the Baseline visit occurs greater than (>) 14 days after the Final/Early Termination visit of the parent study.

5.3.1.1 Study Procedures

Chest X-ray (CXR)

For Japan only, all subjects will undergo a standard CXR (posterior-anterior [PA] and lateral views) at the Baseline visit, which will be conducted as part of the Final/Early Termination visit in the parent study, and at the Final/Early Termination visit of Study M11-327 to ensure safety of the subjects. In the assessment of the CXR, a radiologist and/or physician for respiratory medicine must note the presence or absence of calcified granulomas and/or pleural scarring/thickening and/or signs of active TB. The Principal Investigator will indicate the clinical significance of any findings and will sign and date the report. In the absence of abnormal findings the Principal Investigator should sign and date the report to indicate review of the report. The CRA will monitor this documentation. Subjects can have a repeat CXR at any time during the study as warranted based on the opinion of the Investigator and/or CXR is inconclusive.

If a subject has a positive TB test at Baseline or Week 42, 90, 138, 186, 234, 282, or 330, subjects will undergo a standard CXR (posterior-anterior [PA] and lateral views) to rule out the presence of TB or other clinically relevant findings.

In addition, other diagnostic imaging tests may be performed as needed if pulmonary involvement is suspected based on the investigator's clinical assessment.

Dispense Study Drug

Study drug will be administered to subjects by study site medical staff, by himself/herself or by a designee (family member or health care professional) throughout the study.

Subjects in Japan will be administered the study drug at the investigative site throughout the study when the dose of prednisone or prednisone equivalent is > 10 mg/day to secure the safety of the subjects.

Subjects or a designated family member will be trained to administer study medication during the first visit or several times, if appropriate. This training must be documented in the subject's source document.

Subjects or a trained designated family member or a Health Care Professional will administer the injections of the study medication in the subject's home or in the clinic during the weeks the subjects are not in the office for scheduled study visits.

Subjects will maintain a log for all study medication administered outside of the study visit (i.e., at home). The dosing records will be reviewed and verified for compliance at each clinic visit. All relevant dosing information will be retained by study personnel. Additionally, any discernible departure from the protocol regarding study drug administration will be documented appropriately. A sample of the Subject Dosing Diary is presented in Appendix E.

For subjects that cannot/will not self-administer study drug or do not have adequate support (family member) at home, administration will occur in the clinic.

At all office visits, subjects should be observed after study drug administration until judged clinically stable by the study personnel. If an anaphylactic reaction or other serious allergic reaction occurs, administration of study medication should be discontinued immediately and appropriate therapy initiated. When dosing at home, subjects should be instructed to contact the site immediately with any signs or symptoms of a reaction.

For subjects who deviate from the dosing schedule, every effort should be made to bring the subject back to the original dosing schedule as soon as possible.

The subject must be instructed to return study drug at each clinic visit for the purpose of compliance assessment and drug accountability as detailed in Section 5.5.6.1.

6.5 Adverse Event Reporting

In Japan, the Principal Investigator will provide documentation of all serious adverse events to the Director of the investigative site and the Sponsor.

7.0 Protocol Deviations

In Japan, the Investigator will record all protocol deviations in the appropriate medical records at site.

9.3.1 Informed Consent Form and Explanatory Material

In Japan, the Principal Investigator will prepare the consent form and explanatory material required to obtain subject's consent to participate in the study in cooperation with the sponsor and will revise these documents as required. The prepared or revised consent forms and explanatory material will be submitted to the sponsor. Approval of the IRB will be obtained prior to use in the study.

9.3.2 Revision of the Consent Form and Explanatory Material

In Japan, when important new information related to the subject's consent becomes available, the Principal Investigator will revise without delay the consent form and explanatory material based on the information and will obtain the approval of the IRB prior to use in the study. The Investigator will provide the information, without delay, to each subject already participating in the study, and will confirm the intention of each subject to continue in the study or not. The Investigator will also provide further explanation using the revised consent form and explanatory material and will obtain written consent from each subject of their own free will to continue participation in the study.

13.0 Completion of the Study

The Investigator will conduct the study in compliance with the protocol and complete the study within the timeframe specified in the contract between the Investigator (Director of

the Site in Japan) and AbbVie. Continuation of this study beyond this date must be mutually agreed upon in writing by both the Investigator (Director of the Site in Japan) and AbbVie. The Investigator will provide a final report to the IEC/IRB following conclusion of the study, and will forward a copy of this report to AbbVie or their representative.

The Investigator (Director of the Site in Japan) must retain any records related to the study according to local requirements. If the Investigator (Director of the Site in Japan) is not able to retain the records, he/she must notify AbbVie to arrange alternative archiving options.

16.0 Clinical Expense and Compensation

16.1 Expenditure of the Clinical Expense

The sponsor will pay the expenses related to this study to the investigative site in accordance with "Special Healthcare Expenditure." The expenses for screening test, etc. will be paid based on the contract agreed upon with each investigative site. To lighten the burden imposed on the subject with participation to the study, transportation expenses, etc. will be paid to the subjects via participating investigative site in accordance with the rules of the investigative site.

16.2 Compensation for Health Impairment and Insurance

1. If a subject suffers some sort of health impairment due to this study, the investigative site will provide treatment and other necessary measures. Among the expenses required for the treatment, the amount not covered by health insurance that the patient must pay directly will be borne by the sponsor only when the event is associated with the use of the study drug.
2. When a subject suffers health impairment during this study and a dispute occurs or might potentially occur between the investigative site and the subject, the investigative site will immediately report this to the sponsor and resolve it. The sponsor will work with the investigative site in resolving any issues or problems.

3. When the investigative site must compensate subject for any health impairment caused by this study, the compensation paid by the investigative site and the expenses related to any dispute will be borne in full by the sponsor, except in cases where the responsibility for the problem is attributed to the investigative site. This shall not apply to cases where the health impairment occurred because the investigative site performed the study with marked deviation from the GCP or the protocol or because of a deliberate action or a major error by the investigative site.
4. When a subject suffers health impairment during this study and liability for compensation arises, the sponsor will compensate in accordance with the SOP regarding the compensation prepared in advance.
5. The sponsor will obtain clinical study insurance and will take other necessary measures to cover the claims and compensation required in such cases.

17.0 Storage of Records

The directors of the investigative sites will retain the "Essential documents to be retained by study institutions" specified in the Section 4.9.5 of ICH guideline for the period specified in the following.

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents are no longer need to be retained.

18.0 Study Period

For Japan sub-study, the study will conclude immediately after study drug receives country regulatory approval for uveitis. The study will be discontinued approximately three months after discontinuation of the uveitis program due to study cancellation or non-approval by the regulatory agencies, if applicable. Subjects will be instructed to return for their next scheduled visit for a final visit at this time.

Investigator's Agreement - Japan

The Principal Investigator will agree to the following: 1) I have received and reviewed the Investigator's Brochure for Adalimumab I have read this protocol and agree that the study is ethical; 3) I agree to conduct the study as outlined and in accordance with all applicable regulations and guidelines; 4) I agree to maintain the confidentiality of all information received or developed in connection with this protocol and 5) I agree with the Sponsor about the contents of the protocol and CRFs and to comply with them.

Study Title:	A Multicenter Open-Label Study of the Long-term Safety and Efficacy of the Human Anti-TNF Monoclonal Antibody Adalimumab in Subjects with Non-infectious Intermediate-, Posterior-, or Pan-uveitis – VISUAL III
Protocol Number:	M11-327
Issue Date:	☐ Protocol: Version , / / ☐ CRF: Version , / /
Site–specific Change ☐ No ☐ Yes	Site Number: Contents of Change:

Investigator	Site: Title: Name: Date: / /	Seal
Trial Director	Sponsor: Title: Name: Date: / /	Seal

Appendix L. Protocol Amendment: List of Changes

The summary of changes is listed in Section 1.1.

Protocol Specific Changes:

Section 1.0 Title Page
"Sponsor/Emergency Contact:" previously read:

Sponsor/Emergency Contact:	**US, Canada, Latin America:** [redacted]	**Europe, Israel, and Australia:**
	Japan: [redacted]	

Has been changed to read:

Sponsor/Emergency Contact:	**US, Canada, Latin America:**	**Europe, Israel, and Australia:**
	[redacted]	
	Japan:	
	[redacted]	

Section 1.2 Synopsis
Subsection <u>Duration of Treatment:</u>
Previously read:

The entire study will be terminated in March 2016.

Has been changed to read:

The entire study will be terminated in March 2018.

Figure 1. Study Schematic
Figure note "*" previously read:

* Visits will occur every 12 weeks following Week 66 until the end of the study (not to exceed 15 March 2016).

Has been changed to read:

* Visits will occur every 12 weeks following Week 66 until the end of the study (not to exceed 15 March 2018).

Section 5.1 Overall Study Design and Plan: Description
Last paragraph previously read:

The entire study will be terminated in March 2016. Subjects who remain active in this clinical trial on 15 February 2016 should be contacted by the site to return for their study termination visit. Sites should complete the termination visit by 15 March 2016 for all of the remaining active subjects. These subjects will be considered as having completed the study.

Has been changed to read:

The entire study will be terminated in March 2018. Subjects who remain active in this clinical trial on 15 February 2018 should be contacted by the site to return for their study termination visit. Sites should complete the termination visit by 15 March 2018 for all of the remaining active subjects. These subjects will be considered as having completed the study.

Table 1. Study Activities
Table note "j.," "k.," and "r." previously read:

j. An annual TB test must be completed at the Week 42, 90, 138, 186, and 234 visits for all subjects. Please reference Section 5.3.1.1 Study Procedures for further information.
k. If the TB test is missed at the Week 42, 90, 138, 186, or 234 visits, the subject must be brought in within 30 days of the visit to have the test completed.
r. Subjects will have study visits every 12 weeks following Week 66 until the end of study (not to exceed 15 March 2016).

Has been changed to read:

j. An annual TB test must be completed at the Week 42, 90, 138, 186, 234, 282, or 330 visits for all subjects. Please reference Section 5.3.1.1 Study Procedures for further information.

k. If the TB test is missed at the Week 42, 90, 138, 186, 234, 282, or 330 visits, the subject must be brought in within 30 days of the visit to have the test completed.

r. Subjects will have study visits every 12 weeks following Week 66 until the end of study (not to exceed 15 March 2018).

Section 5.3.1.1 Study Procedures
First paragraph previously read:

Subjects will have clinic visits at Baseline, Week 2, Week 4, Week 8, Week 12, Week 18 and every 12 weeks thereafter until the final visit which should occur no later than March 2016.

Has been changed to read:

Subjects will have clinic visits at Baseline, Week 2, Week 4, Week 8, Week 12, Week 18 and every 12 weeks thereafter until the final visit which should occur no later than March 2018.

Section 5.3.1.1 Study Procedures
Third paragraph, first sentence previously read:

At Baseline (as part of the Final/Early Termination visit in the parent studies), Weeks 8, 18, 30, 42, 54, 66, every 12 weeks thereafter until the final visit which should occur no later than March 2016, and at the Final/Early Termination visit, the questionnaire assessments (to be completed in the following order: VFQ-25, EQ-5D, WPAI-SHP and the HRU) required for that visit should be completed first, followed by vital signs and eye exam assessments.

Has been changed to read:

At Baseline (as part of the Final/Early Termination visit in the parent studies), Weeks 8, 18, 30, 42, 54, 66, every 12 weeks thereafter until the final visit which should occur no later than March 2018, and at the Final/Early Termination visit, the questionnaire

assessments (to be completed in the following order: VFQ-25, EQ-5D, WPAI-SHP and the HRU) required for that visit should be completed first, followed by vital signs and eye exam assessments.

Section 5.3.1.1 Study Procedures
Subsection Clinical Laboratory Tests
Last paragraph previously read:

The central laboratory chosen for this study (ICON Central Laboratories) will provide instructions regarding the collection, processing and shipping of these samples.

Has been changed to read:

The central laboratory chosen for this study (ICON Laboratory Services) will provide instructions regarding the collection, processing and shipping of these samples.

Section 5.3.1.1 Study Procedures
Subsection TB Screening
Third paragraph, first, second and third sentence previously read:

For the TB Screening, either a PPD skin test (alternatively, also known as tuberculin skin test) must be placed or the QuantiFERON®-TB Gold test (or IGRA equivalent) must be performed during the Baseline visit and Week 42, 90, 138, 186, and 234 visits for all subjects. The same type of TB test should be done at Weeks 42, 90, 138, 186, and 234 that was done at Baseline. For subjects with a positive PPD skin test in the parent protocol, a QuantiFERON®-TB Gold test (or IGRA equivalent) must be performed at the Baseline and Week 42, 90, 138, 186, and 234 visits.

Has been changed to read:

For the TB Screening, either a PPD skin test (alternatively, also known as tuberculin skin test) must be placed or the QuantiFERON®-TB Gold test (or IGRA equivalent) must be performed during the Baseline visit and Week 42, 90, 138, 186, 234, 282, and 330 visits for all subjects. The same type of TB test should be done at Weeks 42, 90, 138, 186, 234, 282 and 330 that was done at Baseline. For subjects with a positive PPD skin test in the

parent protocol, a QuantiFERON®-TB Gold test (or IGRA equivalent) must be performed at the Baseline and Week 42, 90, 138, 186, 234, 282, and 330 visits.

Section 5.3.1.1 Study Procedures
Subsection Chest X-ray (CXR)
First paragraph previously read:

If a subject has a positive TB test at Baseline or Weeks 42, 90, 138, 186, or 234, subjects will undergo a standard CXR (posterior anterior [PA] and lateral views) to rule out the presence of TB or other clinically relevant findings.

Has been changed to read:

If a subject has a positive TB test at Baseline or Weeks 42, 90, 138, 186, 234, 282, or 330, subjects will undergo a standard CXR (posterior anterior [PA] and lateral views) to rule out the presence of TB or other clinically relevant findings.

Section 5.3.1.1 Study Procedures
Subsection Dispense Study Drug
Fourth paragraph, last sentence previously read:

A sample of the Subject Dosing Diary is presented in 0.

Has been changed to read:

A sample of the Subject Dosing Diary is presented in Appendix E.

Section 5.4.1 Discontinuation of Individual Subjects
Sixth bullet following second paragraph previously read:

Subject has positive PPD test or positive (or indeterminate re-test) QuantiFERON®-TB Gold test (or IGRA equivalent) result at Baseline, Week 42, 90, 138, 186, or 234.

Has been changed to read:

Subject has positive PPD test or positive (or indeterminate re-test) QuantiFERON®-TB Gold test (or IGRA equivalent) result at Baseline, Week 42, 90, 138, 186, 234, 282, or 330.

Section 5.4.1 Discontinuation of Individual Subjects
Last paragraph previously read:

The entire study will be terminated in March 2016. Subjects who remain active in this clinical trial on 15 February 2016 should be contacted by the site to return for their study termination visit. Sites should complete the termination visit by 15 March 2016 for all of the remaining active subjects. These subjects will be considered as having completed the study.

Has been changed to read:

The entire study will be terminated in March 2018. Subjects who remain active in this clinical trial on 15 February 2018 should be contacted by the site to return for their study termination visit. Sites should complete the termination visit by 15 March 2018 for all of the remaining active subjects. These subjects will be considered as having completed the study.

Section 5.5.2.2 Storage and Disposition of Study Drugs
First paragraph, fifth sentence previously read:

The maximum, minimum and current temperature for both refrigerator and room temperature must be documented and reviewed for temperature excursions.

Has been changed to read:

The maximum, minimum and current temperature for refrigerator temperature must be documented and reviewed for temperature excursions.

Section 5.5.6 Treatment Compliance
Second paragraph, third sentence previously read:

In order to document compliance with the treatment regimen, the subject will be given a Subject Dosing Diary (0) to record all injection dates and times.

Has been changed to read:

In order to document compliance with the treatment regimen, the subject will be given a Subject Dosing Diary (Appendix E) to record all injection dates and times.

Section 5.6.4 Selection of Doses in the Study
Last paragraph previously read:

In total, adalimumab has now been tested in clinical studies in over 24,000 subjects representing more than 47,000 patient years, of which more than 90% of subjects were dosed with 40 mg eow at any given time.

Has been changed to read:

In total, adalimumab has now been tested in clinical studies in over 29,000 subjects representing more than 56,000 patient years.

Section 6.0 Complaints
Add: new section number and text

6.0 Complaints

A Complaint is any written, electronic, or oral communication that alleges deficiencies related to the physical characteristics, identity, quality, purity, potency, durability, reliability, safety, effectiveness, or performance of a product/device after it is released for distribution.

The investigational product in this trial contains both:

- Biologic compound(s) and
- Device component(s) (pre-filled syringe).

Complaints associated with any component of this investigational product must be reported to the Sponsor (Section 6.2.2). For adverse events, please refer to Sections 6.1 through 6.1.6. For product complaints, please refer to Section 6.2.

Section 6.0 through 6.6
Section number and title previously read:

6.0 Adverse Events

6.1 Definitions

6.1.1 Adverse Event

6.1.1.1 Uveitis-Related Events

6.1.2 Serious Adverse Events

6.2 Adverse Event Severity

6.3 Relationship to Study Drug

6.4 Adverse Event Collection Period

6.5 Adverse Event Reporting

Has been changed to read:

6.0 Complaints

6.1 Medical Complaints

6.1.1 Definitions

6.1.1.1 Adverse Event

6.1.1.1.1 Uveitis-Related Events

6.1.1.2 Serious Adverse Events

6.1.2 Adverse Event Severity

6.1.3 Relationship to Study Drug

6.1.4 Adverse Event Collection Period

6.1.5 Adverse Event Reporting

Section 6.5 Adverse Event Reporting
Previously read:

In the event of a serious adverse event, and additionally, any non-serious event of malignancy in subjects 30 years of age and younger, whether related to study drug or not, the physician will notify the AbbVie Immunology Clinical Safety Management Team within 24 hours of the physician becoming aware of the event by entering the serious adverse event or non-serious event of malignancy in subjects 30 years of age and younger data into the electronic data capture (EDC) system. Serious adverse events and non-serious events of malignancy in subjects 30 years of age and younger, that occur prior to the site having access to the Rave system should be faxed to the Immunology Clinical Safety Team within 24 hours of being made aware of the adverse event.

FAX to: [redacted]

For serious adverse event concerns, contact the Immunology Safety Team at:

Immunology Safety Team
Immunology Development
[redacted]
AbbVie
1 North Waukegan Road
North Chicago, IL 60064
USA

Fax:
Safety Hotline:
Email:
[redacted]

For any subject safety concerns, please contact the AbbVie Medical Monitors listed below:

For US, Canada, Latin America and Japan

[redacted]

For Europe, Israel and Australia

[redacted]

In the EU, the sponsor will be responsible for Suspected Unexpected Serious Adverse Reactions (SUSAR) reporting for the Investigational Medicinal Product (IMP) in accordance with Directive 2001/20/EC. The reference document used for SUSAR reporting in EU countries for adalimumab will be the most current version of the Investigator's Brochure.

Has been changed to read:

In the event of a serious adverse event, and additionally, any nonserious event of malignancy in subjects 30 years of age and younger, whether related to study drug or not, the investigator will notify Clinical Pharmacovigilance within 24 hours of the site being aware of the event by entering the serious adverse event or nonserious event of malignancy in subjects 30 years of age and younger data into the electronic data capture (EDC) system. Serious adverse events and nonserious events of malignancy in subjects 30 years of age and younger, that occur prior to the site having access to the RAVE system or if RAVE is not operable should be sent to Clinical Pharmacovigilance within 24 hours of site being made aware of the adverse event.

FAX to:	[redacted]
Email:	

For serious adverse event concerns, contact the Immunology Safety Team at:

Immunology Safety Team
Immunology Development
[redacted]
AbbVie
1 North Waukegan Road
North Chicago, IL 60064
USA

Fax:
Safety Hotline:
Email:
[redacted]

For any subject safety concerns, please contact the AbbVie Medical Monitors listed below:

For US, Canada, and Latin America:

[redacted]

For Europe, Israel, Australia and Japan:

[redacted]

Secondary Contact for Japan (Regional Medical Monitor):

[redacted]

[redacted] and [redacted] cover for each other. For any subject safety concerns or medical emergencies in which both medical monitors are unavailable, please call the following central back-up number:

Phone: [redacted]

In the EU, the sponsor will be responsible for Suspected Unexpected Serious Adverse Reactions (SUSAR) reporting for the Investigational Medicinal Product (IMP) in

accordance with Directive 2001/20/EC. The reference document used for SUSAR reporting in EU countries for adalimumab will be the most current version of the Investigator's Brochure.

Section 6.6 Pregnancy
Section number and title previously read:

6.6 Pregnancy

Has been changed to read:

6.1.6 Pregnancy

Section 6.2 Product Complaint
Add: new section and text, renumber subsequent sections

6.2 Product Complaint

6.2.1 Definition

A Product Complaint is any Complaint (see Section 6.0 for the definition) related to the biologic or drug component of the product or to the medical device component(s).

For a product this may include, but is not limited to, damaged/broken product or packaging, product appearance whose color/markings do not match the labeling, labeling discrepancies/inadequacies in the labeling/instructions (example: printing illegible), missing components/product, device not working properly, or packaging issues.

For medical devices, a product complaint also includes all deaths of a patient using the device, any illness, injury, or adverse event in the proximity of the device, an adverse event that could be a result of using the device, any event needing medical or surgical intervention including hospitalization while using the device and use errors.

Any information available to help in the determination of causality by the device to the events outlined directly above should be captured.

6.2.2 Reporting

Product Complaints concerning the investigational product and/or device must be reported to the Sponsor within 24 hours of the study site's knowledge of the event via the Product Complaint form. Product Complaints occurring during the study will be followed-up to a satisfactory conclusion. All follow-up information is to be reported to the Sponsor (or an authorized representative) and documented in source as required by the Sponsor. Product Complaints associated with adverse events will be reported in the study summary. All other complaints will be monitored on an ongoing basis.

Product Complaints may require return of the product with the alleged complaint condition (syringe). In instances where a return is requested, every effort should be made by the investigator to return the product within 30 days. If returns cannot be accommodated within 30 days, the site will need to provide justification and an estimated date of return.

The description of the complaint is important for AbbVie in order to enable AbbVie to investigate and determine if any corrective actions are required.

Section 7.0 Protocol Deviations
First paragraph previously read:

The Investigator should not implement any deviation from the protocol without prior review and agreement by the Sponsor and in accordance with the Independent Ethics Committee (IEC)/Independent Review Board (IRB) and local regulations, except when necessary to eliminate an immediate hazard to study subjects. When a deviation from the protocol is deemed necessary for an individual subject, the Investigator must contact the AbbVie Medical Monitor listed in Section 1.0 and Section 6.5.

Has been changed to read:

AbbVie does not allow intentional/prospective deviations from the protocol. The Principal Investigator is responsible for complying with all protocol requirements, and applicable global and local laws regarding protocol deviations. If a protocol deviation

occurs (or is identified) after a subject has been enrolled, the Principal Investigator is responsible for notifying Independent Ethics Committee (IEC)/Independent Review Board (IRB) regulatory authorities (as applicable), and the AbbVie Clinical Monitor(s) assigned to your site. Alternative contacts are as follows:

Alternate Contacts

North America, Latin America, and Japan	Europe, Israel, and Australia
[redacted]	

Such contact must be made as soon as possible to permit a review by AbbVie to determine the impact of the deviation on the subject and/or the study.

Section 7.0 Protocol Deviations
Delete: third paragraph

Such contact must be made as soon as possible to permit a review by AbbVie to determine the impact of the deviation on the subject and/or the study. Any significant protocol deviations affecting subject eligibility and/or safety must be reviewed and/or approved by the IEC/IRB and regulatory authorities, as applicable, prior to implementation.

Appendix B. List of Protocol Signatories
Previously read:

Name	Title	Functional Area
[redacted]		Clinical
		Clinical
		Statistics
		Clinical

Has been changed to read:

Name	Title	Functional Area
[redacted]		Clinical
		Clinical
		Statistics
		Clinical

Appendix E. Subject Dosing Diary
Last page of diary previously read:

M11-327

___-___ ___-___ ___-___ ___
Subject Identification Number

Adalimumab Dosing Diary

Date	Week #	Kit Number	Time of Study Drug Administration	Was the entire volume injected? (Y/N)	Initials of Person Administering Study Medication	Comments
19-Mar-13	EXAMPLE	101010	9:35	Y	MM	none
	Week 276					
	Week 278					
	Week 280					

20120312 Dosing Diary Uveitis
White Copy (site)

Abbott Laboratories

Adalimumab Dosing
Yellow Copy (diary)

Has been changed to read:

M11-327

___-___ ___-___ ___-___ ___
Subject Identification Number

Adalimumab Dosing Diary

Date	Week #	Kit Number	Time of Study Drug Administration	Was the entire volume injected? (Y/N)	Initials of Person Administering Study Medication	Comments
19-Mar-13	EXAMPLE	101010	9:35	Y	MM	none
	Week 276					
	Week 278					
	Week 280					
	Week 282					
	Week 284					
	Week 286					
	Week 288					
	Week 290					

20120312 Dosing Diary Uveitis
White Copy (site)

Abbott Laboratories

Adalimumab Dosing
Yellow Copy (diary)

M11-327

___-___ ___-___ ___-___ ___
Subject Identification Number

Adalimumab Dosing Diary

Date	Week #	Kit Number	Time of Study Drug Administration	Was the entire volume injected? (Y/N)	Initials of Person Administering Study Medication	Comments
19-Mar-13	EXAMPLE	101010	9:35	Y	MM	none
	Week 292					
	Week 294					
	Week 296					
	Week 298					
	Week 300					
	Week 302					
	Week 304					
	Week 306					

20120312 Dosing Diary Uveitis
White Copy (site)

Abbott Laboratories

Adalimumab Dosing
Yellow Copy (diary)

M11-327

___-___ ___-___ ___-___ ___
Subject Identification Number

Adalimumab Dosing Diary

Date	Week #	Kit Number	Time of Study Drug Administration	Was the entire volume injected? (Y/N)	Initials of Person Administering Study Medication	Comments
19-Mar-13	EXAMPLE	101010	9:35	Y	MM	none
	Week 308					
	Week 310					
	Week 312					
	Week 314					
	Week 316					
	Week 318					
	Week 320					
	Week 322					

20120312 Dosing Diary Uveitis
White Copy (site)

Abbott Laboratories

Adalimumab Dosing
Yellow Copy (diary)

M11-327

___-___ ___-___ ___-___ ___
Subject Identification Number

Adalimumab Dosing Diary

Date	Week #	Kit Number	Time of Study Drug Administration	Was the entire volume injected? (Y/N)	Initials of Person Administering Study Medication	Comments
19-Mar-13	EXAMPLE	101010	9:35	Y	MM	none
	Week 324					
	Week 326					
	Week 328					
	Week 330					
	Week 332					
	Week 334					
	Week 336					
	Week 338					

20120312 Dosing Diary Uveitis
White Copy (site)

Abbott Laboratories

Adalimumab Dosing
Yellow Copy (diary)

M11-327

___-___ ___-___ ___-___ ___
Subject Identification Number

Adalimumab Dosing Diary

Date	Week #	Kit Number	Time of Study Drug Administration	Was the entire volume injected? (Y/N)	Initials of Person Administering Study Medication	Comments
19-Mar-13	EXAMPLE	101010	9:35	Y	MM	none
	Week 340					
	Week 342					
	Week 344					
	Week 346					
	Week 348					
	Week 350					
	Week 352					
	Week 354					

20120312 Dosing Diary Uveitis
White Copy (site)

Abbott Laboratories

Adalimumab Dosing
Yellow Copy (diary)

M11-327

___-___ ___-___ ___-___ ___
Subject Identification Number

Adalimumab Dosing Diary

Date	Week #	Kit Number	Time of Study Drug Administration	Was the entire volume injected? (Y/N)	Initials of Person Administering Study Medication	Comments
19-Mar-13	EXAMPLE	101010	9:35	Y	MM	none
	Week 356					
	Week 358					
	Week 360					
	Week 362					
	Week 364					
	Week 366					
	Week 368					
	Week 370					

20120312 Dosing Diary Uveitis
White Copy (site)

Abbott Laboratories

Adalimumab Dosing
Yellow Copy (diary)

M11-327

___-___ ___-___ ___-___ ___
Subject Identification Number

Adalimumab Dosing Diary

Date	Week #	Kit Number	Time of Study Drug Administration	Was the entire volume injected? (Y/N)	Initials of Person Administering Study Medication	Comments
19-Mar-13	EXAMPLE	101010	9:35	Y	MM	none
	Week 372					
	Week 374					
	Week 376					
	Week 378					
	Week ___					
	Week ___					

20120312 Dosing Diary Uveitis
White Copy (site)

Abbott Laboratories

Adalimumab Dosing
Yellow Copy (diary)

Appendix F. AREDS 2008 Clinical Lens Opacity Grading Procedures
Delete: last paragraph

Website: http://eyephoto.ophth.wisc.edu/ResearchAreas.html

Appendix K. Japan Appendix
Section 5.3.1.1 Study Procedures
Subsection Chest X-ray (CXR)
Second paragraph previously read:

If a subject has a positive TB test at Baseline or Week 42, 90, 138, 186, or 234, subjects will undergo a standard CXR (posterior-anterior [PA] and lateral views) to rule out the presence of TB or other clinically relevant findings.

Has been changed to read:

If a subject has a positive TB test at Baseline or Week 42, 90, 138, 186, 234, 282, or 330, subjects will undergo a standard CXR (posterior-anterior [PA] and lateral views) to rule out the presence of TB or other clinically relevant findings.

Appendix K. Japan Appendix
Section 5.3.1.1 Study Procedures
Subsection Dispense Study Drug
Second paragraph previously read:

Subjects in Japan will be administered the study drug by the medical staff throughout the study when the dose of prednisone or prednisone equivalent is ≤ 10 mg/day to secure the safety of the subjects.

Has been changed to read:

Subjects in Japan will be administered the study drug at the investigative site throughout the study when the dose of prednisone or prednisone equivalent is > 10 mg/day to secure the safety of the subjects.

Table 1. Study Activities (Continued)

Activity	Baseline[a]	Week 2	Week 4	Week 8	Week 12	Week 18	Week 30	Week 42	Week 54	Week 66	Every 12 weeks following Week 66[r]	Final/ ET Visit	Unscheduled Visit[b]	70-Day Follow-up[c]
Physical Exam[g]	X				X		X		X		X[g]	X	X	
Symptom Directed Physical Exam[g]		X	X	X		X		X		X	X[g]			
Urine Pregnancy Test[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	
Hematology/Chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X	
Urinalysis[i]	X		X		X		X		X		X	X	X	
TB Screening[j] (PPD Skin Test or QuantiFERON®-TB Gold or IGRA equivalent)	X							X[k]			X[j,k]			
Chest X-ray[l]	X[l]							X[l]			X[l]		X	
Antinuclear Antibody (ANA/Anti-dsDNA[m,n])													X	
Monitor Adverse Events[o]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Monitor Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	
Monitor Compliance		X	X	X	X	X	X	X	X	X	X	X	X	
Dispense Adalimumab Study Drug (Contact IXRS)	X		X	X	X[p]	X	X	X	X	X	X			
Perform Drug Accountability[q]		X	X	X	X	X	X	X	X	X	X	X		

Table 1. Study Activities (Continued)

a. All activities for Baseline except Informed Consent, Inclusion criteria, Exclusion criteria and Dispensing of Study Drug, will be completed as part of the Final/Early Termination visit in the parent study and will be used in analysis for Study M11-327. If the Baseline visit occurs greater than (>) 14 days after the Final/Early Termination visit of the parent study, all procedures listed in the Baseline visit must be completed. The maximum amount of time allowed between the Final/Early Termination visit of the parent study and the Baseline visit of Study M11-327 is 28 days.

b. If a subject presents at a site for an Unscheduled visit investigators should complete unscheduled visit procedures at their discretion.

c. The 70-day follow-up calculated from last dose of study drug should be conducted by telephone or at a routine clinic visit to collect any potential safety information.

d. Questionnaire will be administered by site staff (interview administered) prior to any study procedure or examination.

e. Questionnaire will be completed by the subject unless impaired vision prohibits. Site staff should complete the questionnaire with the subject, if the subject has impaired vision that precludes him/her from reading and completing the questionnaire.

f. Height used in analysis will be taken from the Screening visit of the parent study in which the subject enrolled. Weight will be measured at Baseline (measurement taken at the Final/Early Termination visit of the parent protocol), Unscheduled visit (if applicable) and Final/Early Termination visit. Vital sign determinations of sitting blood pressure, heart rate, respiratory rate and body temperature will be obtained at each visit.

g. A full physical exam will be performed at Baseline, Week 12, Week 30, Week 54, Unscheduled visit (if applicable), and every other visit (every 24 weeks) following Week 66 and Final/Early Termination Visit. An abbreviated symptom-directed physical exam will be completed at all other visits as warranted.

h. All females of childbearing potential will have a urine pregnancy test performed locally at the Baseline visit and all subsequently scheduled study visits. The frequency can be increased if local regulations require. Any subject with a positive urine pregnancy test result must have a negative serum test result performed at the central laboratory prior to enrollment or continuation in the study.

i. The central laboratory will perform the urine dipstick. If the urinalysis results are abnormal by dipstick, the central laboratory will perform a microscopic analysis.

j. An annual TB test must be completed at the Week 42, 90, 138, 186, 234, 282, or 330 visits for all subjects. Please reference Section 5.3.1.1 Study Procedures for further information.

k. If the TB test is missed at the Week 42, 90, 138, 186, 234, 282, or 330 visits, the subject must be brought in within 30 days of the visit to have the test completed.

l. Must include a PA and lateral view. The CXR is only required if a TB test result is positive. A CXR may be repeated at any time during the study as warranted based on the opinion of the Investigator and/or CXR is inconclusive. Other diagnostic imaging tests may be performed as needed if pulmonary involvement is suspected based on the investigator's clinical assessment. See Section 5.3.1.1 for details.

Table 1. Study Activities (Continued)

m. If a subject is enrolled in M11-327 prior to IEC/IRB approval of Global Protocol Amendment 4 of the parent study, the ANA/dsDNA sample will be collected at the subject's next scheduled visit following regulatory approval of M11-327 Global Amendment 4.

n. If a subject develops signs and symptoms of lupus, an ANA test may be repeated based on the investigator's clinical judgment.

o. All SAEs will be captured from the time that the subject signs the Informed Consent Form and all AEs reported from the time of study drug administration through study completion or Early Termination and at the 70-day follow up. Any adverse events experienced prior to first study drug administration in M11-327 will be reported in the parent protocol.

p. At the Week 12 clinic visit, the subject will be dispensed two kits that include a total of four syringes. One syringe should be removed from these kits and sent back to AbbVie per the Drug Destruction guidelines. If dosing at home, the remaining three syringes from these kits will be injected at home at Weeks 12, 14 and 16. At the Week 18 clinic visit, the subject will be dispensed three kits that include a total of six syringes which should be taken at Weeks 18, 20, 22, 24, 26 and 28.

q. Collect the packaging and any remaining drug from the last clinic visit.

r. Subjects will have study visits every 12 weeks following Week 66 until the end of study (not to exceed 15 March 2018).

5.3.1.1 Study Procedures

Subjects will have clinic visits at Baseline, Week 2, Week 4, Week 8, Week 12, Week 18 and every 12 weeks thereafter until the final visit which should occur no later than March 2018.

All activities for the Baseline visit except Informed Consent, Inclusion/Exclusion and Dispensing of Study Drug will be completed as part of the Final/Early Termination visit in the parent study and will be used in analysis for Study M11-327. If the Baseline visit occurs greater than (>) 14 days after the Final/Early Termination visit of the parent study, all procedures listed in the Baseline visit must be completed. The maximum amount of time allowed between the Final/Early Termination visit of the parent study and the Baseline visit of Study M11-327 is 28 days.

At Baseline (as part of the Final/Early Termination visit in the parent studies), Weeks 8, 18, 30, 42, 54, 66, every 12 weeks thereafter until the final visit which should occur no later than March 2018, and at the Final/Early Termination visit, the questionnaire assessments (to be completed in the following order: VFQ-25, EQ-5D, WPAI-SHP and the HRU) required for that visit should be completed first, followed by vital signs and eye exam assessments. The order of the eye examinations may occur according to established site procedures as long as the slit lamp examination for AC cells is performed prior to the application of mydriatic eye drops to dilate subject's pupils for further assessment.

Informed Consent

A signed informed consent will be obtained from the subject or their legally authorized representative before any study-related procedures are undertaken. Details about how informed consent will be obtained and documented are provided in Section 9.3.

If the parent studies are prematurely stopped based upon the recommendation of the IDMC, and this recommendation is based on safety concerns, subjects will be required to return for their Final/Early Termination visit in Study M11-327.

Inclusion/Exclusion Criteria

Subjects will be eligible for study participation if he/she meets all inclusion criteria and none of the exclusion criteria at the Baseline visit.

Assignment of Subject Numbers

Subjects will keep the same subject number that they were assigned in the parent study (Study M10-877 or Study M10-880).

Visual Functioning Questionnaire (VFQ-25)

The VFQ-25 will be completed at the Baseline visit (or as part of the Final/Early Termination visit of Study M10-877 or Study M10-880), Week 8, Week 18 and every visit thereafter prior to any study procedure or examination. A copy of the questionnaire is located in Appendix G.

The questionnaire will be interview administered. The site will complete this questionnaire directly onto the CRFs and will be considered source documents.

EuroQol-5D Questionnaire (EQ-5D)

Subjects will complete the EQ-5D questionnaire at the Baseline visit (or as part of the Final/Early Termination visit of Study M10-877 or Study M10-880), Week 8, Week 18 and every visit thereafter prior to any study procedure or examination. A copy of the questionnaire is located in Appendix H. The subject will complete this questionnaire directly onto the CRFs and will be considered source documents.

Site staff should complete the questionnaire with the subject, if the subject has impaired vision that precludes him/her from reading and completing the questionnaire.

Work Productivity and Activity Impairment, Questionnaire: Specific Health Problem Questionnaire (WPAI-SHP)

Subjects will complete the WPAI-SHP questionnaire at the Baseline visit (or as part of the Final/Early Termination visit of Study M10-877 or Study M10-880), Week 8, Week 18

and every visit thereafter prior to any study procedure or examination. A copy of the questionnaire is located in Appendix J. The subject will complete this questionnaire directly onto the CRFs and will be considered source documents.

Site staff should complete the questionnaire with the subject, if the subject has impaired vision that precludes him/her from reading and completing the questionnaire.

Health Resource Utilization Questionnaire (HRU)

Sites will complete the HRU questionnaire at the Baseline visit (or as part of the Final/Early Termination visit of Study M10-877 or Study M10-880), and at all subsequent visits in the study. A copy of the questionnaire is located in Appendix I.

The questionnaire will be interview administered by the site. The answers will be documented on the source worksheet provided by the sponsor and entered in the eCRF.

Vital Signs/Weight/Height

Vital signs will be obtained at each visit. This includes sitting blood pressure, heart rate, respiratory rate and body temperature. Each subject's height used in the analysis will be taken from the Screening visit of the parent study (Study M10-877 or Study M10-880). For this study, Baseline weight and vital signs measurements will be taken from the final visit of the parent study for the purposes of analysis if Study M11-327 Baseline visit occurs ≤ 14 days since the last visit from the parent study (Study M10-877 or Study M10-880). If the Baseline visit occurs greater than (>) 14 days after the last visit from the parent study, baseline weight and vital signs measurements will be taken at that Baseline visit. Weight will be measured at the Unscheduled visit (if applicable) and Final/Early Termination visit.

Best Corrected Visual Acuity Testing

Refraction and assessment of best corrected visual acuity (BCVA) will be assessed at every visit.

At each visit, subjects should undergo refraction and the result of refraction for each eye will be recorded on the eCRF.

Using the appropriate corrective lenses based on that visit's refraction, subject's BCVA is measured using an ETDRS chart which will be specified and provided if necessary by the sponsor. Please refer to the Visual Acuity Manual provided by the sponsor for instructions.

A qualified and trained health care professional must perform the refraction and BCVA testing. Specific training and instructions will be provided by the sponsor.

Slit Lamp Exam

The slit lamp exam will be conducted at each study visit to assess the following findings: Anterior chamber cell count and Age-Related Eye Disease Study (AREDS) lens opacity grading.[3,37,38] Slit lamp examination for AC cells is performed prior to application of mydriatic eyedrops to dilate subject's pupils for further assessment.

The AREDS classification does not apply to a subject, if he/she has pseudophakia.

The number of AC cells observed within a 1 mm × 1 mm slit beam will be recorded for each eye. The reported number will be used to determine the grade according to the SUN criteria[3] (Table 2).

Table 2. Anterior Chamber Cells

Grade	Cells in Field
0	< 1
0.5 +	1 – 5
1 +	6 – 15
2 +	16 – 25
3 +	26 – 50
4 +	> 50

Using the AREDS standard photographs as reference, the degree of lens opacity will be graded for each type: nuclear, cortical, and posterior subcapsular (PSC) (Table 3).[37,38] See Appendix F for further instructions regarding lens opacity grading procedures.

Table 3. Lens Opacity Grading

Grading for Nuclear Lens Opacity	
< 1.0	no nuclear opacity, or less than NS Std. No. 1
1.0	opacity similar to NS No. 1
1.5	opacity between NS No. 1 and NS Std. No. 2
2.0	opacity similar to NS No. 2
2.5	opacity between NS No. 2 and NS Std. No. 3
3.0	opacity similar to NS No. 3
> 3.0	opacity greater than NS No. 3
8.0	cannot evaluate
Grading for Cortical Lens Opacity	
< 1.0	no cortical opacity, or opacity obviously less than CO Std. No. 1
1.0	opacity similar to cortical opacity Std. No. 1
1.5	opacity between CO Std. No. 1 and Std. No. 2
2.0	opacity similar to CO Std. No. 2
2.5	opacity between CO Std. No. 2 and Std. No. 3
3.0	opacity similar to CO No. 3
> 3.0	cortical opacity obviously greater than Std. No. 3
8.0	cannot evaluate
Grading for Posterior Subcapsular (PSC) Opacity	
< 1.0	no PSC opacity, or opacity obviously < PSC Std. No. 1
1.0	opacity similar to PSC No. 1
1.5	opacity between PSC No. 1 and Std. No. 2
2.0	opacity similar to PSC No. 2
2.5	opacity between PSC No. 2 and Std. No. 3
3.0	opacity similar to PSC No. 3
> 3.0	PSC obviously greater than PSC No. 3
8.0	cannot evaluate

Optical Coherence Tomography

Optical Coherence Tomography will be performed at every visit. Sites must use one of three OCT machines for this clinical trial to determine central retinal thickness and the presence of macular edema:

- Stratus OCT (Carl Zeiss Meditec, Inc.)
- Cirrus HD-OCT (Carl Zeiss Meditec, Inc.)
- Spectralis (Heidelberg Engineering)

Each subject will undergo OCT measurements of the central retinal thickness (1 mm subfield) to evaluate for macular edema at every visit using the same protocol approved machine throughout the study. The same OCT machine that was used in Study M10-877 or Study M10-880 should be used in Study M11-327. OCT images will be sent to the Central Reader for transmission to AbbVie. Although it is preferred to complete the OCT measurements following pupil dilation, it is important that the site conducts the scans consistently across each subject (using the same model of OCT device for each patient) throughout the study.

Tonometry

Tonometry will be performed at every visit to measure the intraocular pressure for both eyes. Applanation tonometry is preferred but non-contact tonometry can also be used if the site does not have the equipment to perform applanation tonometry. However, the same technique should be used for all visits for an individual patient.

Dilated Indirect Ophthalmoscopy

Subject's eyes should be dilated in preparation for indirect ophthalmoscopy. The examination technique and instrument used should remain consistent for each subject throughout the study.

Dilated indirect ophthalmoscopy is performed to determine both vitreous haze grading and the absence/presence of inflammatory chorioretinal and/or inflammatory retinal vascular lesions.

Lesion location(s), number, size(s) and whether the lesions are active or inactive should be documented with a retinal drawing in the subject's source documentation, if a lesion is identified.

Grading of vitreous haze (Table 4) will be based on the publication from the National Eye Institute (NEI) which has also been adapted by the SUN working group.[3,39]

Sites will use the standard photographs given to them by the sponsor and the description in Table 4 when determining the grade for vitreous haze.

Table 4. Vitreous Haze Grading

Grade	Description
0	No evident vitreal haze
0.5 +	Slight blurring of the optic disc margin because of the haze; normal striations and reflex of the nerve fiber layer cannot be visualized
1 +	Permits a better definition of both the optic nerve head and the retinal vessels (compared to higher grades)
2 +	Permits better visualization of the retinal vessels (compared to higher grades)
3 +	Permits the observer to see the optic nerve head, but the borders are quite blurry
4 +	Optic nerve head is obscured

At all visits dilated indirect ophthalmoscopy will be performed to determine the presence/absence of new inflammatory chorioretinal and/or inflammatory retinal vascular lesions compared to the findings from the final visit of the parent study (Study M10-877 or Study M10-880) based on the Investigators' clinical judgment.

Physical Examination

Medically qualified personnel who routinely do a complete physical exam should perform this assessment at the designated study visits listed in Table 1. At all other visits, a symptom directed physical exam will be performed either by the investigator or the medically qualified personnel who performed the complete physical exam. Abnormalities noted after the Baseline visit of the parent study should be evaluated and documented by the Investigator as to whether or not these are adverse events.

Pregnancy Tests

At the Baseline visit and all subsequent visits thereafter, subjects of childbearing potential will have a urine pregnancy test (provided by the central laboratory) performed locally by designated study personnel. The frequency can be increased if local regulations require. Subjects of non-childbearing potential are defined as postmenopausal for at least 1 year or surgically sterile (bilateral tubal ligation, bilateral oophorectomy and/or hysterectomy).

If any urine pregnancy test is positive, a serum pregnancy test must be requested on the central laboratory requisition form and performed by the central laboratory prior to enrollment or continuation in the study. A lactating or pregnant female will not be eligible for participation or continuation in this study.

Clinical Laboratory Tests

Lab evaluations will be performed according to the schedule outlined in Table 1.

Blood draws should be performed after completion of questionnaires (i.e., VFQ-25, EQ-5D, WPAI-SHP, HRU) and vital sign determinations during a study visit, but before study drug administration, if applicable.

A certified central laboratory will be utilized to process and provide results for the general laboratory tests. The investigator will review all laboratory test results. All laboratory test results that are considered clinically significant by the investigator will be followed to a satisfactory conclusion. Laboratory abnormalities are considered to be adverse events only if these result in discontinuation from the study, necessitate therapeutic intervention, and/or the investigator considers them to be adverse events.

In cases where laboratory tests are performed locally for specific study purposes, certifications and laboratory reference ranges will be collected for the tests which are performed.

The central laboratory chosen for this study (ICON Laboratory Services) will provide instructions regarding the collection, processing and shipping of these samples.

Table 5. Clinical Laboratory Tests

Hematology[a]	Clinical Chemistry	Urinalysis[b]	Serology	Other[e]
Hematocrit Hemoglobin Red Blood Cell (RBC) count White Blood Cell (WBC) count Neutrophils Bands Lymphocytes Monocytes Basophils Eosinophils Platelet count (estimate not acceptable)	Blood Urea Nitrogen (BUN) Creatinine Total bilirubin Serum glutamic-pyruvic transaminase (SGPT/ALT) Serum glutamic-oxaloacetic transaminase (SGOT/AST) Alkaline phosphatase Sodium Potassium Calcium Inorganic phosphorus Uric acid Cholesterol Total protein Glucose Triglycerides Albumin	Specific gravity Ketones[c] pH Protein Blood Glucose	Antinuclear Antibody (ANA)/Anti-dsDNA[d] QuantiFERON®-TB Gold test[f]	Human Chorionic Gonadotropin (HCG)

a. Automated basic hematology testing does not include band reporting. If a manual differential is required, only band results over 5 are reported.

b. Microscopic urinalysis performed by the central laboratory at all visits if dipstick UA is abnormal.

c. The result should be interpreted in the context of additional clinical and test information.

d. If a subject enrolls in Study M11-327 prior to IEC/IRB approval of Global Amendment 4 in either parent study, an antinuclear antibody (ANA)/Anti-dsDNA sample will be collected at the subject's next scheduled visit. However, if a subject develops signs and symptoms of lupus, an ANA/Anti-dsDNA test may be repeated based on the investigator's clinical judgment.

e. Urine pregnancy test is performed on all female subjects of child bearing potential at the Baseline visit (Final visit of parent protocol), and all subsequent visits thereafter. A serum HCG test must be requested on the central laboratory requisition if urine HCG is positive. Any subject with a positive urine pregnancy test must have a negative serum test result at the central laboratory prior to enrollment or continuation in the study.

f. If TB screening tests are not available locally, the central laboratory can be used to perform the QuantiFERON®-TB Gold test. For countries that ship to ICON New York, the estimated turnaround time is 5 to 8 days. For countries that ship to ICON Dublin, the estimated turnaround time is 9 to 12 days. For ICON Singapore, the estimated turnaround time is 11 to 14 days.

Note: Baseline laboratory values will be taken from the parent study (Study M10-877 or Study M10-880) unless the Baseline visit occurs greater than (>) 14 days since the last visit in the parent study (Study M10-877 or Study M10-880).

Urinalysis

Urine samples will be obtained for urinalysis testing as noted in Table 1. The central laboratory will perform a urine dipstick analysis and if the results are abnormal, the central laboratory will perform a microscopic urinalysis.

TB Screening

The TB screening tests are diagnostic test results to be interpreted in the context of the patient's epidemiology, history, exam findings, etc. and it is the responsibility of the investigator to determine if a patient has previous, active or latent tuberculosis or not in conjunction with a negative TB Screening test.

Under no circumstances can a patient with a positive PPD result or positive QuantiFERON®-TB Gold test (or IGRA equivalent) continue in the study.

For the TB Screening, either a PPD skin test (alternatively, also known as tuberculin skin test) must be placed or the QuantiFERON®-TB Gold test (or IGRA equivalent) must be performed during the Baseline visit and Week 42, 90, 138, 186, 234, 282, and 330 visits for all subjects. The same type of TB test should be done at Weeks 42, 90, 138, 186, 234, 282 and 330 that was done at Baseline. For subjects with a positive PPD skin test in the parent protocol, a QuantiFERON®-TB Gold test (or IGRA equivalent) must be performed at the Baseline and Week 42, 90, 138, 186, 234, 282, and 330 visits. For subjects with a negative TB test in the parent protocol, the same type of test that was used in the parent protocol (either PPD or QuantiFERON®-TB Gold [or IGRA equivalent]) must be used for every TB test in Study M11-327. If a subject had a negative PPD test or negative QuantiFERON®-TB Gold test (or IGRA equivalent) within 90 days prior to Baseline, and all protocol required documentation is available, the test does not need to be repeated, provided nothing has changed in the subject's medical history to warrant a repeat test.

If the subject has a positive TB Screening test (either positive PPD test or positive QuantiFERON®-TB Gold test [or IGRA equivalent]), the subject must be discontinued. If the subject has a repeat indeterminate QuantiFERON®-TB Gold test (or IGRA

equivalent), the subject must be discontinued. The subject should be brought back in immediately for an Early Termination visit. For subjects with a prior history of Bacille Calmette-Guérin (BCG) administration, the QuantiFERON®-TB Gold test (or IGRA equivalent) test is recommended.

The TB screening tests are preferably performed locally. If TB screening tests (PPD test and/or QuantiFERON®-TB Gold test) are not available locally, the central laboratory can be used to perform the QuantiFERON®-TB Gold test. Sites utilizing the central lab for the QuantiFERON®-TB Gold test should be aware the results for samples sent to ICON New York require an estimated turnaround time of 5 to 8 days, samples sent to ICON Dublin require an estimated turnaround time of 9 to 12 days and samples sent to ICON Singapore require an estimated turnaround time of 11 to 14 days. It is also required to incubate samples for 16 to 24 hours at 37°C prior to shipping, frozen, to the central lab for processing.

For the PPD test:

> The subject will be required to have the PPD test read by a licensed healthcare professional 48 to 72 hours after placement (or as per local guidelines), when the induration is maximal. An induration (not erythema) of 5 mm or greater will be considered as PPD positive. The absence of induration should be recorded, as "0 mm," not "negative."
>
> Subjects who have had an ulcerating reaction to a PPD skin test in the past should not be re-exposed. Therefore, they should not be tested with PPD and instead must have a QuantiFERON®-TB Gold test (or IGRA equivalent) performed to rule out active or latent TB. If the subject has a history of an ulcerative reaction and has a positive or repeat indeterminate QuantiFERON®-TB Gold test (or IGRA equivalent) the subject cannot continue in the study.

If there are sites where the available testing materials are not accepted, an alternative tuberculin skin test may be substituted, but the method must be submitted and approved by AbbVie prior to use with study subjects.

If QuantiFERON®-TB Gold test (or IGRA equivalent) result is indeterminate, the test should be repeated with a fresh blood sample. If a repeat QuantiFERON®-TB Gold (or IGRA equivalent) result is indeterminate, this should be considered a positive test result and the subject should be discontinued.

A corresponding adverse event should be captured on the adverse event page in the eCRF and in the source documents in the case of a positive test result.

For sites participating in the Czech Republic, the following local requirements will also be applicable:

- A pulmonologist will be responsible to obtain a detailed medical history with respect to Tuberculosis exposure. This information needs to include Bacillus Calmette Guérin (BCG) vaccination, cohabitation with individuals who have had TB, and/or who reside or work in TB endemic locations. The information obtained by the pulmonologist must be documented in the patient's source note, dated and signed by the pulmonologist.
- A pulmonologist must review the results of TB Screening Test (PPD skin test or QuantiFERON®-TB Gold test [or IGRA equivalent]) and the chest x-ray and has to give his/her opinion about the continuation of each patient in the study. This opinion must be documented in writing in the patient's source documents.
- All patients with a positive TB Screening test (PPD or QuantiFERON®-TB Gold [or IGRA equivalent]) must be discontinued from the study. Under no circumstances can a patient with a positive TB test result or a prior history of treatment for active or latent tuberculosis be allowed to remain in this trial.

Chest X-ray (CXR)

If a subject has a positive TB test at Baseline or Weeks 42, 90, 138, 186, 234, 282, or 330, subjects will undergo a standard CXR (posterior anterior [PA] and lateral views) to rule out the presence of TB or other clinically relevant findings.

In the assessment of the CXR, a radiologist must specifically note the presence or absence of (1) calcified granulomas, (2) pleural scarring/thickening, and (3) signs of active TB. The Principal Investigator will indicate the clinical significance of any findings and will sign and date the report. In the absence of abnormal findings the Principal Investigator should sign and date the report to indicate review of the report.

Subjects can have a repeat CXR at any time during the study as warranted based on the opinion of the Investigator and/or the CXR is inconclusive.

In addition, other diagnostic imaging tests may be performed as needed if pulmonary involvement is suspected based on the Investigator's clinical assessment.

Antinuclear Antibody (ANA)/Anti-dsDNA Testing

If a subject is enrolled in Study M11-327 prior to the IEC/IRB approval of Global Protocol Amendment 4 in either parent study, the ANA/Anti-ds-DNA sample will be collected at the subject's next scheduled visit following regulatory approval of Study M11-327 Global Protocol Amendment 4.

A repeat ANA/Anti-ds-DNA would be warranted if a subject has clinical signs and symptoms suggestive of lupus. The Anti-ds-DNA antibody testing will be performed in case of a positive ANA result.

All samples will be sent to the central laboratory for processing.

Adverse Events

Adverse events will be assessed at every study visit from Baseline through the Final/Early Termination visit, and during the 70-day phone call or clinic visit (if applicable). A phone

call or routine clinic visit should occur approximately 70 days after last dose of study medication to obtain follow-up information on any ongoing or new adverse events (Section 6.0 and Appendix D).

Any ongoing adverse events at the time of the Termination visit in the previous Study M10-877 or Study M10-880 will be automatically transferred onto the Study M11-327 eCRF.

Concomitant Medication

All medications (including, but not limited to, prescription or over-the-counter medicines such as aspirin, antacids, vitamins, mineral supplements, and herbal preparations) used from the Baseline visit through the end of the study must be recorded on the appropriate eCRF. Any ongoing systemic or local therapy at the time of Termination visit in the previous study M10-877 or M10-880 will be automatically transferred onto the M11-327 eCRF.

Contact the AbbVie Medical Monitor identified in Section 6.1.5, if there are any questions regarding concomitant or prior therapy(ies).

Each vaccine administered to the subject should be listed as a concomitant medication on the Other Medications eCRF. Live vaccines may not be given concurrently while on study drug or for 70 days after the last dose of adalimumab.

Concomitant use of nutritional supplements should be recorded as concomitant medications (generic and/or brand name, dose [if known], frequency) on the Other Medications eCRF.

Dispense Study Drug

Study drug will be administered to subjects by study site medical staff, by himself/herself or by a designee (friend, family member or health care professional) throughout the study.

Subjects, a designated family member or friend, will be trained to administer study medication during the first visit or several times, if appropriate. This training must be documented in the subject's source document.

Subjects or a trained designated family member or friend or a health care professional will administer the injections of the study medication in the subject's home or in the clinic during the weeks the subjects are not in the office for scheduled study visits.

Subjects will maintain a Subject Dosing Diary for all study medication administered outside of the study visit (i.e., at home). The Subject Dosing Diary will be reviewed and verified for compliance at each clinic visit. All relevant dosing information will be retained by study personnel. Additionally, any discernible departure from the protocol regarding study drug administration will be documented appropriately. A sample of the Subject Dosing Diary is presented in Appendix E.

For subjects that cannot/will not self-administer study drug or do not have adequate support (friend, family member or healthcare professional) at home, administration will occur in the clinic.

At all office visits, subjects should be observed after study drug administration until judged clinically stable by the study personnel. If an anaphylactic reaction or other serious allergic reaction occurs, administration of study medication should be discontinued immediately and appropriate therapy initiated. When dosing at home, subjects should be instructed to contact the site immediately with any signs or symptoms of a reaction.

For subjects who deviate from the dosing schedule, every effort should be made to bring the subject back to the original dosing schedule as soon as possible.

The subject must be instructed to return study drug at each clinic visit for the purpose of compliance assessment and drug accountability as detailed in Section 5.5.6.1.

5.3.2 Drug Concentration Measurements

There will be no drug concentration measurements in this protocol.

5.3.3 Efficacy Variables

Efficacy will be determined at each visit by the following criteria. Both of the subjects' eyes will be assessed. The following endpoints will be used to evaluate the long-term efficacy of adalimumab to treat subjects with non-infectious intermediate-, posterior-, or pan-uveitis.

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

uveitis when they entered the study and to Week 8 for subjects who had active uveitis when they entered the study.[40]

5.3.3.1 Other Variables

Other variables for which data will be collected and analyzed include:

- Work Productivity and Activity Impairment, Questionnaire: Specific Health Problem Questionnaire (WPAI-SHP)
- EuroQol-5D Questionnaire (EQ-5D)
- Health Resource Utilization Questionnaire (HRU)

5.3.4 Safety Variables

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

5.3.5 Pharmacokinetic Variables

There will be no pharmacokinetics performed as part of this study.

5.4 Removal of Subjects from Therapy or Assessment

5.4.1 Discontinuation of Individual Subjects

A subject may withdraw from the study at any time. The Investigator may discontinue any subject's participation for any reason, including an adverse event, safety concerns or failure to comply with the protocol. Please refer to Section 6.3, Toxicity Management, for more information regarding the type and duration of follow-up of subjects after adverse events.

Subjects will be withdrawn from the study immediately if any one of the following occurs:

- Clinically significant abnormal laboratory result(s) or adverse event(s), as determined by the Investigator in consultation with the AbbVie Medical Monitor.
- The Investigator believes it is in the best interest of the subject.
- The subject requests withdrawal from the study.
- Inclusion and exclusion criteria violation was noted after the subject started study drug, when continuation of the study drug would place the subject at risk as determined by the AbbVie Medical Monitor.
- Introduction of prohibited medications or dosages when continuation of the study drug would place the subject at risk as determined by the AbbVie Medical Monitor.
- Subject has positive PPD test or positive (or indeterminate re-test) QuantiFERON®-TB Gold test (or IGRA equivalent) result at Baseline, Week 42, 90, 138, 186, 234, 282, or 330.
- Subject is non-compliant with TB prophylaxis (for those subjects who entered the parent study prior to Study M10-877 Amendment 6 or Study M10-880 Amendment 7 and were still taking TB Prophylaxis when they entered Study M11-327).
- Subject becomes pregnant while on study medication.
- Subject has known dysplasia of the gastrointestinal tract (a colonoscopy is not required to enter the study) or a malignancy, except for localized non-melanoma skin cancer. Discontinuation for carcinoma in-situ of the cervix is at the discretion of the Investigator.
- Subject is diagnosed with lupus-like syndrome, multiple sclerosis or demyelinating disease.
- Subject is significantly non-compliant with study procedures which would put the subject at risk for continued participation in the trial as determined by the Investigator, in consultation with the AbbVie Medical Monitor.

If, during the course of study drug administration, the subject prematurely discontinues study drug use, the procedures outlined for the Final/Early Termination Visit must be completed within 2 weeks of the last dose of study drug, and preferably prior to the

initiation of another therapy. However, these procedures should not interfere with the initiation of any new treatments or therapeutic modalities that the Investigator feels are necessary to treat the subject's condition. Following discontinuation of the study drug, the subject will be treated in accordance with the Investigator's best clinical judgment.

All attempts must be made to determine the date of the last dose of study drug and the primary reason for premature discontinuation. The information will be recorded on the appropriate eCRF page. Subjects who prematurely discontinue will not be replaced.

A final phone call or clinic visit will be completed approximately 70 days after the last dose of study drug to determine the status of any ongoing adverse events/serious adverse events or the occurrence of any new adverse events/serious adverse events. The call/visit information should be documented in the subject's source documents per Appendix D, Day 70 Follow-up (Phone Call or Clinic Visit). The 70-day follow-up phone call or clinic visit will not be required for any subject that initiates adalimumab therapy not supplied in the context of the clinical trial after the end of study participation.

For subjects that are considered lost to follow-up, reasonable attempts must be made to obtain information on the final status of the subject. At a minimum, two phone calls must be made and one certified letter must be sent.

Following country and local (if applicable) regulatory approval and/or applicable local reimbursement approval of the study drug in a country, subjects should return to their next scheduled study visit as specified in the protocol. The termination visit should be conducted in place of their regular scheduled study visit. These subjects will be considered as having completed the study.

The entire study will be terminated in March 2018. Subjects who remain active in this clinical trial on 15 February 2018 should be contacted by the site to return for their study termination visit. Sites should complete the termination visit by 15 March 2018 for all of the remaining active subjects. These subjects will be considered as having completed the study.

5.4.2 Discontinuation of Entire Study

AbbVie reserves the right to discontinue a site's participation in the study at any time and to remove all study materials. Possible reasons for termination of the study at a site include, but are not limited to:

- Safety concerns based on reported data
- Unsatisfactory enrollment with respect to quantity or quality
- Inaccurate or incomplete data collection
- Falsification of records
- Significant non-compliance with protocol requirements
- Recommendation by the IDMC to discontinue the uveitis investigational program due to safety concerns.

AbbVie may terminate this study prematurely, either in its entirety or at any study site, for reasonable cause provided that written notice is submitted in advance of the intended termination. The Investigator may also terminate the study at their site for reasonable cause, after providing written notice to AbbVie in advance of the intended termination. Advance notice is not required by either party if the study is stopped due to safety concerns.

5.5 Treatments

5.5.1 Treatments Administered

Study drug will be provided as a sterile, preservative-free solution for injection contained in 1 mL prefilled syringes containing adalimumab 40 mg/0.8 mL. Drug will be subcutaneously administered as a 40 mg dose every other week at approximately the same time of day starting at Baseline.

5.5.2 Identity of Investigational Products

The individual study drug information is presented in Table 6.

Table 6. Identity of Investigational Products

Drug	Dosage Form	Device	Formulation	Manufacturer
Adalimumab	Parenteral	Prefilled syringe	40 mg/0.8 mL solution for injection Adalimumab/Mannitol, Citric acid monohydrate, Sodium citrate, Disodium phosphate dihydrate, Sodium dihydrogen phosphate dihydrate, Sodium chloride, Polysorbate 80, Water for injections, Sodium hydroxide added as necessary to adjust pH	AbbVie/Abbott

5.5.2.1 Packaging and Labeling

Adalimumab 40 mg/0.8 mL Prefilled Syringes:

Subject cartons will contain two prefilled syringes of adalimumab 40 mg/0.8 mL. The number of kits dispensed will be managed by the IVR/IWR system. At a minimum, the following information will appear on either the syringe and/or carton labels:

- Caution statement(s)
- Sponsor identification
- Protocol number
- Drug identification
- Quantity of contents
- Storage conditions
- Dosing instructions
- Kit number
- Route of administration
- Excipients (as required)
- Blank spaces to write the subject's identification number, and date dispensed (as required)
- Finishing lot number

- Expiry date (as required)

Each drug will be labeled as required per country requirements. Labels must remain affixed to study drug as applicable.

5.5.2.2 Storage and Disposition of Study Drugs

Adalimumab prefilled syringes are to be stored protected from light at 2° to 8°C/36° to 46°F. Study drug **must not be frozen** at any time. A storage temperature log is to be maintained to document proper storage conditions. The refrigerator temperature must be recorded each business day to document proper function. The maximum, minimum and current temperature for refrigerator temperature must be documented and reviewed for temperature excursions. Malfunctions or any temperature excursion must be reported to AbbVie immediately. Study medication should be quarantined and not dispensed until AbbVie Global Pharmaceutical Research and Development (GPRD) or Abbott Temperature Excursion Management System (ATEMS) deems the medication as acceptable.

All clinical supplies must be stored and locked in a secure place until they are dispensed for subject use or are returned to AbbVie.

Investigational products are for investigational use only and are to be used only within the context of this study. The clinical supplies for this study must be maintained under adequate security and stored under conditions specified on the label.

5.5.3 Method of Assigning Subjects to Treatment Groups

All subjects will be centrally registered by the Interactive Voice Response System, (IVRS)/Interactive Web Response System (IWRS) at the Baseline study visit. This study is open-label therefore all subjects will be assigned to active treatment. The sites will be provided with appropriate kit number(s) for drug-dispensing purpose for each subject by the IVRS/IWRS. Before the study is initiated, the telephone number and call-in directions

for the IVRS/IWRS will be provided to each site. Study drug will be dispensed at the study visits summarized in Table 1.

The IVRS/IWRS will be maintained by Bracket (formerly United BioSource Corporation):

Bracket
303 Second Street, Suite 700
7th Floor South Tower
San Francisco, CA 94107 USA

5.5.4 Selection and Timing of Dose for Each Subject

Subjects should take study medication as outlined in Section 5.5.1.

Each subject will be assigned to open-label eow adalimumab dosing. If a subject should forget to administer the injection of study medication on their regularly scheduled dosing date, they should take the forgotten injection as soon as they remember the dose was missed up to the day of their next scheduled dose. The subject should not administer two doses on the same day.

In the event the incorrect dose is taken or a dose is missed, the subject should be instructed to contact the site to determine how to proceed with dosing. The subject must record all dosing information on the Subject Dosing Diary (Appendix E).

Doses not administered (e.g., not taken before next dose is scheduled), should be recorded as not taken in the source. The extra dose should be returned to the study site full. The subject should resume their regular dosing schedule based on the date of first dose at Baseline.

5.5.5 Masking

This study is open-label. There is no masking of treatment assignment.

5.5.5.1 Data for Independent Data Monitoring Committee (IDMC)

An Independent Data Monitoring Committee (IDMC) will be established to independently monitor and assess data from Study M10-877 (active uveitis), Study M10-880 (inactive uveitis) and Study M11-327 (open-label long-term extension). The IDMC will be in effect until the end of both Study M10-877 and Study M10-880. At each committee meeting, the IDMC will undertake a comprehensive review and assessment of the cumulative safety data. The IDMC will meet every 6 months or at a frequency determined by the IDMC and render their recommendation for either the termination or continuation of the study or an amendment to the study. The IDMC analysis will be conducted by a statistics vendor external to AbbVie in order for the sponsor to remain masked to the results of the study.

If the parent studies are prematurely stopped based upon the recommendation of the IDMC, and this recommendation is based on safety concerns, subjects will be required to return for their Final/Early Termination visit in Study M11-327.

5.5.6 Treatment Compliance

The Investigator or his/her designated representatives will dispense study drug only for use by subjects enrolled in the study in accordance with the protocol. The study drug must not be used for reasons other than that described in the protocol.

The subject or their qualified designee will administer all doses of study drug when not at the site. Appropriate site staff will supervise the subject's administration of the study drug at the Baseline office study visit to ensure proper injection technique. In order to document compliance with the treatment regimen, the subject will be given a Subject Dosing Diary (Appendix E) to record all injection dates and times. Compliance information will be documented on the appropriate eCRF. Subjects will be counseled on missed doses of medication. If the subject does not return the Subject Dosing Diary, IP cartons and sharp containers (when applicable), the site should question the subject and obtain as much information as possible as to the dosing of the study drug.

The information should be documented on the source documents as per "best recollection" and when possible, re-verified when the Subject Dosing Diary is returned before completing on the applicable eCRF page.

5.5.6.1 Drug Accountability

The Investigator or designee will verify that study drug supplies are received intact, at the appropriate temperature, (in the US adequate temperature is cool to the touch, outside of the US temperature recording devices [TempTale®] are provided in the shipments), and in the correct amounts from the drug depot. This will be accomplished by documenting the condition of the shipment, verifying the kit numbers in the package against the Proof of Receipt (POR) or similar document included with each drug shipment, and documenting this verification by signing and dating the POR or similar document. The original POR Note or similar document will be kept in the site files as a record of what was received.

In addition, an interactive web response system (IWRS) will be used to document Investigational Product Accountability including but not limited to date received, the lot number, kit number(s), date dispensed, subject number and the identification with date of person dispensing the drug.

All empty pre-filled syringe cartons and used prefilled syringes will be inventoried by the site. Each subject will be given their own sharps disposal container to store used pre-filled syringes. Empty IP cartons and Sharps containers should be returned by the subject at each visit for accountability and compliance purposes and new containers issued as necessary. Empty cartons and returned Sharps containers will be retained (unless prohibited by local law) until the CRA is on site to confirm the returned medication. CRAs and site staff will complete study medication accountability via IVRS/IWRS, source documents, Subject Dosing Diaries, empty IP cartons and by visually inspecting the syringes in the Sharps container whenever possible. Used Sharps containers should never be opened. Once the CRA has verified drug accountability at the site, the site staff and CRA will document that the used prefilled syringes have been destroyed, using appropriate biohazard precautions, when appropriate. A copy of the

destruction methodology should be maintained at the site's facility. Unused medication will be returned by the CRA after drug accountability has been completed at the site.

An overall accountability of the study drug will be performed and verified by the CRA throughout the study and at the site closeout visit.

The investigator and/or named the sub-investigators agree not to supply study medication to any persons not enrolled in the study.

5.6 Discussion and Justification of Study Design

5.6.1 Discussion of Study Design and Choice of Control Groups

The design of this clinical trial was chosen to gather long-term safety and tolerability data for adalimumab in this subject population and to further evaluate the long-term effectiveness of adalimumab in the treatment of non-infectious uveitis.

5.6.2 Appropriateness of Measurements

Standard statistical, clinical, and laboratory procedures will be utilized in this study. All efficacy measurements in this study are standard for assessing disease activity in subjects with uveitis. All clinical and laboratory procedures in this study are standard and generally accepted.

5.6.3 Suitability of Subject Population

Subjects with uveitis who met the endpoint treatment failures or have successfully completed Study M10-877 or Study M10-880 may be eligible for this study. These subjects are candidates for systemic immunosuppressive therapy to allow reduction and/or discontinuation of corticosteroid therapy.

5.6.4 Selection of Doses in the Study

Dosing of adalimumab in this study is the same as that proposed in the parent Phase 3 Study M10-877 and Study M10-880. Since it will be unknown whether a subject entering

this study was randomized to adalimumab or placebo in the parent study, no loading dose will be given in this study.

In total, adalimumab has now been tested in clinical studies in over 29,000 subjects representing more than 56,000 patient years.

6.0 Complaints

A Complaint is any written, electronic, or oral communication that alleges deficiencies related to the physical characteristics, identity, quality, purity, potency, durability, reliability, safety, effectiveness, or performance of a product/device after it is released for distribution.

The investigational product in this trial contains both:

- Biologic compound(s) and
- Device component(s) (pre-filled syringe).

Complaints associated with any component of this investigational product must be reported to the Sponsor (Section 6.2.2). For adverse events, please refer to Sections 6.1 through 6.1.6. For product complaints, please refer to Section 6.2.

6.1 Medical Complaints

The Investigator will monitor each subject for clinical and laboratory evidence of adverse events on a routine basis throughout the study. The Investigator will assess and record any adverse event in detail including the date of onset, event diagnosis (if known) or sign/symptom, severity, time course, duration and outcome, relationship of the adverse event to study drug and any action(s) taken. For serious adverse events, if the investigator's opinion of possibly, probably not, or not related to study drug is given, an 'Other' cause of event must be provided by the investigator for the adverse event. For adverse events to be considered intermittent, the events must be of similar nature and

severity. Adverse events, whether in response to a query, observed by site personnel, or reported spontaneously by the subject will be recorded.

All adverse events will be followed to a satisfactory conclusion.

6.1.1 Definitions

6.1.1.1 Adverse Event

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not the event is considered causally related to the use of the product.

Such an event can result from use of the drug as stipulated in the protocol or labeling, as well as from accidental or intentional overdose, drug abuse, or drug withdrawal. Any worsening of a pre-existing condition or illness is considered an adverse event. Worsening in severity of a reported adverse event should be reported as a new adverse event. Laboratory abnormalities and changes in vital signs are considered to be adverse events only if they result in discontinuation from the study, necessitate therapeutic medical intervention, (meets protocol specific criteria [refer to Section 6.3 regarding toxicity management]) and/or if the Investigator considers them to be adverse events.

An elective surgery/procedure scheduled to occur during a study will not be considered an adverse event if the surgery/procedure is being performed for a pre-existing condition and the surgery/procedure has been preplanned prior to study entry. However, if the pre-existing condition deteriorates unexpectedly during the study (e.g., surgery performed earlier than planned), then, the deterioration of the condition for which the elective surgery/procedure is being done will be considered an adverse event.

6.1.1.1.1 Uveitis-Related Events

The following events are known complications related to the condition being treated and will be classified as uveitis-related events. These events will be analyzed separately from other adverse events in the final study report.

The following events are not a complete list of all potential uveitis-related events (e.g., choroidal thickening, choroidal detachment, retinal effusion, are not included but could possibly be events related to uveitis). The investigator must determine if a specific event is uveitis-related.

- Loss of transparency of the cornea
- Band keratopathy
- Synechiae
- Cataracts
- Glaucoma/increased intraocular pressure
- Vitreous hemorrhage
- Macular edema
- Retinal detachment
- Epiretinal membrane
- Vitreo-macular traction
- Retinal ischemia
- Vision loss
- Hypotony

6.1.1.2 Serious Adverse Events

If an adverse event meets any of the following criteria, it is to be reported to AbbVie as a serious adverse event (SAE) within 24 hours of the site being made aware of the serious adverse event.

Death of Subject	An event that results in the death of a subject.
Life-Threatening	An event that, in the opinion of the Investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
Hospitalization or Prolongation of Hospitalization	An event that results in an admission to the hospital for any length of time or prolongs the subject's hospital stay. This does not include an emergency room visit or admission to an outpatient facility.
Congenital Anomaly	An anomaly detected at or after birth, or any anomaly that results in fetal loss.
Persistent or Significant Disability/Incapacity	An event that results in a condition that substantially interferes with the activities of daily living of a study subject. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle).
Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome	An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of subject, life-threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Additionally, any elective or spontaneous abortion or stillbirth is considered an important medical event. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.
Spontaneous Abortion	Miscarriage experienced by study subject.

Elective Abortion	Elective abortion performed on study subject.

6.1.2 Adverse Event Severity

The Investigator will use the following definitions to rate the severity of each adverse event:

Mild	The adverse event is transient and easily tolerated by the subject.
Moderate	The adverse event causes the subject discomfort and interrupts the subject's usual activities.
Severe	The adverse event causes considerable interference with the subject's usual activities and may be incapacitating or life-threatening.

6.1.3 Relationship to Study Drug

The Investigator will use the following definitions to assess the relationship of the adverse event to the use of study drug:

Probably Related	An adverse event has a strong temporal relationship to study drug or recurs on re-challenge and an Other cause of event is unlikely or significantly less likely.
Possibly Related	An adverse event has a strong temporal relationship to the study drug and an Other cause of event is equally or less likely compared to the potential relationship to study drug.
Probably Not Related	An adverse event has little or no temporal relationship to the study drug and/or a more likely Other cause of event exists.
Not Related	An adverse event is due to an underlying or concurrent illness or effect of another drug and is not related to the study drug (e.g., has no temporal relationship to study drug or has a much more likely Other cause of event).

For causality assessments, events meeting the categories of probably or possibly related will be considered "associated." Events that are probably not or not related will be

considered "not associated." In addition, when the Investigator has not reported a causality or deemed it not assessable, AbbVie will consider the event associated.

If an Investigator's opinion of possibly, probably not, or not related to study drug is given, an 'Other' cause of event must be provided by the Investigator for the serious adverse event.

6.1.4 Adverse Event Collection Period

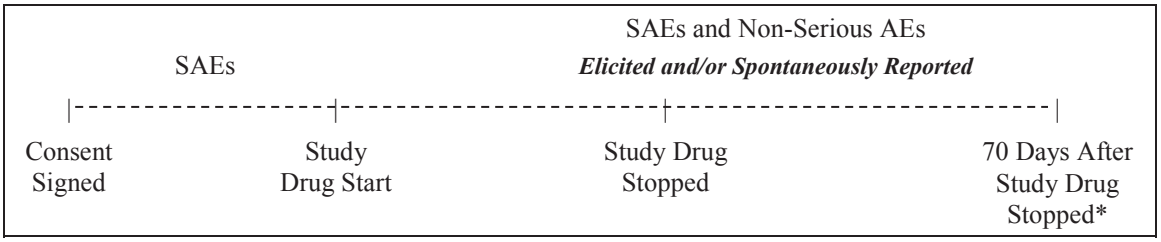
All adverse events reported from the time of study drug administration until 70 days, following discontinuation of study drug administration have elapsed will be collected, whether solicited or spontaneously reported by the subject. In addition, serious adverse events will be collected from the time the subject signs the study-specific informed consent if the subject does not have the Baseline visit on the same day. Any adverse events experienced prior to first study drug administration in M11-327 will be reported in the parent protocol. Adverse event information will be collected and recorded on the appropriate eCRFs. In the event of a death, the date and reason for death should be collected.

Subjects will be contacted approximately 70 days following study drug discontinuation for an assessment of any new or ongoing AEs except those subjects who continue on adalimumab therapy after the end of study participation. These subjects are not required to complete the 70-day follow-up and any new Adverse Events should be reported through the mechanism used for all post marketing adverse experiences.

There may be instances where a 70-day follow-up phone call or clinic visit occurs after the locking of the clinical database. In this situation, any adverse events reported to AbbVie from this 70-day follow-up phone call or clinic visit will be evaluated for inclusion in the clinical database. All SAEs or Adverse Events of Special Interest, as defined by AbbVie, reported during the 70-day follow-up phone call or clinic visit must be captured in the clinical database. The 70-day follow-up phone call will not be required for any subject that initiates commercial adalimumab after the end of study participation.

Adverse event information will be collected as shown in Figure 2.

Figure 2. Adverse Event Collection



* Except for subjects who continue on adalimumab therapy after the end of study participation.

6.1.5 Adverse Event Reporting

In the event of a serious adverse event, and additionally, any nonserious event of malignancy in subjects 30 years of age and younger, whether related to study drug or not, the investigator will notify Clinical Pharmacovigilance within 24 hours of the site being aware of the event by entering the serious adverse event or nonserious event of malignancy in subjects 30 years of age and younger data into the electronic data capture (EDC) system. Serious adverse events and nonserious events of malignancy in subjects 30 years of age and younger, that occur prior to the site having access to the RAVE system or if RAVE is not operable should be sent to Clinical Pharmacovigilance within 24 hours of site being made aware of the adverse event.

FAX to:	[redacted]
Email:	

For serious adverse event concerns, contact the Immunology Safety Team at:

Immunology Safety Team
Immunology Development
[redacted]
AbbVie
1 North Waukegan Road
North Chicago, IL 60064
USA

Fax:
Safety Hotline:
Email:
[redacted]

For any subject safety concerns, please contact the AbbVie Medical Monitors listed below:

For US, Canada, and Latin America:

[redacted]

For Europe, Israel, Australia and Japan:

[redacted]

Secondary Contact for Japan (Regional Medical Monitor):

[redacted]

[redacted] and [redacted] cover for each other. For any subject safety concerns or medical emergencies in which both medical monitors are unavailable, please call the following central back-up number:

Phone: [redacted]

In the EU, the sponsor will be responsible for Suspected Unexpected Serious Adverse Reactions (SUSAR) reporting for the Investigational Medicinal Product (IMP) in

accordance with Directive 2001/20/EC. The reference document used for SUSAR reporting in EU countries for adalimumab will be the most current version of the Investigator's Brochure.

6.1.6 Pregnancy

Pregnancy in a study subject must be reported to AbbVie within 1 working day of the site becoming aware of the pregnancy. Subjects who become pregnant during the study must be discontinued (Section 5.4.1). Pregnancies will be collected from the date of the first dose through 150 days following the last dose of study medication.

Information regarding a pregnancy occurrence in a study subject and the outcome of the pregnancy will be collected. Pregnancy in a study subject is not considered an AE. However, the medical outcome of an elective or spontaneous abortion, stillbirth or congenital anomaly is considered a SAE and must be reported to AbbVie within 24 hours of the site becoming aware of the event.

6.2 Product Complaint

6.2.1 Definition

A Product Complaint is any Complaint (see Section 6.0 for the definition) related to the biologic or drug component of the product or to the medical device component(s).

For a product this may include, but is not limited to, damaged/broken product or packaging, product appearance whose color/markings do not match the labeling, labeling discrepancies/inadequacies in the labeling/instructions (example: printing illegible), missing components/product, device not working properly, or packaging issues.

For medical devices, a product complaint also includes all deaths of a patient using the device, any illness, injury, or adverse event in the proximity of the device, an adverse event that could be a result of using the device, any event needing medical or surgical intervention including hospitalization while using the device and use errors.

Any information available to help in the determination of causality by the device to the events outlined directly above should be captured.

6.2.2 Reporting

Product Complaints concerning the investigational product and/or device must be reported to the Sponsor within 24 hours of the study site's knowledge of the event via the Product Complaint form. Product Complaints occurring during the study will be followed-up to a satisfactory conclusion. All follow-up information is to be reported to the Sponsor (or an authorized representative) and documented in source as required by the Sponsor. Product Complaints associated with adverse events will be reported in the study summary. All other complaints will be monitored on an ongoing basis.

Product Complaints may require return of the product with the alleged complaint condition (syringe). In instances where a return is requested, every effort should be made by the investigator to return the product within 30 days. If returns cannot be accommodated within 30 days, the site will need to provide justification and an estimated date of return.

The description of the complaint is important for AbbVie in order to enable AbbVie to investigate and determine if any corrective actions are required.

6.3 Toxicity Management

For the purpose of medical management, all adverse events and laboratory abnormalities that occur during the study must be evaluated by the Investigator. Subjects who develop a new infection while receiving study drug should be monitored closely. Administration of study injections should be interrupted if a subject develops an infection requiring IV anti-infective treatment or if an infection meets the definition of "serious" (refer to Section 6.1.1.2 for definitions). Study medication may be restarted once the physician determines that the infection has been successfully treated. Otherwise prohibited concomitant medications may be given if medically necessary. Prior to use, every attempt

should be made to contact the AbbVie Study Physician for direction on re-introduction of study drug after prohibited medication administration.

If the subject must undergo elective surgery, the study injections must be interrupted 2 weeks prior to the surgery. If the subject must undergo emergency surgery, the study injections must be interrupted at the time of the surgery. The injectable study medication can recommence at least 2 weeks after surgery once the physician has examined the surgical site and determined that it has healed and there is no sign of infection.

7.0 Protocol Deviations

AbbVie does not allow intentional/prospective deviations from the protocol. The Principal Investigator is responsible for complying with all protocol requirements, and applicable global and local laws regarding protocol deviations. If a protocol deviation occurs (or is identified) after a subject has been enrolled, the Principal Investigator is responsible for notifying Independent Ethics Committee (IEC)/Independent Review Board (IRB) regulatory authorities (as applicable), and the AbbVie Clinical Monitor(s) assigned to your site. Alternative contacts are as follows:

Alternate Contacts

North America, Latin America, and Japan	Europe, Israel, and Australia
[redacted]	

Such contact must be made as soon as possible to permit a review by AbbVie to determine the impact of the deviation on the subject and/or the study.

For purposes of this protocol, reportable deviations are defined as:

- Subject entered into the study even though they did not satisfy entry criteria
- Subject who developed withdrawal criteria during the study and was not withdrawn
- Subject who received wrong treatment or incorrect dose
- Subject who received excluded or prohibited concomitant treatment

8.0 Statistical Methods and Determination of Sample Size

8.1 Statistical Analysis Plans

The primary objective of the statistical analysis is to evaluate the long-term safety and efficacy of adalimumab 40 mg given every other week (eow) subcutaneously (SC) in subjects with non-infectious intermediate-, posterior-, or pan-uveitis who participated in Study M10-877 or Study M10-880. The following statistical analysis will be done in the total set of subjects. Efficacy analysis will be performed in the Intent to Treat (ITT) set. The safety analysis will be conducted in the Safety set.

The analysis strategy described below will be supplemented by a detailed statistical analysis plan (SAP) which will be completed prior to database lock.

8.1.1 Analysis Population

Both, the ITT set and the safety set include all subjects who received at least one dose of study medication.

No per protocol analysis will be done.

8.1.2 Planned Methods of Statistical Analysis

Descriptive statistics will be provided. These include the number of observations, means, standard deviation, minimum, 1st quartile, median, 3rd quartile, and maximum for

continuous variables; and counts and percentages for discrete variables. The analyses will be performed using SAS (SAS Institute Inc., Cary, NC, USA).

8.1.3 Analysis of Demographics and Baseline Characteristics

Demographics and Baseline characteristics of the study subjects will be summarized using descriptive statistics.

8.1.4 Analysis of Efficacy

All statistical analyses will be descriptive. Results will be stratified between subjects who entered into the study with active versus inactive uveitis. For subjects who had active uveitis when they entered the study, the efficacy analyses will start at Week 8. For subjects who had inactive uveitis when they entered the study, the efficacy analyses will start at Week 0. Continuous variables will be summarized by the number of non-missing observations, mean, standard deviation, median, quartiles, minimum and maximum. Categorical variables will be summarized by counts and percentages.

8.1.5 Analysis of Safety

Treatment-emergent AEs will be summarized using descriptive statistics. Treatment-emergent AEs are defined as events with an onset date on or after the first study drug administration until 70 days following the last study drug administration. In case of increasing severity of an existing AE, the worsening will be considered as a new AE with a new onset date.

AEs will be tabulated by system organ class and preferred term whereby the most current implemented MedDRA dictionary will be used. Also, summaries by severity and relationship to study drug will be done. Certain AEs, like serious or severe, leading to premature withdrawal, will be listed and described in detail. AEs of special interest for treatment with biologics will be defined in the SAP and analyzed separately.

Other safety variables like laboratory data and vital signs will be described by descriptive statistics as mentioned before. In addition, shift tables and listings will be provided for abnormal values whereby the normal range of the analyzing laboratory will be used.

The IDMC will undertake a comprehensive review and assessment of the cumulative safety data until the completion of Study M10-877 and Study M10-880. Please refer to Section 5.5.5.1 for additional information regarding IDMC review.

8.2 Determination of Sample Size

The sample size of this study will depend on how many subjects rollover into the extension study, who have either discontinued from M10-877 or M10-880 due to a "Treatment Failure" or have successfully completed M10-877 or M10-880.

9.0 Ethics

9.1 Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

Good Clinical Practice (GCP) requires that the clinical protocol, any protocol amendments, the Investigator's Brochure, the informed consent and all other forms of subject information related to the study (e.g., advertisements used to recruit subjects) and any other necessary documents be reviewed by an IEC/IRB. The IEC/IRB will review the ethical, scientific and medical appropriateness of the study before it is conducted. IEC/IRB approval of the protocol, informed consent and subject information and/or advertising, as relevant, will be obtained prior to the authorization of drug shipment to a study site.

Any amendments to the protocol will require IEC/IRB approval prior to implementation of any changes made to the study design. The Investigator will be required to submit, maintain and archive study essential documents according to ICH GCP.

Any serious adverse events that meet the reporting criteria, as dictated by local regulations, will be reported to both responsible Ethics Committees and Regulatory

Agencies, as required by local regulations. During the conduct of the study, the Investigator should promptly provide written reports (e.g., ICH Expedited Reports, and any additional reports required by local regulations) to the IEC/IRB of any changes that affect the conduct of the study and/or increase the risk to subjects. Written documentation of the submission to the IEC/IRB should also be provided to AbbVie.

9.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, ICH guidelines, applicable regulations and guidelines governing clinical study conduct and the ethical principles that have their origin in the Declaration of Helsinki, and all applicable local regulations. Responsibilities of the clinical investigator are specified in Appendix A.

9.3 Subject Information and Consent

The Investigator or his/her representative will explain the nature of the study to the subject, and answer all questions regarding this study. Prior to any study-related Baseline procedures being performed on the subject, the informed consent statement will be reviewed and signed and dated by the subject, the person who administered the informed consent, and any other signatories according to local requirements. A copy of the signed and dated informed consent form will be given to the subject and the original will be placed in the subject's medical record. An entry must also be made in the subject's dated source documents to confirm that informed consent was obtained prior to any study-related procedures and that the subject received a signed copy.

For subjects that complete or terminate early from the study, but are within the 70-day follow-up window: if an updated informed consent form is approved these subjects will not be required to return to the study site for the purposes of signing the updated informed consent form, provided the subject is contacted regarding the changes and there is documentation of the contact in the subject's source documents.

If the parent studies are prematurely stopped based upon the recommendation of the IDMC, and this recommendation is based on safety concerns, subjects will be required to return for their Final/Early Termination visit in Study M11-327.

10.0 Source Documents and Case Report Form Completion

10.1 Source Documents

Source documents are defined as original documents, data and records. This may include hospital records, clinical and office charts, laboratory data/information, subjects' diaries or evaluation checklists, pharmacy dispensing and other records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, and/or x-rays. Data collected during this study must be recorded on the appropriate source documents.

The investigator(s)/institution(s) will permit study-related monitoring, audits, IEC/IRB review, and regulatory inspection(s), providing direct access to source data documents.

The following assessments that will be completed by the subject or physician will be considered source documentation:

- NEI Visual Functioning Questionnaire (VFQ-25)
- EuroQol-5D Questionnaire (EQ-5D)
- Health Resource Utilization Questionnaire (HRU)
- Work Productivity and Activity Impairment, Questionnaire: Specific Health Problem Questionnaire (WPAI-SHP)

The adverse event eCRF data segments of: alternate etiology, severity, frequency and relationship to study drug, may also be used as source and will require an Investigator approval on the eCRF as verification of the accuracy of the information.

10.2 Case Report Forms

Electronic case report forms (eCRF) must be completed for each subject screened/enrolled in this study. These forms will be used to transmit information collected during the study to AbbVie and regulatory authorities, as applicable. The eCRF data for this study are being collected with an electronic data capture (EDC) system called Rave® provided by the technology vendor Medidata Solutions Incorporated, NY, USA. The EDC system and the study-specific electronic Case Report Forms (eCRFs) will comply with Title 21 CFR Part 11. The documentation related to the validation of the EDC system is available through the vendor, Medidata, while the validation of the study-specific eCRFs will be conducted by AbbVie and will be maintained in the Trial Master File at AbbVie.

The Investigator will document subject data in his/her own subject files. These subject files will serve as source data for the study. All eCRF data required by this protocol will be recorded by investigative site personnel in the EDC system. All data entered into the eCRF will be supported by source documentation. The central laboratory will send hard copies of laboratory results to sites which must be reviewed by the Investigator and filed as source data.

The Investigator or an authorized member of the Investigator's staff will make any necessary corrections to the eCRF. All change information, including the date and person performing the corrections, will be available via the audit trail, which is part of the EDC system. For any correction, a reason for the alteration will be provided. The eCRFs will be reviewed periodically for completeness, legibility, and acceptability by AbbVie personnel (or their representatives). AbbVie (or their representatives) will also be allowed access to all source documents pertinent to the study in order to verify eCRF entries. The Principal Investigator will review the eCRFs for completeness and accuracy and provide his or her electronic signature and date to eCRFs as evidence thereof.

Medidata will provide access to the EDC system for the duration of the trial through a password-protected method of internet access. Such access will be removed from investigator sites at the end of the site's participation in the study. Data from the EDC

system will be archived on appropriate data media (CD-ROM, etc.) and provided to the Investigator at that time as a durable record of the site's eCRF data. It will be possible for the Investigator to make paper printouts from that media.

The site will complete the VFQ-25 and HRU questionnaires via interview. The remaining questionnaires listed below will be completed by the subject, except when subjects with impaired vision cannot complete the questionnaires on their own, the site may administer the questionnaire. Except for the HRU which will be entered into EDC by the site, the subjects and site will enter responses on paper Case Report Forms provided by AbbVie and forwarded to AbbVie CDM for double data entry.

Any corrections to the questionnaires can only be made by the original respondent. All changed information, including the date and person performing the corrections, will be available via the audit trail.

- NEI Visual Functioning Questionnaire (VFQ-25)
- EuroQol-5D Questionnaire (EQ-5D)
- Health Resource Utilization Questionnaire (HRU)
- Work Productivity and Activity Impairment, Questionnaire: Specific Health Problem Questionnaire (WPAI-SHP)

11.0 Data Quality Assurance

Prior to the initiation of the study, a meeting will be held with AbbVie personnel, the Investigators and appropriate site personnel. This meeting will include a detailed discussion of the protocol, performance of study procedures, eCRF, Subject Questionnaires and Subject Diary completion, and specimen collection methods.

The AbbVie CRA will monitor each site throughout the study.

Source document verification will be performed.

All data entered in the database will be verified at AbbVie. Any discrepancies will be reviewed. The data will be reviewed and computer logic checks will be run to identify items such as inconsistent study dates. A manual review of selected line listings also will be performed at the end of the study. Queries will be generated in the EDC system. Any necessary corrections will be made to the eCRF.

The data from the central laboratory analyses will be electronically transferred from the central laboratory to the study database. A final review of all laboratory results will be conducted by a physician and clinical review team at AbbVie.

12.0 Use of Information and Publication

12.1 Use of Information

All information concerning adalimumab and AbbVie operations, such as AbbVie patent applications, formulas, manufacturing processes, basic scientific data, or formulation information, supplied by AbbVie and not previously published is considered confidential information.

The information developed during the conduct of this clinical trial is also considered confidential and will be used by AbbVie in connection with the development of adalimumab. This information may be disclosed as deemed necessary by AbbVie to other clinical Investigators, other pharmaceutical companies, to the FDA and to other government agencies. To allow for the use of the information derived from this clinical trial and to ensure complete and thorough analysis, the Investigator is obligated to provide AbbVie with complete test results and all data developed in this study and to provide direct access to source data/documents for trial-related monitoring, audits, IEC/IRB review, and regulatory inspection.

This confidential information shall remain the sole property of AbbVie, shall not be disclosed to others without the written consent of AbbVie, and shall not be used except in the performance of this study.

The Investigator will maintain a confidential subject identification code list of all subjects enrolled in the study (by name and subject number). This list will be maintained at the site and will not be retrieved by AbbVie.

Information regarding this study may be posted on various internet web sites and will maximally include study name, number, general population to be enrolled, entrance qualifications, brief description of the study, study objectives, doses, accruing Investigators (upon their approval) and number of subjects to be enrolled.

Please refer to your Investigator site contract for information related to publication practices.

13.0 Completion of the Study

The investigator will conduct the study in compliance with the protocol and complete the study within the timeframe specified in the contract between the investigator (Director of the Site in Japan) and AbbVie. Continuation of this study beyond this date must be mutually agreed upon in writing by both the investigator (Director of the Site in Japan) and AbbVie. The investigator will provide a final report to the IEC/IRB following conclusion of the study, and will forward a copy of this report to AbbVie or their representative.

The investigator (Director of the Site in Japan) must retain any records related to the study according to local requirements. If the investigator (Director of the Site in Japan) is not able to retain the records, he/she must notify AbbVie to arrange alternative archiving options.

AbbVie will select the signatory investigator from the investigators who participate in the study. Selection criteria for this investigator will include level of participation as well as significant knowledge of the clinical research, investigational drug and study protocol. The signatory investigator for the study will review and sign the final study report in accordance with the European Medicines Agency (EMA) Guidance on Investigator's Signature for Study Reports.

The end-of-study is defined as the date of the last subject's last scheduled visit or the actual date of follow-up contact, whichever is later.

AbbVie may terminate this study prematurely, for reasonable cause, provided that written notice is submitted a reasonable time in advance of the intended termination. Advance notice is not required if the study is stopped due to safety concerns.

14.0 Investigator's Agreement

1. I have received and reviewed the Investigator's Brochure for adalimumab.
2. I have read this protocol and agree that the study is ethical.
3. I agree to conduct the study as outlined and in accordance with all applicable regulations and guidelines.
4. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.
5. I agree that all electronic signatures will be considered the equivalent of a handwritten signature and will be legally binding.

Protocol Title:	A Multicenter Open-Label Study of the Long-term Safety and Efficacy of the Human Anti-TNF Monoclonal Antibody Adalimumab in Subjects with Non-infectious Intermediate-, Posterior-, or Pan-uveitis – VISUAL III
Protocol Date:	04 June 2015

Signature of Principal Investigator	Date
Name of Principal Investigator (printed or typed)	

15.0 Reference List

1. Mazurek GH, Jereb J, Vernon A, et al. Updated guidelines for using Interferon Gamma Release Assays to detect Mycobacterium tuberculosis infection – United States, 2010. MMWR Recomm Rep. 2010 Jun 25;59(RR-5):1-25.
2. Yanoff M, Duker JS, editors. Yanoff and Duker: Ophthalmology, 3rd ed. Elsevier Health Sciences; 2009.
3. Jabs DA, Nussenblatt RB, Rosenbaum JT. The standardization of uveitis nomenclature (SUN) working group. Standardization of uveitis nomenclature for reporting clinical data. Results of the First International Workshop. Am J Ophthalmol. 2005;140(3):509-16.
4. Rothova A, Suttorp-van Schulten MS,Treffers WF, Kijlstra A. Causes and frequency of blindness in patients with intraocular inflammatory disease. Br J Ophthalmol. 1996;80(4):332-6.
5. Wakefield D, Chang JH. International Ophthalmology Clinics. 2005 Spring 45(2):1-13.
6. Jabs DA, Rosenbaum JT, Foster CS, Holland GN, Jaffe GJ, Louie JS, 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):492-513.
7. Cervantes-Castaneda RA, Jawed N, Foster CS. Immunosuppressive therapy for noninfectious uveitis. Retinal Physician. 2007;March:30-8.
8. Becker MD, Smith JR, Max R, Fiehn C. Management of sight-threatening uveitis: new therapeutic options. Drugs. 2005;65(4):497-519.
9. Smith JR, Rosenbaum JT. Management of Uveitis: A rheumatologic perspective. Arthritis Rheum. 2002;46(2):309-18.
10. Nussenblatt R. The natural history of uveitis. Int Ophthalmology. 1990;14:303-8.
11. Retisert (fluocinolone acetonide intravitreal implant [Package Insert]. Rochester, NY: Bausch & Lomb; 2007.

12. Jaffe GJ, Martin D, Callanan D, Pearson PA, Levy B. Fluocinolone acetonide implant (Retisert) for noninfectious posterior uveitis: Thirty-four-week results of a multicenter randomized clinical study. Ophthalmology. 2006;113:1020-7.
13. Callanan DG, Jaffe GJ, Martin DF, Pearson PA, Comstock TL. Treatment of posterior uveitis with a fluocinolone acetonide implant: Three-year clinical trial results. Arch Ophthalmol. 2008;126(9):1191-1201.
14. Caspi RR, Sun B, Agarwal RK. T cell mechanisms in experimental autoimmune uveoretinitis: susceptibility is a function of the cytokine response profile. Eye. 1997;11:209-12.
15. Murphy CC, Duncan L, Forrester JV, Dick AD. Systemic CD4+ T cell phenotype and activation status in intermediate uveitis. Br J Ophthalmol. 2004;88:412-6.
16. Deschenes J, Char DH, Kaleta S. Activated T lymphocytes in uveitis. Br J Ophthalmol. 1988;72:83-7.
17. Dick AD, Forrester JV, Liversidge J, Cope AP. The role of tumour necrosis factor (TNF-a) in experimental autoimmune uveoretinitis (EAU). Progress in Retinal and Eye Research. 2004;23:617-37.
18. Okada AA, Sakai J, Usui M, Mizuguchi J. Intraocular cytokine quantification of experimental autoimmune uveoretinitis in rats. Ocular Immunology and Inflammation. 1998;6(2):111-20.
19. Sartani G, Silver PB, Rizzo LV, Chan C, Wiggert B, Mastorakos G, et al. Anti-tumor necrosis factor alpha therapy suppresses the induction of experimental autoimmune uveoretinitis in mice by inhibiting antigen priming. Invest Ophthalmol Vis Sci. 1996;37:2211-8.
20. Dick AD, Duncan L, Hale G, Waldmann H, Isaacs J. Neutralizing TNF-alpha activity modulates T-cell phenotype and function in experimental autoimmune uveoretinitis. J of Autoimmunity. 1998;11:255-64.
21. Callejas-Rubio JL, Sánchez-Cano D, García Serrano JL, Ortego-Centeno N. Letter to the Editor: Adalimumab therapy for refractory uveitis: A pilot study. J Ocul Pharmac Ther. 2008;24(6):613-4.

22. Mushtaq B, Saeed T, Situnayake RD, Murray PI. Adalimumab for sight-threatening uveitis in Behcet's disease. Eye. 2007;21:824-5.

23. Diaz-Llopis M, Garcia-Delpech S, Salom D, Udaondo P, Hernandez-Garfella M, Bosch-Morell F, et al. Adalimumab therapy for refractory uveitis: A pilot study. J Ocul Pharmacol Ther. 2008;24:351-61.

24. Vazquez-Cobian LB, Flynn T, Lehman TJA. Adalimumab therapy for childhood uveitis. J Pediatr. 2006;149:572-5.

25. Tognon S, Graziani G, Marcolongo R. Anti-TNF-Therapy in seven patients with Behcet's uveitis: advantages and controversial aspects. Ann. N.Y. Acad. Sci. 2007;1110:474-84.

26. Saurenmann RK, Levin AV, Rose JB, Parker S, Rabinovitch T. Tumour necrosis factor a inhibitors in the treatment of childhood uveitis. Rheumatology. 2006;45:982-9.

27. Niccoli L, Nannini C, Benucci M, Chindamo C, Cassara E. Long-term efficacy of infliximab in refractory posterior uveitis of Behcet's disease: a 24-month follow-up study. Rheumatology. 2007;46:1161-4.

28. Lindstedt EW, Baarsma GS, Kuijpers RWAM, van Hagen PM. Anti-TNF-a therapy for sight threatening uveitis. Br J Ophthalmol. 2005;89:533-6.

29. Suhler EB, Smith JR, Wertheim MS, Lauer AK, Kurz DE. A prospective trial of infliximab therapy for refractory uveitis. Arch Ophthalmol. 2005;123:903-12.

30. Suhler EB, Smith JR, Giles TR, Lauer AK, Wertheim MS. Infliximab therapy for refractory uveitis: 2-year results of a prospective trial. Arch Ophthalmol. 2009;127(6):819-22.

31. Schmeling H, Horneff G. Etanercept and uveitis in patients with juvenile idiopathic arthritis. Rheumatology. 2005;44:1008-11.

32. Foster CS, Tufail F, Waheed NK, Chu D, Miserocchi E. Efficacy of etanercept in preventing relapse of uveitis controlled by methotrexate. Arch Ophthalmol. 2003;121(4):437-40.

33. Jakob E, Reuland MS, Mackensen F, Harsch N, Fleckenstein M, Lorenz HM, et al. Uveitis subtypes in a german interdisciplinary uveitis center – analysis of 1916 patients. J Rheumatol. 2009;36(1):127-36.

34. Biester S, Deuter C, Michels H, Haefner R, Kuemmerle-Deschner J, Doycheva D, et al. Adalimumab in the therapy of uveitis in childhood. Br J Ophthalmol. 2007;91:319-24.

35. Rudwaleit M, Rodevand E, Holck P, Vanhoof J, Kron M, Kary S, et al. Adalimumab effectively reduces the rate of anterior uveitis flares in patients with active ankylosing spondylitis. Ann Rheum Dis. 2009;68:696-701.

36. Suhler EB, Goldstein DA, Lowder CY, Giles TR, Liesegang TL. Adalimumab (Humira) for the treatment of refractory uveitis: preliminary results of a multicenter prospective phase II clinical trial. Oral Presentation, Association of Research in Vision and Ophthalmology annual meeting. Fort Lauderdale, FL. 2009.

37. The Age-Related Eye Diseases Study Group. The age-related eye disease study (AREDS) system for classifying cataracts from photographs: AREDS report no. 4. Am J Ophthalmol. 2001 Feb;131(2):167-75.

38. Chew EY, Kim J, Sperduto R, Datiles MB III, Coleman H, Smith J, et al. Evaluation of the Age-Related Eye Disease Study (AREDS) Clinical Lens Grading System. Accepted for publication in Ophthalmology.

39. Nussenblatt RB, Palestine AG, Chan C, Roberge F. Standardization of vitreal inflammatory activity in intermediate and posterior uveitis. Ophthalmology. 1985;92:467-71.

40. Nussenblatt RB, Peterson JS, Foster CS, Rao NA, See RF. Initial Evaluation of Subcutaneous Daclizumab Treatments for Noninfectious Uveitis. Ophthalmology. 2005;112:764-770.

41. Díaz-Llopis M, Salom D, Garcia-de-Vicuña C, et al. Treatment of refractory uveitis with adalimumab: a prospective multicenter study of 131 patients. Ophthalmology. 2012;119(8):1575-81.

Appendix A. Responsibilities of the Clinical Investigator

Clinical research studies sponsored by AbbVie are subject to the Good Clinical Practices (GCP) and local regulations and guidelines governing the study at the site location. In signing the Investigator Agreement in Section 14.0 of this protocol, the Investigator is agreeing to the following:

1. Conducting the study in accordance with the relevant, current protocol, making changes in a protocol only after notifying AbbVie, except when necessary to protect the safety, rights or welfare of subjects.
2. Personally conducting or supervising the described investigation(s).
3. Informing all subjects, or persons used as controls, that the drugs are being used for investigational purposes and complying with the requirements relating to informed consent and ethics committees [e.g., independent ethics committee (IEC) or institutional review board (IRB)] review and approval of the protocol and amendments.
4. Reporting adverse experiences that occur in the course of the investigation(s) to AbbVie and the site director.
5. Reading the information in the Investigator's Brochure/safety material provided, including the instructions for use and the potential risks and side effects of the investigational product(s).
6. Informing all associates, colleagues, and employees assisting in the conduct of the study about their obligations in meeting the above commitments.
7. Maintaining adequate and accurate records of the conduct of the study, making those records available for inspection by representatives of AbbVie and/or the appropriate regulatory agency, and retaining all study-related documents until notification from AbbVie.
8. Maintaining records demonstrating that an ethics committee reviewed and approved the initial clinical investigation and all amendments.

9. Reporting promptly, all changes in the research activity and all unanticipated problems involving risks to human subjects or others, to the appropriate individuals (e.g., coordinating Investigator, institution Director) and/or directly to the ethics committees and AbbVie.

10. Following the protocol and not making any changes in the research without ethics committee approval, except where necessary to eliminate apparent immediate hazards to human subjects.

Appendix B. List of Protocol Signatories

Name	Title	Functional Area
[redacted]		Clinical
		Clinical
		Statistics
		Clinical

Appendix C. Non-Drug Materials Provided to the Study Sites

Study sites will receive the following supplies prior to or during the study:

- Tote Bags
- Coolers
- Sharps Containers
- Ice Packs
- Subject Dosing Diary

Appendix D. Day 70 Follow-up (Phone Call or Clinic Visit)

Site Name/Number: _____/_____

Subject Number: _____

Please contact all subjects approximately 70 days following last study drug administration.

Date of Call/Visit: _____

☐ Lost to Follow-up (Please check this box if subject was not willing to provide any follow-up information or you were unable to speak to the subject following at least two phone call attempts and one certified letter).

☐ No Events Reported

List any Adverse Events (AE) and/or Serious Adverse Events (SAE) that occurred since the subject's last study drug administration. Please document all adverse events on a 500 AE CRF in the EDC system. (Please report all SAEs to AbbVie within 24 hours of being made aware of the event). **In addition, please note stop dates to any adverse events that were ongoing at the last study visit. If an adverse event is determined to be ongoing at the 70 day call/visit, please note in source documents and in EDC.**

_____	_____
_____	_____
_____	_____
_____	_____

Name of person completing form (printed): _____

Signature of person completing form: _____

Date: _____

Please fax this form to AbbVie at [redacted]

Subject Injection Instructions

0.8 mL dose

(Administered as a single dose-pre-filled syringe)

Protocol M11-327

Table of Contents

Dosing Schedule

General Information and Supplies

Injection Procedures

Dosing Diary
Adalimumab

Instructions: To be completed for every study dose. Study medication should be taken at about the same time of day, on the same day of the week as directed by your study doctor. Please refer to the Self Injection Instructions provided to you for additional dosing information. Call the doctor's office if you are having problems administering your study medication.

Appendix F. AREDS 2008 Clinical Lens Opacity Grading Procedures

AREDS Study Group

- Dilate pupils to at least 5 mm diameter
- Use slit lamp with ~10× magnification
- Use brightest beam intensity
- Nuclear opacity
  - Orient beam at 45° to viewing axis
  - Adjust slit beam to standard parameters: 8 mm height and 0.3 mm width
  - Compare opalescence of nucleus with that in standard photos
- Cortical and PSC opacities
  - Select wide slit beam setting optimum for retro-illumination of lens
  - Visualize lens opacities against red fundus reflex background
  - Count only opacities definitely visible against red reflex
  - Mentally combine all cortical opacities into one contiguous area
  - Compare total opacity area with that in standard photos
- Classify each opacity with scale defined by 3 standard photos
- Select nearest half-step
  - Similar to standard or between two standards
  - Obviously less than mildest standard or greater than most severe

3. How much of the time do you worry about your eyesight?
(Circle One)

READ CATEGORIES:		
	None of the time	1
	A little of the time	2
	Some of the time	3
	Most of the time	4
	All of the time?	5

4. How much pain or discomfort have you had in and around your eyes (for example, burning, itching, or aching)? Would you say it is:
(Circle One)

READ CATEGORIES:		
	None	1
	Mild	2
	Moderate	3
	Severe, or	4
	Very severe?	5

PART 2 - DIFFICULTY WITH ACTIVITIES

The next questions are about how much difficulty, if any, you have doing certain activities wearing your glasses or contact lenses if you use them for that activity.

5. How much difficulty do you have reading ordinary print in newspapers? Would you say you have:
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

6. **How much difficulty do you have doing work or hobbies that require you to see well up close, such as cooking, sewing, fixing things around the house, or using hand tools? Would you say:**
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

7. **Because of your eyesight, how much difficulty do you have finding something on a crowded shelf?**
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

8. **How much difficulty do you have reading street signs or the names of stores?**
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

9. **Because of your eyesight, how much difficulty do you have going down steps, stairs, or curbs in dim light or at night?**

(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

10. Because of your eyesight, how much difficulty do you have noticing objects off to the side while you are walking along?
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

11. Because of your eyesight, how much difficulty do you have seeing how people react to things you say?
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

12. **Because of your eyesight, how much difficulty do you have picking out and matching your own clothes?**
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

13. **Because of your eyesight, how much difficulty do you have visiting with people in their homes, at parties, or in restaurants ?**
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

14. **Because of your eyesight, how much difficulty do you have going out to see movies, plays, or sports events?**
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

15. Now, I'd like to ask about driving a car. Are you currently driving, at least once in a while?

(Circle One)

Yes	1	*Skip To Q 15c*
No	2	

15a. IF NO, ASK: Have you never driven a car or have you given up driving?

(Circle One)

Never drove	1	*Skip To Part 3, Q 17*
Gave up	2	

15b. IF GAVE UP DRIVING: Was that mainly because of your eyesight, mainly for some other reason, or because of both your eyesight and other reasons?

(Circle One)

Mainly eyesight	1	*Skip To Part 3, Q 17*
Mainly other reasons	2	*Skip To Part 3, Q 17*
Both eyesight and other reasons	3	*Skip To Part 3, Q 17*

15c. IF CURRENTLY DRIVING: How much difficulty do you have driving during the daytime in familiar places? Would you say you have:

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4

For each of the following statements, please tell me if it is definitely true, mostly true, mostly false, or definitely false for you or you are not sure.

(Circle One On Each Line)

	Definitely True	Mostly True	Not Sure	Mostly False	Definitely False
20. I stay home most of the time because of my eyesight.	1	2	3	4	5
21. I feel frustrated a lot of the time because of my eyesight.	1	2	3	4	5
22. I have much less control over what I do, because of my eyesight.	1	2	3	4	5
23. Because of my eyesight, I have to rely too much on what other people tell me...	1	2	3	4	5
24. I need a lot of help from others because of my eyesight.	1	2	3	4	5
25. I worry about doing things that will embarrass myself or others, because of my eyesight.	1	2	3	4	5

That's the end of the interview. Thank you very much for your time and your help.

Appendix H. EuroQol-5D Questionnaire (EQ-5D)

EQ-5D

Health Questionnaire

(English version for the US)

By placing a checkmark in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about	☐
I have some problems in walking about	☐
I am confined to bed	☐

Self-Care

I have no problems with self-care	☐
I have some problems washing or dressing myself	☐
I am unable to wash or dress myself	☐

Usual Activities (*e.g., work, study, housework, family or leisure activities*)

I have no problems with performing my usual activities	☐
I have some problems with performing my usual activities	☐
I am unable to perform my usual activities	☐

Pain/Discomfort

I have no pain or discomfort	☐
I have moderate pain or discomfort	☐
I have extreme pain or discomfort	☐

Anxiety/Depression

I am not anxious or depressed	☐
I am moderately anxious or depressed	☐
I am extremely anxious or depressed	☐

Appendix I. Health Resource Utilization Questionnaire (HRU)

Since the last study visit has the subject had any visits for their uveitis other than the protocol required visit?

YES: ____
NO: ____
If YES, please provide the following:

1. Since the last protocol required visit, has the subject been seen by a health care professional for their uveitis?

   YES: ____
   NO: ____
   If YES, how many times: ____

2. Since the last protocol required visit, has the subject been seen in the Emergency Room for their uveitis?

   YES: ____
   NO: ____
   If YES, how many times: ____

3. Since the last protocol required visit, has the subject been admitted to the hospital due to their uveitis?

   YES: ____
   NO: ____

   If YES, please list the ADMISSION DATE: __ __/___ ___ ___/ ___ ___ ___ __
   DD MMM YYYY

   DISCHARGE DATE: __ __/___ ___ ___/ ___ ___ ___ __
   DD MMM YYYY

Appendix J. Work Productivity and Activity Impairment, Questionnaire: Specific Health Problem Questionnaire V2.0 (WPAI-SHP)

The following questions ask about the effect of your UVEITIS on your ability to work and perform regular activities. *Please fill in the blanks or circle a number, as indicated.*

1. Are you currently employed (working for pay)? _____ NO ___ YES
   If NO, check "NO" and skip to question 6.

The next questions are about the **past 7 days**, not including today.

2. During the past 7 days, how many hours did you miss from work because of problems associated with your UVEITIS? Include hours you missed on sick days, times you went in late, left early, etc., because of your UVEITIS. Do not include time you missed to participate in this study.

   _____HOURS

3. During the past seven days, how many hours did you miss from work because of any other reason, such as vacation, holidays, time off to participate in this study?

   _____HOURS

4. During the past seven days, how many hours did you actually work?
   _____HOURS *(If "0," skip to question 6.)*

5. During the past 7 days, how much did your UVEITIS affect your productivity <u>while you were working</u>?

Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as usual. If UVEITIS affected your work only a little, choose a low number. Choose a high number if UVEITIS affected your work a great deal.

Consider only how much UVEITIS affected productivity while you were working.

UVEITIS had no effect on my work	0	1	2	3	4	5	6	7	8	9	10	UVEITIS completely prevented me from working

CIRCLE A NUMBER

6. During the past 7 days, how much did your UVEITIS affect your ability to do your regular daily activities, other than work at a job?

By regular activities, we mean the usual activities you do, such as work around the house, shopping, childcare, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could do and times you accomplished less than you would like. If UVEITIS affected your activities only a little, choose a low number. Choose a high number if UVEITIS affected your activities a great deal.

Consider only how much UVEITIS affected your ability to do your regular daily activities, other than work at a job.

UVEITIS had no effect on my daily activities	0	1	2	3	4	5	6	7	8	9	10	UVEITIS completely prevented me from doing my daily activities

CIRCLE A NUMBER

WPAI:SHP V2.0 (US English)

Appendix K. Japan Appendix

In Japan only, the above protocol is to be followed except where indicated in the sections below. It is anticipated that approximately 400 adult subjects with non-infectious intermediate-, posterior-, or pan-uveitis will be enrolled at up to 102 investigational sites in the United States, Canada, Europe, Israel, Latin America, Japan and Australia.

5.3.1 Efficacy and Safety Measurements Assessed and Flow Chart

Safety data will be collected in the form of adverse events, physical examinations, vital signs and laboratory tests throughout the treatment period. Adverse events will also be collected up to 70 days after the last injection in this study. The 70-day follow-up phone call will not be required for any subject that initiates commercial adalimumab after the end of study participation.

The visit window for all scheduled visits is ±7 days for all visits. If a subject has an out of window visit, the next visit should occur as originally scheduled based on the first date of study drug administration (Baseline visit).

Study procedures will be performed per the main protocol as summarized in the visit schedule presented in Table 1 except where indicated in the sections below.

Table 1. Study Activities - Japan Only

Activity	Baseline[J1]	Week 2	Week 4	Week 8	Week 12	Week 18	Week 30	Week 42	Week 54	Week 66	Every 12 Weeks Following Week 66[r]	Final/Early Termination Visit	Unscheduled Visit	70-Day Follow-up
Chest X-ray	X							X				X	X	

These footnotes only pertain to the Japan portion of the study and do not replace any procedures in the main protocol.

J1. The chest x-ray does not need to be repeated even if the Baseline visit occurs greater than (>) 14 days after the Final/Early Termination visit of the parent study.

5.3.1.1 Study Procedures

Chest X-ray (CXR)

For Japan only, all subjects will undergo a standard CXR (posterior-anterior [PA] and lateral views) at the Baseline visit, which will be conducted as part of the Final/Early Termination visit in the parent study, and at the Final/Early Termination visit of Study M11-327 to ensure safety of the subjects. In the assessment of the CXR, a radiologist and/or physician for respiratory medicine must note the presence or absence of calcified granulomas and/or pleural scarring/thickening and/or signs of active TB. The Principal Investigator will indicate the clinical significance of any findings and will sign and date the report. In the absence of abnormal findings the Principal Investigator should sign and date the report to indicate review of the report. The CRA will monitor this documentation. Subjects can have a repeat CXR at any time during the study as warranted based on the opinion of the Investigator and/or CXR is inconclusive.

If a subject has a positive TB test at Baseline or Week 42, 90, 138, 186, 234, 282, or 330, subjects will undergo a standard CXR (posterior-anterior [PA] and lateral views) to rule out the presence of TB or other clinically relevant findings.

In addition, other diagnostic imaging tests may be performed as needed if pulmonary involvement is suspected based on the investigator's clinical assessment.

Dispense Study Drug

Study drug will be administered to subjects by study site medical staff, by himself/herself or by a designee (family member or health care professional) throughout the study.

Subjects in Japan will be administered the study drug at the investigative site throughout the study when the dose of prednisone or prednisone equivalent is > 10 mg/day to secure the safety of the subjects.

Subjects or a designated family member will be trained to administer study medication during the first visit or several times, if appropriate. This training must be documented in the subject's source document.

Subjects or a trained designated family member or a Health Care Professional will administer the injections of the study medication in the subject's home or in the clinic during the weeks the subjects are not in the office for scheduled study visits.

Subjects will maintain a log for all study medication administered outside of the study visit (i.e., at home). The dosing records will be reviewed and verified for compliance at each clinic visit. All relevant dosing information will be retained by study personnel. Additionally, any discernible departure from the protocol regarding study drug administration will be documented appropriately. A sample of the Subject Dosing Diary is presented in Appendix E.

For subjects that cannot/will not self-administer study drug or do not have adequate support (family member) at home, administration will occur in the clinic.

At all office visits, subjects should be observed after study drug administration until judged clinically stable by the study personnel. If an anaphylactic reaction or other serious allergic reaction occurs, administration of study medication should be discontinued immediately and appropriate therapy initiated. When dosing at home, subjects should be instructed to contact the site immediately with any signs or symptoms of a reaction.

For subjects who deviate from the dosing schedule, every effort should be made to bring the subject back to the original dosing schedule as soon as possible.

The subject must be instructed to return study drug at each clinic visit for the purpose of compliance assessment and drug accountability as detailed in Section 5.5.6.1.

6.5 Adverse Event Reporting

In Japan, the Principal Investigator will provide documentation of all serious adverse events to the Director of the investigative site and the Sponsor.

7.0 Protocol Deviations

In Japan, the Investigator will record all protocol deviations in the appropriate medical records at site.

9.3.1 Informed Consent Form and Explanatory Material

In Japan, the Principal Investigator will prepare the consent form and explanatory material required to obtain subject's consent to participate in the study in cooperation with the sponsor and will revise these documents as required. The prepared or revised consent forms and explanatory material will be submitted to the sponsor. Approval of the IRB will be obtained prior to use in the study.

9.3.2 Revision of the Consent Form and Explanatory Material

In Japan, when important new information related to the subject's consent becomes available, the Principal Investigator will revise without delay the consent form and explanatory material based on the information and will obtain the approval of the IRB prior to use in the study. The Investigator will provide the information, without delay, to each subject already participating in the study, and will confirm the intention of each subject to continue in the study or not. The Investigator will also provide further explanation using the revised consent form and explanatory material and will obtain written consent from each subject of their own free will to continue participation in the study.

13.0 Completion of the Study

The Investigator will conduct the study in compliance with the protocol and complete the study within the timeframe specified in the contract between the Investigator (Director of

the Site in Japan) and AbbVie. Continuation of this study beyond this date must be mutually agreed upon in writing by both the Investigator (Director of the Site in Japan) and AbbVie. The Investigator will provide a final report to the IEC/IRB following conclusion of the study, and will forward a copy of this report to AbbVie or their representative.

The Investigator (Director of the Site in Japan) must retain any records related to the study according to local requirements. If the Investigator (Director of the Site in Japan) is not able to retain the records, he/she must notify AbbVie to arrange alternative archiving options.

16.0 Clinical Expense and Compensation

16.1 Expenditure of the Clinical Expense

The sponsor will pay the expenses related to this study to the investigative site in accordance with "Special Healthcare Expenditure." The expenses for screening test, etc. will be paid based on the contract agreed upon with each investigative site. To lighten the burden imposed on the subject with participation to the study, transportation expenses, etc. will be paid to the subjects via participating investigative site in accordance with the rules of the investigative site.

16.2 Compensation for Health Impairment and Insurance

1. If a subject suffers some sort of health impairment due to this study, the investigative site will provide treatment and other necessary measures. Among the expenses required for the treatment, the amount not covered by health insurance that the patient must pay directly will be borne by the sponsor only when the event is associated with the use of the study drug.
2. When a subject suffers health impairment during this study and a dispute occurs or might potentially occur between the investigative site and the subject, the investigative site will immediately report this to the sponsor and resolve it. The sponsor will work with the investigative site in resolving any issues or problems.

3. When the investigative site must compensate subject for any health impairment caused by this study, the compensation paid by the investigative site and the expenses related to any dispute will be borne in full by the sponsor, except in cases where the responsibility for the problem is attributed to the investigative site. This shall not apply to cases where the health impairment occurred because the investigative site performed the study with marked deviation from the GCP or the protocol or because of a deliberate action or a major error by the investigative site.
4. When a subject suffers health impairment during this study and liability for compensation arises, the sponsor will compensate in accordance with the SOP regarding the compensation prepared in advance.
5. The sponsor will obtain clinical study insurance and will take other necessary measures to cover the claims and compensation required in such cases.

17.0 Storage of Records

The directors of the investigative sites will retain the "Essential documents to be retained by study institutions" specified in the Section 4.9.5 of ICH guideline for the period specified in the following.

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents are no longer need to be retained.

18.0 Study Period

For Japan sub-study, the study will conclude immediately after study drug receives country regulatory approval for uveitis. The study will be discontinued approximately three months after discontinuation of the uveitis program due to study cancellation or non-approval by the regulatory agencies, if applicable. Subjects will be instructed to return for their next scheduled visit for a final visit at this time.

Investigator's Agreement - Japan

The Principal Investigator will agree to the following: 1) I have received and reviewed the Investigator's Brochure for Adalimumab I have read this protocol and agree that the study is ethical; 3) I agree to conduct the study as outlined and in accordance with all applicable regulations and guidelines; 4) I agree to maintain the confidentiality of all information received or developed in connection with this protocol and 5) I agree with the Sponsor about the contents of the protocol and CRFs and to comply with them.

Study Title:	A Multicenter Open-Label Study of the Long-term Safety and Efficacy of the Human Anti-TNF Monoclonal Antibody Adalimumab in Subjects with Non-infectious Intermediate-, Posterior-, or Pan-uveitis – VISUAL III
Protocol Number:	M11-327
Issue Date:	☐ Protocol: Version , / / ☐ CRF: Version , / /
Site–specific Change ☐ No ☐ Yes	Site Number: Contents of Change:

Investigator	Site: Title: Name: Date: / /	Seal
Trial Director	Sponsor: Title: Name: Date: / /	Seal

Appendix L. Protocol Amendment: List of Changes

The summary of changes is listed in Section 1.1.

Protocol Specific Changes:

Section 1.0 Title Page
"Sponsor/Emergency Contact:" previously read:

Sponsor/Emergency Contact:	**US, Canada, Latin America:** [redacted]	**Europe, Israel, and Australia:**
	Japan: [redacted]	

Has been changed to read:

Sponsor/Emergency Contact:	**US, Canada, Latin America:**	**Europe, Israel, and Australia:**
	[redacted]	
	Japan:	
	[redacted]	

Section 1.2 Synopsis
Subsection <u>Duration of Treatment:</u>
Previously read:

The entire study will be terminated in March 2016.

Has been changed to read:

The entire study will be terminated in March 2018.

Figure 1. Study Schematic
Figure note "*" previously read:

* Visits will occur every 12 weeks following Week 66 until the end of the study (not to exceed 15 March 2016).

Has been changed to read:

* Visits will occur every 12 weeks following Week 66 until the end of the study (not to exceed 15 March 2018).

Section 5.1 Overall Study Design and Plan: Description
Last paragraph previously read:

The entire study will be terminated in March 2016. Subjects who remain active in this clinical trial on 15 February 2016 should be contacted by the site to return for their study termination visit. Sites should complete the termination visit by 15 March 2016 for all of the remaining active subjects. These subjects will be considered as having completed the study.

Has been changed to read:

The entire study will be terminated in March 2018. Subjects who remain active in this clinical trial on 15 February 2018 should be contacted by the site to return for their study termination visit. Sites should complete the termination visit by 15 March 2018 for all of the remaining active subjects. These subjects will be considered as having completed the study.

Table 1. Study Activities
Table note "j.," "k.," and "r." previously read:

j. An annual TB test must be completed at the Week 42, 90, 138, 186, and 234 visits for all subjects. Please reference Section 5.3.1.1 Study Procedures for further information.
k. If the TB test is missed at the Week 42, 90, 138, 186, or 234 visits, the subject must be brought in within 30 days of the visit to have the test completed.
r. Subjects will have study visits every 12 weeks following Week 66 until the end of study (not to exceed 15 March 2016).

Has been changed to read:

j. An annual TB test must be completed at the Week 42, 90, 138, 186, 234, 282, or 330 visits for all subjects. Please reference Section 5.3.1.1 Study Procedures for further information.

k. If the TB test is missed at the Week 42, 90, 138, 186, 234, 282, or 330 visits, the subject must be brought in within 30 days of the visit to have the test completed.

r. Subjects will have study visits every 12 weeks following Week 66 until the end of study (not to exceed 15 March 2018).

Section 5.3.1.1 Study Procedures
First paragraph previously read:

Subjects will have clinic visits at Baseline, Week 2, Week 4, Week 8, Week 12, Week 18 and every 12 weeks thereafter until the final visit which should occur no later than March 2016.

Has been changed to read:

Subjects will have clinic visits at Baseline, Week 2, Week 4, Week 8, Week 12, Week 18 and every 12 weeks thereafter until the final visit which should occur no later than March 2018.

Section 5.3.1.1 Study Procedures
Third paragraph, first sentence previously read:

At Baseline (as part of the Final/Early Termination visit in the parent studies), Weeks 8, 18, 30, 42, 54, 66, every 12 weeks thereafter until the final visit which should occur no later than March 2016, and at the Final/Early Termination visit, the questionnaire assessments (to be completed in the following order: VFQ-25, EQ-5D, WPAI-SHP and the HRU) required for that visit should be completed first, followed by vital signs and eye exam assessments.

Has been changed to read:

At Baseline (as part of the Final/Early Termination visit in the parent studies), Weeks 8, 18, 30, 42, 54, 66, every 12 weeks thereafter until the final visit which should occur no later than March 2018, and at the Final/Early Termination visit, the questionnaire

assessments (to be completed in the following order: VFQ-25, EQ-5D, WPAI-SHP and the HRU) required for that visit should be completed first, followed by vital signs and eye exam assessments.

Section 5.3.1.1 Study Procedures
Subsection Clinical Laboratory Tests
Last paragraph previously read:

The central laboratory chosen for this study (ICON Central Laboratories) will provide instructions regarding the collection, processing and shipping of these samples.

Has been changed to read:

The central laboratory chosen for this study (ICON Laboratory Services) will provide instructions regarding the collection, processing and shipping of these samples.

Section 5.3.1.1 Study Procedures
Subsection TB Screening
Third paragraph, first, second and third sentence previously read:

For the TB Screening, either a PPD skin test (alternatively, also known as tuberculin skin test) must be placed or the QuantiFERON®-TB Gold test (or IGRA equivalent) must be performed during the Baseline visit and Week 42, 90, 138, 186, and 234 visits for all subjects. The same type of TB test should be done at Weeks 42, 90, 138, 186, and 234 that was done at Baseline. For subjects with a positive PPD skin test in the parent protocol, a QuantiFERON®-TB Gold test (or IGRA equivalent) must be performed at the Baseline and Week 42, 90, 138, 186, and 234 visits.

Has been changed to read:

For the TB Screening, either a PPD skin test (alternatively, also known as tuberculin skin test) must be placed or the QuantiFERON®-TB Gold test (or IGRA equivalent) must be performed during the Baseline visit and Week 42, 90, 138, 186, 234, 282, and 330 visits for all subjects. The same type of TB test should be done at Weeks 42, 90, 138, 186, 234, 282 and 330 that was done at Baseline. For subjects with a positive PPD skin test in the

parent protocol, a QuantiFERON®-TB Gold test (or IGRA equivalent) must be performed at the Baseline and Week 42, 90, 138, 186, 234, 282, and 330 visits.

Section 5.3.1.1 Study Procedures
Subsection Chest X-ray (CXR)
First paragraph previously read:

If a subject has a positive TB test at Baseline or Weeks 42, 90, 138, 186, or 234, subjects will undergo a standard CXR (posterior anterior [PA] and lateral views) to rule out the presence of TB or other clinically relevant findings.

Has been changed to read:

If a subject has a positive TB test at Baseline or Weeks 42, 90, 138, 186, 234, 282, or 330, subjects will undergo a standard CXR (posterior anterior [PA] and lateral views) to rule out the presence of TB or other clinically relevant findings.

Section 5.3.1.1 Study Procedures
Subsection Dispense Study Drug
Fourth paragraph, last sentence previously read:

A sample of the Subject Dosing Diary is presented in 0.

Has been changed to read:

A sample of the Subject Dosing Diary is presented in Appendix E.

Section 5.4.1 Discontinuation of Individual Subjects
Sixth bullet following second paragraph previously read:

Subject has positive PPD test or positive (or indeterminate re-test) QuantiFERON®-TB Gold test (or IGRA equivalent) result at Baseline, Week 42, 90, 138, 186, or 234.

Has been changed to read:

Subject has positive PPD test or positive (or indeterminate re-test) QuantiFERON®-TB Gold test (or IGRA equivalent) result at Baseline, Week 42, 90, 138, 186, 234, 282, or 330.

Section 5.4.1 Discontinuation of Individual Subjects
Last paragraph previously read:

The entire study will be terminated in March 2016. Subjects who remain active in this clinical trial on 15 February 2016 should be contacted by the site to return for their study termination visit. Sites should complete the termination visit by 15 March 2016 for all of the remaining active subjects. These subjects will be considered as having completed the study.

Has been changed to read:

The entire study will be terminated in March 2018. Subjects who remain active in this clinical trial on 15 February 2018 should be contacted by the site to return for their study termination visit. Sites should complete the termination visit by 15 March 2018 for all of the remaining active subjects. These subjects will be considered as having completed the study.

Section 5.5.2.2 Storage and Disposition of Study Drugs
First paragraph, fifth sentence previously read:

The maximum, minimum and current temperature for both refrigerator and room temperature must be documented and reviewed for temperature excursions.

Has been changed to read:

The maximum, minimum and current temperature for refrigerator temperature must be documented and reviewed for temperature excursions.

Section 5.5.6 Treatment Compliance
Second paragraph, third sentence previously read:

In order to document compliance with the treatment regimen, the subject will be given a Subject Dosing Diary (0) to record all injection dates and times.

Has been changed to read:

In order to document compliance with the treatment regimen, the subject will be given a Subject Dosing Diary (Appendix E) to record all injection dates and times.

Section 5.6.4 Selection of Doses in the Study
Last paragraph previously read:

In total, adalimumab has now been tested in clinical studies in over 24,000 subjects representing more than 47,000 patient years, of which more than 90% of subjects were dosed with 40 mg eow at any given time.

Has been changed to read:

In total, adalimumab has now been tested in clinical studies in over 29,000 subjects representing more than 56,000 patient years.

Section 6.0 Complaints
Add: new section number and text

6.0 Complaints

A Complaint is any written, electronic, or oral communication that alleges deficiencies related to the physical characteristics, identity, quality, purity, potency, durability, reliability, safety, effectiveness, or performance of a product/device after it is released for distribution.

The investigational product in this trial contains both:

- Biologic compound(s) and
- Device component(s) (pre-filled syringe).

Complaints associated with any component of this investigational product must be reported to the Sponsor (Section 6.2.2). For adverse events, please refer to Sections 6.1 through 6.1.6. For product complaints, please refer to Section 6.2.

Section 6.0 through 6.6
Section number and title previously read:

6.0 Adverse Events

6.1 Definitions

6.1.1 Adverse Event

6.1.1.1 Uveitis-Related Events

6.1.2 Serious Adverse Events

6.2 Adverse Event Severity

6.3 Relationship to Study Drug

6.4 Adverse Event Collection Period

6.5 Adverse Event Reporting

Has been changed to read:

6.0 Complaints

6.1 Medical Complaints

6.1.1 Definitions

6.1.1.1 Adverse Event

6.1.1.1.1 Uveitis-Related Events

6.1.1.2 Serious Adverse Events

6.1.2 Adverse Event Severity

6.1.3 Relationship to Study Drug

6.1.4 Adverse Event Collection Period

6.1.5 Adverse Event Reporting

Section 6.5 Adverse Event Reporting
Previously read:

In the event of a serious adverse event, and additionally, any non-serious event of malignancy in subjects 30 years of age and younger, whether related to study drug or not, the physician will notify the AbbVie Immunology Clinical Safety Management Team within 24 hours of the physician becoming aware of the event by entering the serious adverse event or non-serious event of malignancy in subjects 30 years of age and younger data into the electronic data capture (EDC) system. Serious adverse events and non-serious events of malignancy in subjects 30 years of age and younger, that occur prior to the site having access to the Rave system should be faxed to the Immunology Clinical Safety Team within 24 hours of being made aware of the adverse event.

FAX to: [redacted]

For serious adverse event concerns, contact the Immunology Safety Team at:

Immunology Safety Team
Immunology Development
[redacted]
AbbVie
1 North Waukegan Road
North Chicago, IL 60064
USA

Fax:
Safety Hotline:
Email:
[redacted]

For any subject safety concerns, please contact the AbbVie Medical Monitors listed below:

For US, Canada, Latin America and Japan

[redacted]

For Europe, Israel and Australia

[redacted]

In the EU, the sponsor will be responsible for Suspected Unexpected Serious Adverse Reactions (SUSAR) reporting for the Investigational Medicinal Product (IMP) in accordance with Directive 2001/20/EC. The reference document used for SUSAR reporting in EU countries for adalimumab will be the most current version of the Investigator's Brochure.

Has been changed to read:

In the event of a serious adverse event, and additionally, any nonserious event of malignancy in subjects 30 years of age and younger, whether related to study drug or not, the investigator will notify Clinical Pharmacovigilance within 24 hours of the site being aware of the event by entering the serious adverse event or nonserious event of malignancy in subjects 30 years of age and younger data into the electronic data capture (EDC) system. Serious adverse events and nonserious events of malignancy in subjects 30 years of age and younger, that occur prior to the site having access to the RAVE system or if RAVE is not operable should be sent to Clinical Pharmacovigilance within 24 hours of site being made aware of the adverse event.

FAX to:	[redacted]
Email:	

For serious adverse event concerns, contact the Immunology Safety Team at:

Immunology Safety Team
Immunology Development
[redacted]
AbbVie
1 North Waukegan Road
North Chicago, IL 60064
USA

Fax:
Safety Hotline:
Email:
[redacted]

For any subject safety concerns, please contact the AbbVie Medical Monitors listed below:

For US, Canada, and Latin America:

[redacted]

For Europe, Israel, Australia and Japan:

[redacted]

Secondary Contact for Japan (Regional Medical Monitor):

[redacted]

[redacted] and [redacted] cover for each other. For any subject safety concerns or medical emergencies in which both medical monitors are unavailable, please call the following central back-up number:

Phone: [redacted]

In the EU, the sponsor will be responsible for Suspected Unexpected Serious Adverse Reactions (SUSAR) reporting for the Investigational Medicinal Product (IMP) in

accordance with Directive 2001/20/EC. The reference document used for SUSAR reporting in EU countries for adalimumab will be the most current version of the Investigator's Brochure.

Section 6.6 Pregnancy
Section number and title previously read:

6.6 Pregnancy

Has been changed to read:

6.1.6 Pregnancy

Section 6.2 Product Complaint
Add: new section and text, renumber subsequent sections

6.2 Product Complaint

6.2.1 Definition

A Product Complaint is any Complaint (see Section 6.0 for the definition) related to the biologic or drug component of the product or to the medical device component(s).

For a product this may include, but is not limited to, damaged/broken product or packaging, product appearance whose color/markings do not match the labeling, labeling discrepancies/inadequacies in the labeling/instructions (example: printing illegible), missing components/product, device not working properly, or packaging issues.

For medical devices, a product complaint also includes all deaths of a patient using the device, any illness, injury, or adverse event in the proximity of the device, an adverse event that could be a result of using the device, any event needing medical or surgical intervention including hospitalization while using the device and use errors.

Any information available to help in the determination of causality by the device to the events outlined directly above should be captured.

6.2.2 Reporting

Product Complaints concerning the investigational product and/or device must be reported to the Sponsor within 24 hours of the study site's knowledge of the event via the Product Complaint form. Product Complaints occurring during the study will be followed-up to a satisfactory conclusion. All follow-up information is to be reported to the Sponsor (or an authorized representative) and documented in source as required by the Sponsor. Product Complaints associated with adverse events will be reported in the study summary. All other complaints will be monitored on an ongoing basis.

Product Complaints may require return of the product with the alleged complaint condition (syringe). In instances where a return is requested, every effort should be made by the investigator to return the product within 30 days. If returns cannot be accommodated within 30 days, the site will need to provide justification and an estimated date of return.

The description of the complaint is important for AbbVie in order to enable AbbVie to investigate and determine if any corrective actions are required.

Section 7.0 Protocol Deviations
First paragraph previously read:

The Investigator should not implement any deviation from the protocol without prior review and agreement by the Sponsor and in accordance with the Independent Ethics Committee (IEC)/Independent Review Board (IRB) and local regulations, except when necessary to eliminate an immediate hazard to study subjects. When a deviation from the protocol is deemed necessary for an individual subject, the Investigator must contact the AbbVie Medical Monitor listed in Section 1.0 and Section 6.5.

Has been changed to read:

AbbVie does not allow intentional/prospective deviations from the protocol. The Principal Investigator is responsible for complying with all protocol requirements, and applicable global and local laws regarding protocol deviations. If a protocol deviation

occurs (or is identified) after a subject has been enrolled, the Principal Investigator is responsible for notifying Independent Ethics Committee (IEC)/Independent Review Board (IRB) regulatory authorities (as applicable), and the AbbVie Clinical Monitor(s) assigned to your site. Alternative contacts are as follows:

Alternate Contacts

North America, Latin America, and Japan	Europe, Israel, and Australia
[redacted]	

Such contact must be made as soon as possible to permit a review by AbbVie to determine the impact of the deviation on the subject and/or the study.

Section 7.0 Protocol Deviations
Delete: third paragraph

Such contact must be made as soon as possible to permit a review by AbbVie to determine the impact of the deviation on the subject and/or the study. Any significant protocol deviations affecting subject eligibility and/or safety must be reviewed and/or approved by the IEC/IRB and regulatory authorities, as applicable, prior to implementation.

Appendix B. List of Protocol Signatories
Previously read:

Name	Title	Functional Area
[redacted]		Clinical
		Clinical
		Statistics
		Clinical

Has been changed to read:

Name	Title	Functional Area
[redacted]		Clinical
		Clinical
		Statistics
		Clinical

Appendix E. Subject Dosing Diary
Last page of diary previously read:

M11-327

___-___ ___-___ ___-___ ___
Subject Identification Number

Adalimumab Dosing Diary

Date	Week #	Kit Number	Time of Study Drug Administration	Was the entire volume injected? (Y/N)	Initials of Person Administering Study Medication	Comments
19-Mar-13	EXAMPLE	101010	9:35	Y	MM	none
	Week 276					
	Week 278					
	Week 280					

20120312 Dosing Diary Uveitis
White Copy (site)

Abbott Laboratories

Adalimumab Dosing
Yellow Copy (diary)

Has been changed to read:

M11-327

___-___ ___-___ ___-___ ___
Subject Identification Number

Adalimumab Dosing Diary

Date	Week #	Kit Number	Time of Study Drug Administration	Was the entire volume injected? (Y/N)	Initials of Person Administering Study Medication	Comments
19-Mar-13	EXAMPLE	101010	9:35	Y	MM	none
	Week 276					
	Week 278					
	Week 280					
	Week 282					
	Week 284					
	Week 286					
	Week 288					
	Week 290					

20120312 Dosing Diary Uveitis
White Copy (site)

Abbott Laboratories

Adalimumab Dosing
Yellow Copy (diary)

Appendix F. AREDS 2008 Clinical Lens Opacity Grading Procedures
Delete: last paragraph

Website: http://eyephoto.ophth.wisc.edu/ResearchAreas.html

Appendix K. Japan Appendix
Section 5.3.1.1 Study Procedures
Subsection Chest X-ray (CXR)
Second paragraph previously read:

If a subject has a positive TB test at Baseline or Week 42, 90, 138, 186, or 234, subjects will undergo a standard CXR (posterior-anterior [PA] and lateral views) to rule out the presence of TB or other clinically relevant findings.

Has been changed to read:

If a subject has a positive TB test at Baseline or Week 42, 90, 138, 186, 234, 282, or 330, subjects will undergo a standard CXR (posterior-anterior [PA] and lateral views) to rule out the presence of TB or other clinically relevant findings.

Appendix K. Japan Appendix
Section 5.3.1.1 Study Procedures
Subsection Dispense Study Drug
Second paragraph previously read:

Subjects in Japan will be administered the study drug by the medical staff throughout the study when the dose of prednisone or prednisone equivalent is ≤ 10 mg/day to secure the safety of the subjects.

Has been changed to read:

Subjects in Japan will be administered the study drug at the investigative site throughout the study when the dose of prednisone or prednisone equivalent is > 10 mg/day to secure the safety of the subjects.

Table 1. Study Activities (Continued)

Activity	Baseline[a]	Week 2	Week 4	Week 8	Week 12	Week 18	Week 30	Week 42	Week 54	Week 66	Every 12 weeks following Week 66[r]	Final/ ET Visit	Unscheduled Visit[b]	70-Day Follow-up[c]
Physical Exam[g]	X				X		X		X		X[g]	X	X	
Symptom Directed Physical Exam[g]		X	X	X		X		X		X	X[g]			
Urine Pregnancy Test[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	
Hematology/Chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X	
Urinalysis[i]	X		X		X		X		X		X	X	X	
TB Screening[j] (PPD Skin Test or QuantiFERON®-TB Gold or IGRA equivalent)	X							X[k]			X[j,k]			
Chest X-ray[l]	X[l]							X[l]			X[l]		X	
Antinuclear Antibody (ANA/Anti-dsDNA[m,n])													X	
Monitor Adverse Events[o]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Monitor Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	
Monitor Compliance		X	X	X	X	X	X	X	X	X	X	X	X	
Dispense Adalimumab Study Drug (Contact IXRS)	X		X	X	X[p]	X	X	X	X	X	X			
Perform Drug Accountability[q]		X	X	X	X	X	X	X	X	X	X	X		

Table 1. Study Activities (Continued)

a. All activities for Baseline except Informed Consent, Inclusion criteria, Exclusion criteria and Dispensing of Study Drug, will be completed as part of the Final/Early Termination visit in the parent study and will be used in analysis for Study M11-327. If the Baseline visit occurs greater than (>) 14 days after the Final/Early Termination visit of the parent study, all procedures listed in the Baseline visit must be completed. The maximum amount of time allowed between the Final/Early Termination visit of the parent study and the Baseline visit of Study M11-327 is 28 days.

b. If a subject presents at a site for an Unscheduled visit investigators should complete unscheduled visit procedures at their discretion.

c. The 70-day follow-up calculated from last dose of study drug should be conducted by telephone or at a routine clinic visit to collect any potential safety information.

d. Questionnaire will be administered by site staff (interview administered) prior to any study procedure or examination.

e. Questionnaire will be completed by the subject unless impaired vision prohibits. Site staff should complete the questionnaire with the subject, if the subject has impaired vision that precludes him/her from reading and completing the questionnaire.

f. Height used in analysis will be taken from the Screening visit of the parent study in which the subject enrolled. Weight will be measured at Baseline (measurement taken at the Final/Early Termination visit of the parent protocol), Unscheduled visit (if applicable) and Final/Early Termination visit. Vital sign determinations of sitting blood pressure, heart rate, respiratory rate and body temperature will be obtained at each visit.

g. A full physical exam will be performed at Baseline, Week 12, Week 30, Week 54, Unscheduled visit (if applicable), and every other visit (every 24 weeks) following Week 66 and Final/Early Termination Visit. An abbreviated symptom-directed physical exam will be completed at all other visits as warranted.

h. All females of childbearing potential will have a urine pregnancy test performed locally at the Baseline visit and all subsequently scheduled study visits. The frequency can be increased if local regulations require. Any subject with a positive urine pregnancy test result must have a negative serum test result performed at the central laboratory prior to enrollment or continuation in the study.

i. The central laboratory will perform the urine dipstick. If the urinalysis results are abnormal by dipstick, the central laboratory will perform a microscopic analysis.

j. An annual TB test must be completed at the Week 42, 90, 138, 186, 234, 282, or 330 visits for all subjects. Please reference Section 5.3.1.1 Study Procedures for further information.

k. If the TB test is missed at the Week 42, 90, 138, 186, 234, 282, or 330 visits, the subject must be brought in within 30 days of the visit to have the test completed.

l. Must include a PA and lateral view. The CXR is only required if a TB test result is positive. A CXR may be repeated at any time during the study as warranted based on the opinion of the Investigator and/or CXR is inconclusive. Other diagnostic imaging tests may be performed as needed if pulmonary involvement is suspected based on the investigator's clinical assessment. See Section 5.3.1.1 for details.

Table 1. Study Activities (Continued)

m. If a subject is enrolled in M11-327 prior to IEC/IRB approval of Global Protocol Amendment 4 of the parent study, the ANA/dsDNA sample will be collected at the subject's next scheduled visit following regulatory approval of M11-327 Global Amendment 4.

n. If a subject develops signs and symptoms of lupus, an ANA test may be repeated based on the investigator's clinical judgment.

o. All SAEs will be captured from the time that the subject signs the Informed Consent Form and all AEs reported from the time of study drug administration through study completion or Early Termination and at the 70-day follow up. Any adverse events experienced prior to first study drug administration in M11-327 will be reported in the parent protocol.

p. At the Week 12 clinic visit, the subject will be dispensed two kits that include a total of four syringes. One syringe should be removed from these kits and sent back to AbbVie per the Drug Destruction guidelines. If dosing at home, the remaining three syringes from these kits will be injected at home at Weeks 12, 14 and 16. At the Week 18 clinic visit, the subject will be dispensed three kits that include a total of six syringes which should be taken at Weeks 18, 20, 22, 24, 26 and 28.

q. Collect the packaging and any remaining drug from the last clinic visit.

r. Subjects will have study visits every 12 weeks following Week 66 until the end of study (not to exceed 15 March 2018).

5.3.1.1 Study Procedures

Subjects will have clinic visits at Baseline, Week 2, Week 4, Week 8, Week 12, Week 18 and every 12 weeks thereafter until the final visit which should occur no later than March 2018.

All activities for the Baseline visit except Informed Consent, Inclusion/Exclusion and Dispensing of Study Drug will be completed as part of the Final/Early Termination visit in the parent study and will be used in analysis for Study M11-327. If the Baseline visit occurs greater than (>) 14 days after the Final/Early Termination visit of the parent study, all procedures listed in the Baseline visit must be completed. The maximum amount of time allowed between the Final/Early Termination visit of the parent study and the Baseline visit of Study M11-327 is 28 days.

At Baseline (as part of the Final/Early Termination visit in the parent studies), Weeks 8, 18, 30, 42, 54, 66, every 12 weeks thereafter until the final visit which should occur no later than March 2018, and at the Final/Early Termination visit, the questionnaire assessments (to be completed in the following order: VFQ-25, EQ-5D, WPAI-SHP and the HRU) required for that visit should be completed first, followed by vital signs and eye exam assessments. The order of the eye examinations may occur according to established site procedures as long as the slit lamp examination for AC cells is performed prior to the application of mydriatic eye drops to dilate subject's pupils for further assessment.

Informed Consent

A signed informed consent will be obtained from the subject or their legally authorized representative before any study-related procedures are undertaken. Details about how informed consent will be obtained and documented are provided in Section 9.3.

If the parent studies are prematurely stopped based upon the recommendation of the IDMC, and this recommendation is based on safety concerns, subjects will be required to return for their Final/Early Termination visit in Study M11-327.

Inclusion/Exclusion Criteria

Subjects will be eligible for study participation if he/she meets all inclusion criteria and none of the exclusion criteria at the Baseline visit.

Assignment of Subject Numbers

Subjects will keep the same subject number that they were assigned in the parent study (Study M10-877 or Study M10-880).

Visual Functioning Questionnaire (VFQ-25)

The VFQ-25 will be completed at the Baseline visit (or as part of the Final/Early Termination visit of Study M10-877 or Study M10-880), Week 8, Week 18 and every visit thereafter prior to any study procedure or examination. A copy of the questionnaire is located in Appendix G.

The questionnaire will be interview administered. The site will complete this questionnaire directly onto the CRFs and will be considered source documents.

EuroQol-5D Questionnaire (EQ-5D)

Subjects will complete the EQ-5D questionnaire at the Baseline visit (or as part of the Final/Early Termination visit of Study M10-877 or Study M10-880), Week 8, Week 18 and every visit thereafter prior to any study procedure or examination. A copy of the questionnaire is located in Appendix H. The subject will complete this questionnaire directly onto the CRFs and will be considered source documents.

Site staff should complete the questionnaire with the subject, if the subject has impaired vision that precludes him/her from reading and completing the questionnaire.

Work Productivity and Activity Impairment, Questionnaire: Specific Health Problem Questionnaire (WPAI-SHP)

Subjects will complete the WPAI-SHP questionnaire at the Baseline visit (or as part of the Final/Early Termination visit of Study M10-877 or Study M10-880), Week 8, Week 18

and every visit thereafter prior to any study procedure or examination. A copy of the questionnaire is located in Appendix J. The subject will complete this questionnaire directly onto the CRFs and will be considered source documents.

Site staff should complete the questionnaire with the subject, if the subject has impaired vision that precludes him/her from reading and completing the questionnaire.

Health Resource Utilization Questionnaire (HRU)

Sites will complete the HRU questionnaire at the Baseline visit (or as part of the Final/Early Termination visit of Study M10-877 or Study M10-880), and at all subsequent visits in the study. A copy of the questionnaire is located in Appendix I.

The questionnaire will be interview administered by the site. The answers will be documented on the source worksheet provided by the sponsor and entered in the eCRF.

Vital Signs/Weight/Height

Vital signs will be obtained at each visit. This includes sitting blood pressure, heart rate, respiratory rate and body temperature. Each subject's height used in the analysis will be taken from the Screening visit of the parent study (Study M10-877 or Study M10-880). For this study, Baseline weight and vital signs measurements will be taken from the final visit of the parent study for the purposes of analysis if Study M11-327 Baseline visit occurs ≤ 14 days since the last visit from the parent study (Study M10-877 or Study M10-880). If the Baseline visit occurs greater than (>) 14 days after the last visit from the parent study, baseline weight and vital signs measurements will be taken at that Baseline visit. Weight will be measured at the Unscheduled visit (if applicable) and Final/Early Termination visit.

Best Corrected Visual Acuity Testing

Refraction and assessment of best corrected visual acuity (BCVA) will be assessed at every visit.

At each visit, subjects should undergo refraction and the result of refraction for each eye will be recorded on the eCRF.

Using the appropriate corrective lenses based on that visit's refraction, subject's BCVA is measured using an ETDRS chart which will be specified and provided if necessary by the sponsor. Please refer to the Visual Acuity Manual provided by the sponsor for instructions.

A qualified and trained health care professional must perform the refraction and BCVA testing. Specific training and instructions will be provided by the sponsor.

Slit Lamp Exam

The slit lamp exam will be conducted at each study visit to assess the following findings: Anterior chamber cell count and Age-Related Eye Disease Study (AREDS) lens opacity grading.[3,37,38] Slit lamp examination for AC cells is performed prior to application of mydriatic eyedrops to dilate subject's pupils for further assessment.

The AREDS classification does not apply to a subject, if he/she has pseudophakia.

The number of AC cells observed within a 1 mm × 1 mm slit beam will be recorded for each eye. The reported number will be used to determine the grade according to the SUN criteria[3] (Table 2).

Table 2. Anterior Chamber Cells

Grade	Cells in Field
0	< 1
0.5 +	1 – 5
1 +	6 – 15
2 +	16 – 25
3 +	26 – 50
4 +	> 50

Using the AREDS standard photographs as reference, the degree of lens opacity will be graded for each type: nuclear, cortical, and posterior subcapsular (PSC) (Table 3).[37,38] See Appendix F for further instructions regarding lens opacity grading procedures.

Table 3. Lens Opacity Grading

Grading for Nuclear Lens Opacity	
< 1.0	no nuclear opacity, or less than NS Std. No. 1
1.0	opacity similar to NS No. 1
1.5	opacity between NS No. 1 and NS Std. No. 2
2.0	opacity similar to NS No. 2
2.5	opacity between NS No. 2 and NS Std. No. 3
3.0	opacity similar to NS No. 3
> 3.0	opacity greater than NS No. 3
8.0	cannot evaluate
Grading for Cortical Lens Opacity	
< 1.0	no cortical opacity, or opacity obviously less than CO Std. No. 1
1.0	opacity similar to cortical opacity Std. No. 1
1.5	opacity between CO Std. No. 1 and Std. No. 2
2.0	opacity similar to CO Std. No. 2
2.5	opacity between CO Std. No. 2 and Std. No. 3
3.0	opacity similar to CO No. 3
> 3.0	cortical opacity obviously greater than Std. No. 3
8.0	cannot evaluate
Grading for Posterior Subcapsular (PSC) Opacity	
< 1.0	no PSC opacity, or opacity obviously < PSC Std. No. 1
1.0	opacity similar to PSC No. 1
1.5	opacity between PSC No. 1 and Std. No. 2
2.0	opacity similar to PSC No. 2
2.5	opacity between PSC No. 2 and Std. No. 3
3.0	opacity similar to PSC No. 3
> 3.0	PSC obviously greater than PSC No. 3
8.0	cannot evaluate

Optical Coherence Tomography

Optical Coherence Tomography will be performed at every visit. Sites must use one of three OCT machines for this clinical trial to determine central retinal thickness and the presence of macular edema:

- Stratus OCT (Carl Zeiss Meditec, Inc.)
- Cirrus HD-OCT (Carl Zeiss Meditec, Inc.)
- Spectralis (Heidelberg Engineering)

Each subject will undergo OCT measurements of the central retinal thickness (1 mm subfield) to evaluate for macular edema at every visit using the same protocol approved machine throughout the study. The same OCT machine that was used in Study M10-877 or Study M10-880 should be used in Study M11-327. OCT images will be sent to the Central Reader for transmission to AbbVie. Although it is preferred to complete the OCT measurements following pupil dilation, it is important that the site conducts the scans consistently across each subject (using the same model of OCT device for each patient) throughout the study.

Tonometry

Tonometry will be performed at every visit to measure the intraocular pressure for both eyes. Applanation tonometry is preferred but non-contact tonometry can also be used if the site does not have the equipment to perform applanation tonometry. However, the same technique should be used for all visits for an individual patient.

Dilated Indirect Ophthalmoscopy

Subject's eyes should be dilated in preparation for indirect ophthalmoscopy. The examination technique and instrument used should remain consistent for each subject throughout the study.

Dilated indirect ophthalmoscopy is performed to determine both vitreous haze grading and the absence/presence of inflammatory chorioretinal and/or inflammatory retinal vascular lesions.

Lesion location(s), number, size(s) and whether the lesions are active or inactive should be documented with a retinal drawing in the subject's source documentation, if a lesion is identified.

Grading of vitreous haze (Table 4) will be based on the publication from the National Eye Institute (NEI) which has also been adapted by the SUN working group.[3,39]

Sites will use the standard photographs given to them by the sponsor and the description in Table 4 when determining the grade for vitreous haze.

Table 4. Vitreous Haze Grading

Grade	Description
0	No evident vitreal haze
0.5 +	Slight blurring of the optic disc margin because of the haze; normal striations and reflex of the nerve fiber layer cannot be visualized
1 +	Permits a better definition of both the optic nerve head and the retinal vessels (compared to higher grades)
2 +	Permits better visualization of the retinal vessels (compared to higher grades)
3 +	Permits the observer to see the optic nerve head, but the borders are quite blurry
4 +	Optic nerve head is obscured

At all visits dilated indirect ophthalmoscopy will be performed to determine the presence/absence of new inflammatory chorioretinal and/or inflammatory retinal vascular lesions compared to the findings from the final visit of the parent study (Study M10-877 or Study M10-880) based on the Investigators' clinical judgment.

Physical Examination

Medically qualified personnel who routinely do a complete physical exam should perform this assessment at the designated study visits listed in Table 1. At all other visits, a symptom directed physical exam will be performed either by the investigator or the medically qualified personnel who performed the complete physical exam. Abnormalities noted after the Baseline visit of the parent study should be evaluated and documented by the Investigator as to whether or not these are adverse events.

Pregnancy Tests

At the Baseline visit and all subsequent visits thereafter, subjects of childbearing potential will have a urine pregnancy test (provided by the central laboratory) performed locally by designated study personnel. The frequency can be increased if local regulations require. Subjects of non-childbearing potential are defined as postmenopausal for at least 1 year or surgically sterile (bilateral tubal ligation, bilateral oophorectomy and/or hysterectomy).

If any urine pregnancy test is positive, a serum pregnancy test must be requested on the central laboratory requisition form and performed by the central laboratory prior to enrollment or continuation in the study. A lactating or pregnant female will not be eligible for participation or continuation in this study.

Clinical Laboratory Tests

Lab evaluations will be performed according to the schedule outlined in Table 1.

Blood draws should be performed after completion of questionnaires (i.e., VFQ-25, EQ-5D, WPAI-SHP, HRU) and vital sign determinations during a study visit, but before study drug administration, if applicable.

A certified central laboratory will be utilized to process and provide results for the general laboratory tests. The investigator will review all laboratory test results. All laboratory test results that are considered clinically significant by the investigator will be followed to a satisfactory conclusion. Laboratory abnormalities are considered to be adverse events only if these result in discontinuation from the study, necessitate therapeutic intervention, and/or the investigator considers them to be adverse events.

In cases where laboratory tests are performed locally for specific study purposes, certifications and laboratory reference ranges will be collected for the tests which are performed.

The central laboratory chosen for this study (ICON Laboratory Services) will provide instructions regarding the collection, processing and shipping of these samples.

Table 5. Clinical Laboratory Tests

Hematology[a]	Clinical Chemistry	Urinalysis[b]	Serology	Other[e]
Hematocrit Hemoglobin Red Blood Cell (RBC) count White Blood Cell (WBC) count Neutrophils Bands Lymphocytes Monocytes Basophils Eosinophils Platelet count (estimate not acceptable)	Blood Urea Nitrogen (BUN) Creatinine Total bilirubin Serum glutamic-pyruvic transaminase (SGPT/ALT) Serum glutamic-oxaloacetic transaminase (SGOT/AST) Alkaline phosphatase Sodium Potassium Calcium Inorganic phosphorus Uric acid Cholesterol Total protein Glucose Triglycerides Albumin	Specific gravity Ketones[c] pH Protein Blood Glucose	Antinuclear Antibody (ANA)/Anti-dsDNA[d] QuantiFERON®-TB Gold test[f]	Human Chorionic Gonadotropin (HCG)

a. Automated basic hematology testing does not include band reporting. If a manual differential is required, only band results over 5 are reported.

b. Microscopic urinalysis performed by the central laboratory at all visits if dipstick UA is abnormal.

c. The result should be interpreted in the context of additional clinical and test information.

d. If a subject enrolls in Study M11-327 prior to IEC/IRB approval of Global Amendment 4 in either parent study, an antinuclear antibody (ANA)/Anti-dsDNA sample will be collected at the subject's next scheduled visit. However, if a subject develops signs and symptoms of lupus, an ANA/Anti-dsDNA test may be repeated based on the investigator's clinical judgment.

e. Urine pregnancy test is performed on all female subjects of child bearing potential at the Baseline visit (Final visit of parent protocol), and all subsequent visits thereafter. A serum HCG test must be requested on the central laboratory requisition if urine HCG is positive. Any subject with a positive urine pregnancy test must have a negative serum test result at the central laboratory prior to enrollment or continuation in the study.

f. If TB screening tests are not available locally, the central laboratory can be used to perform the QuantiFERON®-TB Gold test. For countries that ship to ICON New York, the estimated turnaround time is 5 to 8 days. For countries that ship to ICON Dublin, the estimated turnaround time is 9 to 12 days. For ICON Singapore, the estimated turnaround time is 11 to 14 days.

Note: Baseline laboratory values will be taken from the parent study (Study M10-877 or Study M10-880) unless the Baseline visit occurs greater than (>) 14 days since the last visit in the parent study (Study M10-877 or Study M10-880).

Urinalysis

Urine samples will be obtained for urinalysis testing as noted in Table 1. The central laboratory will perform a urine dipstick analysis and if the results are abnormal, the central laboratory will perform a microscopic urinalysis.

TB Screening

The TB screening tests are diagnostic test results to be interpreted in the context of the patient's epidemiology, history, exam findings, etc. and it is the responsibility of the investigator to determine if a patient has previous, active or latent tuberculosis or not in conjunction with a negative TB Screening test.

Under no circumstances can a patient with a positive PPD result or positive QuantiFERON®-TB Gold test (or IGRA equivalent) continue in the study.

For the TB Screening, either a PPD skin test (alternatively, also known as tuberculin skin test) must be placed or the QuantiFERON®-TB Gold test (or IGRA equivalent) must be performed during the Baseline visit and Week 42, 90, 138, 186, 234, 282, and 330 visits for all subjects. The same type of TB test should be done at Weeks 42, 90, 138, 186, 234, 282 and 330 that was done at Baseline. For subjects with a positive PPD skin test in the parent protocol, a QuantiFERON®-TB Gold test (or IGRA equivalent) must be performed at the Baseline and Week 42, 90, 138, 186, 234, 282, and 330 visits. For subjects with a negative TB test in the parent protocol, the same type of test that was used in the parent protocol (either PPD or QuantiFERON®-TB Gold [or IGRA equivalent]) must be used for every TB test in Study M11-327. If a subject had a negative PPD test or negative QuantiFERON®-TB Gold test (or IGRA equivalent) within 90 days prior to Baseline, and all protocol required documentation is available, the test does not need to be repeated, provided nothing has changed in the subject's medical history to warrant a repeat test.

If the subject has a positive TB Screening test (either positive PPD test or positive QuantiFERON®-TB Gold test [or IGRA equivalent]), the subject must be discontinued. If the subject has a repeat indeterminate QuantiFERON®-TB Gold test (or IGRA

equivalent), the subject must be discontinued. The subject should be brought back in immediately for an Early Termination visit. For subjects with a prior history of Bacille Calmette-Guérin (BCG) administration, the QuantiFERON®-TB Gold test (or IGRA equivalent) test is recommended.

The TB screening tests are preferably performed locally. If TB screening tests (PPD test and/or QuantiFERON®-TB Gold test) are not available locally, the central laboratory can be used to perform the QuantiFERON®-TB Gold test. Sites utilizing the central lab for the QuantiFERON®-TB Gold test should be aware the results for samples sent to ICON New York require an estimated turnaround time of 5 to 8 days, samples sent to ICON Dublin require an estimated turnaround time of 9 to 12 days and samples sent to ICON Singapore require an estimated turnaround time of 11 to 14 days. It is also required to incubate samples for 16 to 24 hours at 37°C prior to shipping, frozen, to the central lab for processing.

For the PPD test:

> The subject will be required to have the PPD test read by a licensed healthcare professional 48 to 72 hours after placement (or as per local guidelines), when the induration is maximal. An induration (not erythema) of 5 mm or greater will be considered as PPD positive. The absence of induration should be recorded, as "0 mm," not "negative."
>
> Subjects who have had an ulcerating reaction to a PPD skin test in the past should not be re-exposed. Therefore, they should not be tested with PPD and instead must have a QuantiFERON®-TB Gold test (or IGRA equivalent) performed to rule out active or latent TB. If the subject has a history of an ulcerative reaction and has a positive or repeat indeterminate QuantiFERON®-TB Gold test (or IGRA equivalent) the subject cannot continue in the study.

If there are sites where the available testing materials are not accepted, an alternative tuberculin skin test may be substituted, but the method must be submitted and approved by AbbVie prior to use with study subjects.

If QuantiFERON®-TB Gold test (or IGRA equivalent) result is indeterminate, the test should be repeated with a fresh blood sample. If a repeat QuantiFERON®-TB Gold (or IGRA equivalent) result is indeterminate, this should be considered a positive test result and the subject should be discontinued.

A corresponding adverse event should be captured on the adverse event page in the eCRF and in the source documents in the case of a positive test result.

For sites participating in the Czech Republic, the following local requirements will also be applicable:

- A pulmonologist will be responsible to obtain a detailed medical history with respect to Tuberculosis exposure. This information needs to include Bacillus Calmette Guérin (BCG) vaccination, cohabitation with individuals who have had TB, and/or who reside or work in TB endemic locations. The information obtained by the pulmonologist must be documented in the patient's source note, dated and signed by the pulmonologist.
- A pulmonologist must review the results of TB Screening Test (PPD skin test or QuantiFERON®-TB Gold test [or IGRA equivalent]) and the chest x-ray and has to give his/her opinion about the continuation of each patient in the study. This opinion must be documented in writing in the patient's source documents.
- All patients with a positive TB Screening test (PPD or QuantiFERON®-TB Gold [or IGRA equivalent]) must be discontinued from the study. Under no circumstances can a patient with a positive TB test result or a prior history of treatment for active or latent tuberculosis be allowed to remain in this trial.

Chest X-ray (CXR)

If a subject has a positive TB test at Baseline or Weeks 42, 90, 138, 186, 234, 282, or 330, subjects will undergo a standard CXR (posterior anterior [PA] and lateral views) to rule out the presence of TB or other clinically relevant findings.

In the assessment of the CXR, a radiologist must specifically note the presence or absence of (1) calcified granulomas, (2) pleural scarring/thickening, and (3) signs of active TB. The Principal Investigator will indicate the clinical significance of any findings and will sign and date the report. In the absence of abnormal findings the Principal Investigator should sign and date the report to indicate review of the report.

Subjects can have a repeat CXR at any time during the study as warranted based on the opinion of the Investigator and/or the CXR is inconclusive.

In addition, other diagnostic imaging tests may be performed as needed if pulmonary involvement is suspected based on the Investigator's clinical assessment.

Antinuclear Antibody (ANA)/Anti-dsDNA Testing

If a subject is enrolled in Study M11-327 prior to the IEC/IRB approval of Global Protocol Amendment 4 in either parent study, the ANA/Anti-ds-DNA sample will be collected at the subject's next scheduled visit following regulatory approval of Study M11-327 Global Protocol Amendment 4.

A repeat ANA/Anti-ds-DNA would be warranted if a subject has clinical signs and symptoms suggestive of lupus. The Anti-ds-DNA antibody testing will be performed in case of a positive ANA result.

All samples will be sent to the central laboratory for processing.

Adverse Events

Adverse events will be assessed at every study visit from Baseline through the Final/Early Termination visit, and during the 70-day phone call or clinic visit (if applicable). A phone

call or routine clinic visit should occur approximately 70 days after last dose of study medication to obtain follow-up information on any ongoing or new adverse events (Section 6.0 and Appendix D).

Any ongoing adverse events at the time of the Termination visit in the previous Study M10-877 or Study M10-880 will be automatically transferred onto the Study M11-327 eCRF.

Concomitant Medication

All medications (including, but not limited to, prescription or over-the-counter medicines such as aspirin, antacids, vitamins, mineral supplements, and herbal preparations) used from the Baseline visit through the end of the study must be recorded on the appropriate eCRF. Any ongoing systemic or local therapy at the time of Termination visit in the previous study M10-877 or M10-880 will be automatically transferred onto the M11-327 eCRF.

Contact the AbbVie Medical Monitor identified in Section 6.1.5, if there are any questions regarding concomitant or prior therapy(ies).

Each vaccine administered to the subject should be listed as a concomitant medication on the Other Medications eCRF. Live vaccines may not be given concurrently while on study drug or for 70 days after the last dose of adalimumab.

Concomitant use of nutritional supplements should be recorded as concomitant medications (generic and/or brand name, dose [if known], frequency) on the Other Medications eCRF.

Dispense Study Drug

Study drug will be administered to subjects by study site medical staff, by himself/herself or by a designee (friend, family member or health care professional) throughout the study.

Subjects, a designated family member or friend, will be trained to administer study medication during the first visit or several times, if appropriate. This training must be documented in the subject's source document.

Subjects or a trained designated family member or friend or a health care professional will administer the injections of the study medication in the subject's home or in the clinic during the weeks the subjects are not in the office for scheduled study visits.

Subjects will maintain a Subject Dosing Diary for all study medication administered outside of the study visit (i.e., at home). The Subject Dosing Diary will be reviewed and verified for compliance at each clinic visit. All relevant dosing information will be retained by study personnel. Additionally, any discernible departure from the protocol regarding study drug administration will be documented appropriately. A sample of the Subject Dosing Diary is presented in Appendix E.

For subjects that cannot/will not self-administer study drug or do not have adequate support (friend, family member or healthcare professional) at home, administration will occur in the clinic.

At all office visits, subjects should be observed after study drug administration until judged clinically stable by the study personnel. If an anaphylactic reaction or other serious allergic reaction occurs, administration of study medication should be discontinued immediately and appropriate therapy initiated. When dosing at home, subjects should be instructed to contact the site immediately with any signs or symptoms of a reaction.

For subjects who deviate from the dosing schedule, every effort should be made to bring the subject back to the original dosing schedule as soon as possible.

The subject must be instructed to return study drug at each clinic visit for the purpose of compliance assessment and drug accountability as detailed in Section 5.5.6.1.

5.3.2 Drug Concentration Measurements

There will be no drug concentration measurements in this protocol.

5.3.3 Efficacy Variables

Efficacy will be determined at each visit by the following criteria. Both of the subjects' eyes will be assessed. The following endpoints will be used to evaluate the long-term efficacy of adalimumab to treat subjects with non-infectious intermediate-, posterior-, or pan-uveitis.

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

uveitis when they entered the study and to Week 8 for subjects who had active uveitis when they entered the study.[40]

5.3.3.1 Other Variables

Other variables for which data will be collected and analyzed include:

- Work Productivity and Activity Impairment, Questionnaire: Specific Health Problem Questionnaire (WPAI-SHP)
- EuroQol-5D Questionnaire (EQ-5D)
- Health Resource Utilization Questionnaire (HRU)

5.3.4 Safety Variables

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

5.3.5 Pharmacokinetic Variables

There will be no pharmacokinetics performed as part of this study.

5.4 Removal of Subjects from Therapy or Assessment

5.4.1 Discontinuation of Individual Subjects

A subject may withdraw from the study at any time. The Investigator may discontinue any subject's participation for any reason, including an adverse event, safety concerns or failure to comply with the protocol. Please refer to Section 6.3, Toxicity Management, for more information regarding the type and duration of follow-up of subjects after adverse events.

Subjects will be withdrawn from the study immediately if any one of the following occurs:

- Clinically significant abnormal laboratory result(s) or adverse event(s), as determined by the Investigator in consultation with the AbbVie Medical Monitor.
- The Investigator believes it is in the best interest of the subject.
- The subject requests withdrawal from the study.
- Inclusion and exclusion criteria violation was noted after the subject started study drug, when continuation of the study drug would place the subject at risk as determined by the AbbVie Medical Monitor.
- Introduction of prohibited medications or dosages when continuation of the study drug would place the subject at risk as determined by the AbbVie Medical Monitor.
- Subject has positive PPD test or positive (or indeterminate re-test) QuantiFERON®-TB Gold test (or IGRA equivalent) result at Baseline, Week 42, 90, 138, 186, 234, 282, or 330.
- Subject is non-compliant with TB prophylaxis (for those subjects who entered the parent study prior to Study M10-877 Amendment 6 or Study M10-880 Amendment 7 and were still taking TB Prophylaxis when they entered Study M11-327).
- Subject becomes pregnant while on study medication.
- Subject has known dysplasia of the gastrointestinal tract (a colonoscopy is not required to enter the study) or a malignancy, except for localized non-melanoma skin cancer. Discontinuation for carcinoma in-situ of the cervix is at the discretion of the Investigator.
- Subject is diagnosed with lupus-like syndrome, multiple sclerosis or demyelinating disease.
- Subject is significantly non-compliant with study procedures which would put the subject at risk for continued participation in the trial as determined by the Investigator, in consultation with the AbbVie Medical Monitor.

If, during the course of study drug administration, the subject prematurely discontinues study drug use, the procedures outlined for the Final/Early Termination Visit must be completed within 2 weeks of the last dose of study drug, and preferably prior to the

initiation of another therapy. However, these procedures should not interfere with the initiation of any new treatments or therapeutic modalities that the Investigator feels are necessary to treat the subject's condition. Following discontinuation of the study drug, the subject will be treated in accordance with the Investigator's best clinical judgment.

All attempts must be made to determine the date of the last dose of study drug and the primary reason for premature discontinuation. The information will be recorded on the appropriate eCRF page. Subjects who prematurely discontinue will not be replaced.

A final phone call or clinic visit will be completed approximately 70 days after the last dose of study drug to determine the status of any ongoing adverse events/serious adverse events or the occurrence of any new adverse events/serious adverse events. The call/visit information should be documented in the subject's source documents per Appendix D, Day 70 Follow-up (Phone Call or Clinic Visit). The 70-day follow-up phone call or clinic visit will not be required for any subject that initiates adalimumab therapy not supplied in the context of the clinical trial after the end of study participation.

For subjects that are considered lost to follow-up, reasonable attempts must be made to obtain information on the final status of the subject. At a minimum, two phone calls must be made and one certified letter must be sent.

Following country and local (if applicable) regulatory approval and/or applicable local reimbursement approval of the study drug in a country, subjects should return to their next scheduled study visit as specified in the protocol. The termination visit should be conducted in place of their regular scheduled study visit. These subjects will be considered as having completed the study.

The entire study will be terminated in March 2018. Subjects who remain active in this clinical trial on 15 February 2018 should be contacted by the site to return for their study termination visit. Sites should complete the termination visit by 15 March 2018 for all of the remaining active subjects. These subjects will be considered as having completed the study.

5.4.2 Discontinuation of Entire Study

AbbVie reserves the right to discontinue a site's participation in the study at any time and to remove all study materials. Possible reasons for termination of the study at a site include, but are not limited to:

- Safety concerns based on reported data
- Unsatisfactory enrollment with respect to quantity or quality
- Inaccurate or incomplete data collection
- Falsification of records
- Significant non-compliance with protocol requirements
- Recommendation by the IDMC to discontinue the uveitis investigational program due to safety concerns.

AbbVie may terminate this study prematurely, either in its entirety or at any study site, for reasonable cause provided that written notice is submitted in advance of the intended termination. The Investigator may also terminate the study at their site for reasonable cause, after providing written notice to AbbVie in advance of the intended termination. Advance notice is not required by either party if the study is stopped due to safety concerns.

5.5 Treatments

5.5.1 Treatments Administered

Study drug will be provided as a sterile, preservative-free solution for injection contained in 1 mL prefilled syringes containing adalimumab 40 mg/0.8 mL. Drug will be subcutaneously administered as a 40 mg dose every other week at approximately the same time of day starting at Baseline.

5.5.2 Identity of Investigational Products

The individual study drug information is presented in Table 6.

Table 6. Identity of Investigational Products

Drug	Dosage Form	Device	Formulation	Manufacturer
Adalimumab	Parenteral	Prefilled syringe	40 mg/0.8 mL solution for injection Adalimumab/Mannitol, Citric acid monohydrate, Sodium citrate, Disodium phosphate dihydrate, Sodium dihydrogen phosphate dihydrate, Sodium chloride, Polysorbate 80, Water for injections, Sodium hydroxide added as necessary to adjust pH	AbbVie/Abbott

5.5.2.1 Packaging and Labeling

Adalimumab 40 mg/0.8 mL Prefilled Syringes:

Subject cartons will contain two prefilled syringes of adalimumab 40 mg/0.8 mL. The number of kits dispensed will be managed by the IVR/IWR system. At a minimum, the following information will appear on either the syringe and/or carton labels:

- Caution statement(s)
- Sponsor identification
- Protocol number
- Drug identification
- Quantity of contents
- Storage conditions
- Dosing instructions
- Kit number
- Route of administration
- Excipients (as required)
- Blank spaces to write the subject's identification number, and date dispensed (as required)
- Finishing lot number

- Expiry date (as required)

Each drug will be labeled as required per country requirements. Labels must remain affixed to study drug as applicable.

5.5.2.2 Storage and Disposition of Study Drugs

Adalimumab prefilled syringes are to be stored protected from light at 2° to 8°C/36° to 46°F. Study drug **must not be frozen** at any time. A storage temperature log is to be maintained to document proper storage conditions. The refrigerator temperature must be recorded each business day to document proper function. The maximum, minimum and current temperature for refrigerator temperature must be documented and reviewed for temperature excursions. Malfunctions or any temperature excursion must be reported to AbbVie immediately. Study medication should be quarantined and not dispensed until AbbVie Global Pharmaceutical Research and Development (GPRD) or Abbott Temperature Excursion Management System (ATEMS) deems the medication as acceptable.

All clinical supplies must be stored and locked in a secure place until they are dispensed for subject use or are returned to AbbVie.

Investigational products are for investigational use only and are to be used only within the context of this study. The clinical supplies for this study must be maintained under adequate security and stored under conditions specified on the label.

5.5.3 Method of Assigning Subjects to Treatment Groups

All subjects will be centrally registered by the Interactive Voice Response System, (IVRS)/Interactive Web Response System (IWRS) at the Baseline study visit. This study is open-label therefore all subjects will be assigned to active treatment. The sites will be provided with appropriate kit number(s) for drug-dispensing purpose for each subject by the IVRS/IWRS. Before the study is initiated, the telephone number and call-in directions

for the IVRS/IWRS will be provided to each site. Study drug will be dispensed at the study visits summarized in Table 1.

The IVRS/IWRS will be maintained by Bracket (formerly United BioSource Corporation):

Bracket
303 Second Street, Suite 700
7th Floor South Tower
San Francisco, CA 94107 USA

5.5.4 Selection and Timing of Dose for Each Subject

Subjects should take study medication as outlined in Section 5.5.1.

Each subject will be assigned to open-label eow adalimumab dosing. If a subject should forget to administer the injection of study medication on their regularly scheduled dosing date, they should take the forgotten injection as soon as they remember the dose was missed up to the day of their next scheduled dose. The subject should not administer two doses on the same day.

In the event the incorrect dose is taken or a dose is missed, the subject should be instructed to contact the site to determine how to proceed with dosing. The subject must record all dosing information on the Subject Dosing Diary (Appendix E).

Doses not administered (e.g., not taken before next dose is scheduled), should be recorded as not taken in the source. The extra dose should be returned to the study site full. The subject should resume their regular dosing schedule based on the date of first dose at Baseline.

5.5.5 Masking

This study is open-label. There is no masking of treatment assignment.

5.5.5.1 Data for Independent Data Monitoring Committee (IDMC)

An Independent Data Monitoring Committee (IDMC) will be established to independently monitor and assess data from Study M10-877 (active uveitis), Study M10-880 (inactive uveitis) and Study M11-327 (open-label long-term extension). The IDMC will be in effect until the end of both Study M10-877 and Study M10-880. At each committee meeting, the IDMC will undertake a comprehensive review and assessment of the cumulative safety data. The IDMC will meet every 6 months or at a frequency determined by the IDMC and render their recommendation for either the termination or continuation of the study or an amendment to the study. The IDMC analysis will be conducted by a statistics vendor external to AbbVie in order for the sponsor to remain masked to the results of the study.

If the parent studies are prematurely stopped based upon the recommendation of the IDMC, and this recommendation is based on safety concerns, subjects will be required to return for their Final/Early Termination visit in Study M11-327.

5.5.6 Treatment Compliance

The Investigator or his/her designated representatives will dispense study drug only for use by subjects enrolled in the study in accordance with the protocol. The study drug must not be used for reasons other than that described in the protocol.

The subject or their qualified designee will administer all doses of study drug when not at the site. Appropriate site staff will supervise the subject's administration of the study drug at the Baseline office study visit to ensure proper injection technique. In order to document compliance with the treatment regimen, the subject will be given a Subject Dosing Diary (Appendix E) to record all injection dates and times. Compliance information will be documented on the appropriate eCRF. Subjects will be counseled on missed doses of medication. If the subject does not return the Subject Dosing Diary, IP cartons and sharp containers (when applicable), the site should question the subject and obtain as much information as possible as to the dosing of the study drug.

The information should be documented on the source documents as per "best recollection" and when possible, re-verified when the Subject Dosing Diary is returned before completing on the applicable eCRF page.

5.5.6.1 Drug Accountability

The Investigator or designee will verify that study drug supplies are received intact, at the appropriate temperature, (in the US adequate temperature is cool to the touch, outside of the US temperature recording devices [TempTale®] are provided in the shipments), and in the correct amounts from the drug depot. This will be accomplished by documenting the condition of the shipment, verifying the kit numbers in the package against the Proof of Receipt (POR) or similar document included with each drug shipment, and documenting this verification by signing and dating the POR or similar document. The original POR Note or similar document will be kept in the site files as a record of what was received.

In addition, an interactive web response system (IWRS) will be used to document Investigational Product Accountability including but not limited to date received, the lot number, kit number(s), date dispensed, subject number and the identification with date of person dispensing the drug.

All empty pre-filled syringe cartons and used prefilled syringes will be inventoried by the site. Each subject will be given their own sharps disposal container to store used pre-filled syringes. Empty IP cartons and Sharps containers should be returned by the subject at each visit for accountability and compliance purposes and new containers issued as necessary. Empty cartons and returned Sharps containers will be retained (unless prohibited by local law) until the CRA is on site to confirm the returned medication. CRAs and site staff will complete study medication accountability via IVRS/IWRS, source documents, Subject Dosing Diaries, empty IP cartons and by visually inspecting the syringes in the Sharps container whenever possible. Used Sharps containers should never be opened. Once the CRA has verified drug accountability at the site, the site staff and CRA will document that the used prefilled syringes have been destroyed, using appropriate biohazard precautions, when appropriate. A copy of the

destruction methodology should be maintained at the site's facility. Unused medication will be returned by the CRA after drug accountability has been completed at the site.

An overall accountability of the study drug will be performed and verified by the CRA throughout the study and at the site closeout visit.

The investigator and/or named the sub-investigators agree not to supply study medication to any persons not enrolled in the study.

5.6 Discussion and Justification of Study Design

5.6.1 Discussion of Study Design and Choice of Control Groups

The design of this clinical trial was chosen to gather long-term safety and tolerability data for adalimumab in this subject population and to further evaluate the long-term effectiveness of adalimumab in the treatment of non-infectious uveitis.

5.6.2 Appropriateness of Measurements

Standard statistical, clinical, and laboratory procedures will be utilized in this study. All efficacy measurements in this study are standard for assessing disease activity in subjects with uveitis. All clinical and laboratory procedures in this study are standard and generally accepted.

5.6.3 Suitability of Subject Population

Subjects with uveitis who met the endpoint treatment failures or have successfully completed Study M10-877 or Study M10-880 may be eligible for this study. These subjects are candidates for systemic immunosuppressive therapy to allow reduction and/or discontinuation of corticosteroid therapy.

5.6.4 Selection of Doses in the Study

Dosing of adalimumab in this study is the same as that proposed in the parent Phase 3 Study M10-877 and Study M10-880. Since it will be unknown whether a subject entering

this study was randomized to adalimumab or placebo in the parent study, no loading dose will be given in this study.

In total, adalimumab has now been tested in clinical studies in over 29,000 subjects representing more than 56,000 patient years.

6.0 Complaints

A Complaint is any written, electronic, or oral communication that alleges deficiencies related to the physical characteristics, identity, quality, purity, potency, durability, reliability, safety, effectiveness, or performance of a product/device after it is released for distribution.

The investigational product in this trial contains both:

- Biologic compound(s) and
- Device component(s) (pre-filled syringe).

Complaints associated with any component of this investigational product must be reported to the Sponsor (Section 6.2.2). For adverse events, please refer to Sections 6.1 through 6.1.6. For product complaints, please refer to Section 6.2.

6.1 Medical Complaints

The Investigator will monitor each subject for clinical and laboratory evidence of adverse events on a routine basis throughout the study. The Investigator will assess and record any adverse event in detail including the date of onset, event diagnosis (if known) or sign/symptom, severity, time course, duration and outcome, relationship of the adverse event to study drug and any action(s) taken. For serious adverse events, if the investigator's opinion of possibly, probably not, or not related to study drug is given, an 'Other' cause of event must be provided by the investigator for the adverse event. For adverse events to be considered intermittent, the events must be of similar nature and

severity. Adverse events, whether in response to a query, observed by site personnel, or reported spontaneously by the subject will be recorded.

All adverse events will be followed to a satisfactory conclusion.

6.1.1 Definitions

6.1.1.1 Adverse Event

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not the event is considered causally related to the use of the product.

Such an event can result from use of the drug as stipulated in the protocol or labeling, as well as from accidental or intentional overdose, drug abuse, or drug withdrawal. Any worsening of a pre-existing condition or illness is considered an adverse event. Worsening in severity of a reported adverse event should be reported as a new adverse event. Laboratory abnormalities and changes in vital signs are considered to be adverse events only if they result in discontinuation from the study, necessitate therapeutic medical intervention, (meets protocol specific criteria [refer to Section 6.3 regarding toxicity management]) and/or if the Investigator considers them to be adverse events.

An elective surgery/procedure scheduled to occur during a study will not be considered an adverse event if the surgery/procedure is being performed for a pre-existing condition and the surgery/procedure has been preplanned prior to study entry. However, if the pre-existing condition deteriorates unexpectedly during the study (e.g., surgery performed earlier than planned), then, the deterioration of the condition for which the elective surgery/procedure is being done will be considered an adverse event.

6.1.1.1.1 Uveitis-Related Events

The following events are known complications related to the condition being treated and will be classified as uveitis-related events. These events will be analyzed separately from other adverse events in the final study report.

The following events are not a complete list of all potential uveitis-related events (e.g., choroidal thickening, choroidal detachment, retinal effusion, are not included but could possibly be events related to uveitis). The investigator must determine if a specific event is uveitis-related.

- Loss of transparency of the cornea
- Band keratopathy
- Synechiae
- Cataracts
- Glaucoma/increased intraocular pressure
- Vitreous hemorrhage
- Macular edema
- Retinal detachment
- Epiretinal membrane
- Vitreo-macular traction
- Retinal ischemia
- Vision loss
- Hypotony

6.1.1.2 Serious Adverse Events

If an adverse event meets any of the following criteria, it is to be reported to AbbVie as a serious adverse event (SAE) within 24 hours of the site being made aware of the serious adverse event.

Death of Subject	An event that results in the death of a subject.
Life-Threatening	An event that, in the opinion of the Investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
Hospitalization or Prolongation of Hospitalization	An event that results in an admission to the hospital for any length of time or prolongs the subject's hospital stay. This does not include an emergency room visit or admission to an outpatient facility.
Congenital Anomaly	An anomaly detected at or after birth, or any anomaly that results in fetal loss.
Persistent or Significant Disability/Incapacity	An event that results in a condition that substantially interferes with the activities of daily living of a study subject. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle).
Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome	An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of subject, life-threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Additionally, any elective or spontaneous abortion or stillbirth is considered an important medical event. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.
Spontaneous Abortion	Miscarriage experienced by study subject.

Elective Abortion	Elective abortion performed on study subject.

6.1.2 Adverse Event Severity

The Investigator will use the following definitions to rate the severity of each adverse event:

Mild	The adverse event is transient and easily tolerated by the subject.
Moderate	The adverse event causes the subject discomfort and interrupts the subject's usual activities.
Severe	The adverse event causes considerable interference with the subject's usual activities and may be incapacitating or life-threatening.

6.1.3 Relationship to Study Drug

The Investigator will use the following definitions to assess the relationship of the adverse event to the use of study drug:

Probably Related	An adverse event has a strong temporal relationship to study drug or recurs on re-challenge and an Other cause of event is unlikely or significantly less likely.
Possibly Related	An adverse event has a strong temporal relationship to the study drug and an Other cause of event is equally or less likely compared to the potential relationship to study drug.
Probably Not Related	An adverse event has little or no temporal relationship to the study drug and/or a more likely Other cause of event exists.
Not Related	An adverse event is due to an underlying or concurrent illness or effect of another drug and is not related to the study drug (e.g., has no temporal relationship to study drug or has a much more likely Other cause of event).

For causality assessments, events meeting the categories of probably or possibly related will be considered "associated." Events that are probably not or not related will be

considered "not associated." In addition, when the Investigator has not reported a causality or deemed it not assessable, AbbVie will consider the event associated.

If an Investigator's opinion of possibly, probably not, or not related to study drug is given, an 'Other' cause of event must be provided by the Investigator for the serious adverse event.

6.1.4 Adverse Event Collection Period

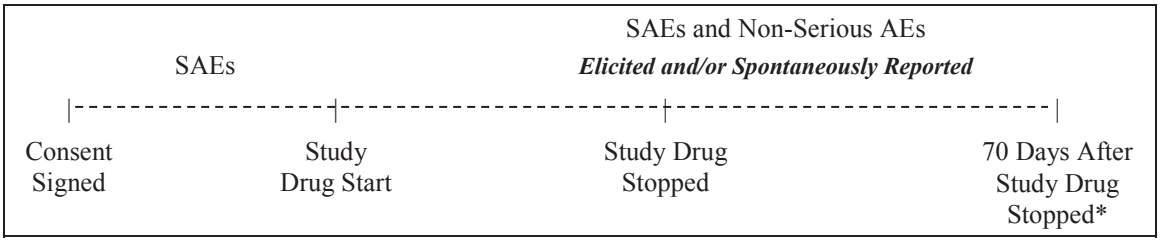
All adverse events reported from the time of study drug administration until 70 days, following discontinuation of study drug administration have elapsed will be collected, whether solicited or spontaneously reported by the subject. In addition, serious adverse events will be collected from the time the subject signs the study-specific informed consent if the subject does not have the Baseline visit on the same day. Any adverse events experienced prior to first study drug administration in M11-327 will be reported in the parent protocol. Adverse event information will be collected and recorded on the appropriate eCRFs. In the event of a death, the date and reason for death should be collected.

Subjects will be contacted approximately 70 days following study drug discontinuation for an assessment of any new or ongoing AEs except those subjects who continue on adalimumab therapy after the end of study participation. These subjects are not required to complete the 70-day follow-up and any new Adverse Events should be reported through the mechanism used for all post marketing adverse experiences.

There may be instances where a 70-day follow-up phone call or clinic visit occurs after the locking of the clinical database. In this situation, any adverse events reported to AbbVie from this 70-day follow-up phone call or clinic visit will be evaluated for inclusion in the clinical database. All SAEs or Adverse Events of Special Interest, as defined by AbbVie, reported during the 70-day follow-up phone call or clinic visit must be captured in the clinical database. The 70-day follow-up phone call will not be required for any subject that initiates commercial adalimumab after the end of study participation.

Adverse event information will be collected as shown in Figure 2.

Figure 2. Adverse Event Collection



* Except for subjects who continue on adalimumab therapy after the end of study participation.

6.1.5 Adverse Event Reporting

In the event of a serious adverse event, and additionally, any nonserious event of malignancy in subjects 30 years of age and younger, whether related to study drug or not, the investigator will notify Clinical Pharmacovigilance within 24 hours of the site being aware of the event by entering the serious adverse event or nonserious event of malignancy in subjects 30 years of age and younger data into the electronic data capture (EDC) system. Serious adverse events and nonserious events of malignancy in subjects 30 years of age and younger, that occur prior to the site having access to the RAVE system or if RAVE is not operable should be sent to Clinical Pharmacovigilance within 24 hours of site being made aware of the adverse event.

FAX to:	[redacted]
Email:	

For serious adverse event concerns, contact the Immunology Safety Team at:

Immunology Safety Team
Immunology Development
[redacted]
AbbVie
1 North Waukegan Road
North Chicago, IL 60064
USA

Fax:
Safety Hotline:
Email:
[redacted]

For any subject safety concerns, please contact the AbbVie Medical Monitors listed below:

For US, Canada, and Latin America:

[redacted]

For Europe, Israel, Australia and Japan:

[redacted]

Secondary Contact for Japan (Regional Medical Monitor):

[redacted]

[redacted] and [redacted] cover for each other. For any subject safety concerns or medical emergencies in which both medical monitors are unavailable, please call the following central back-up number:

Phone: [redacted]

In the EU, the sponsor will be responsible for Suspected Unexpected Serious Adverse Reactions (SUSAR) reporting for the Investigational Medicinal Product (IMP) in

accordance with Directive 2001/20/EC. The reference document used for SUSAR reporting in EU countries for adalimumab will be the most current version of the Investigator's Brochure.

6.1.6 Pregnancy

Pregnancy in a study subject must be reported to AbbVie within 1 working day of the site becoming aware of the pregnancy. Subjects who become pregnant during the study must be discontinued (Section 5.4.1). Pregnancies will be collected from the date of the first dose through 150 days following the last dose of study medication.

Information regarding a pregnancy occurrence in a study subject and the outcome of the pregnancy will be collected. Pregnancy in a study subject is not considered an AE. However, the medical outcome of an elective or spontaneous abortion, stillbirth or congenital anomaly is considered a SAE and must be reported to AbbVie within 24 hours of the site becoming aware of the event.

6.2 Product Complaint

6.2.1 Definition

A Product Complaint is any Complaint (see Section 6.0 for the definition) related to the biologic or drug component of the product or to the medical device component(s).

For a product this may include, but is not limited to, damaged/broken product or packaging, product appearance whose color/markings do not match the labeling, labeling discrepancies/inadequacies in the labeling/instructions (example: printing illegible), missing components/product, device not working properly, or packaging issues.

For medical devices, a product complaint also includes all deaths of a patient using the device, any illness, injury, or adverse event in the proximity of the device, an adverse event that could be a result of using the device, any event needing medical or surgical intervention including hospitalization while using the device and use errors.

Any information available to help in the determination of causality by the device to the events outlined directly above should be captured.

6.2.2 Reporting

Product Complaints concerning the investigational product and/or device must be reported to the Sponsor within 24 hours of the study site's knowledge of the event via the Product Complaint form. Product Complaints occurring during the study will be followed-up to a satisfactory conclusion. All follow-up information is to be reported to the Sponsor (or an authorized representative) and documented in source as required by the Sponsor. Product Complaints associated with adverse events will be reported in the study summary. All other complaints will be monitored on an ongoing basis.

Product Complaints may require return of the product with the alleged complaint condition (syringe). In instances where a return is requested, every effort should be made by the investigator to return the product within 30 days. If returns cannot be accommodated within 30 days, the site will need to provide justification and an estimated date of return.

The description of the complaint is important for AbbVie in order to enable AbbVie to investigate and determine if any corrective actions are required.

6.3 Toxicity Management

For the purpose of medical management, all adverse events and laboratory abnormalities that occur during the study must be evaluated by the Investigator. Subjects who develop a new infection while receiving study drug should be monitored closely. Administration of study injections should be interrupted if a subject develops an infection requiring IV anti-infective treatment or if an infection meets the definition of "serious" (refer to Section 6.1.1.2 for definitions). Study medication may be restarted once the physician determines that the infection has been successfully treated. Otherwise prohibited concomitant medications may be given if medically necessary. Prior to use, every attempt

should be made to contact the AbbVie Study Physician for direction on re-introduction of study drug after prohibited medication administration.

If the subject must undergo elective surgery, the study injections must be interrupted 2 weeks prior to the surgery. If the subject must undergo emergency surgery, the study injections must be interrupted at the time of the surgery. The injectable study medication can recommence at least 2 weeks after surgery once the physician has examined the surgical site and determined that it has healed and there is no sign of infection.

7.0 Protocol Deviations

AbbVie does not allow intentional/prospective deviations from the protocol. The Principal Investigator is responsible for complying with all protocol requirements, and applicable global and local laws regarding protocol deviations. If a protocol deviation occurs (or is identified) after a subject has been enrolled, the Principal Investigator is responsible for notifying Independent Ethics Committee (IEC)/Independent Review Board (IRB) regulatory authorities (as applicable), and the AbbVie Clinical Monitor(s) assigned to your site. Alternative contacts are as follows:

Alternate Contacts

North America, Latin America, and Japan	Europe, Israel, and Australia
[redacted]	

Such contact must be made as soon as possible to permit a review by AbbVie to determine the impact of the deviation on the subject and/or the study.

For purposes of this protocol, reportable deviations are defined as:

- Subject entered into the study even though they did not satisfy entry criteria
- Subject who developed withdrawal criteria during the study and was not withdrawn
- Subject who received wrong treatment or incorrect dose
- Subject who received excluded or prohibited concomitant treatment

8.0 Statistical Methods and Determination of Sample Size

8.1 Statistical Analysis Plans

The primary objective of the statistical analysis is to evaluate the long-term safety and efficacy of adalimumab 40 mg given every other week (eow) subcutaneously (SC) in subjects with non-infectious intermediate-, posterior-, or pan-uveitis who participated in Study M10-877 or Study M10-880. The following statistical analysis will be done in the total set of subjects. Efficacy analysis will be performed in the Intent to Treat (ITT) set. The safety analysis will be conducted in the Safety set.

The analysis strategy described below will be supplemented by a detailed statistical analysis plan (SAP) which will be completed prior to database lock.

8.1.1 Analysis Population

Both, the ITT set and the safety set include all subjects who received at least one dose of study medication.

No per protocol analysis will be done.

8.1.2 Planned Methods of Statistical Analysis

Descriptive statistics will be provided. These include the number of observations, means, standard deviation, minimum, 1st quartile, median, 3rd quartile, and maximum for

continuous variables; and counts and percentages for discrete variables. The analyses will be performed using SAS (SAS Institute Inc., Cary, NC, USA).

8.1.3 Analysis of Demographics and Baseline Characteristics

Demographics and Baseline characteristics of the study subjects will be summarized using descriptive statistics.

8.1.4 Analysis of Efficacy

All statistical analyses will be descriptive. Results will be stratified between subjects who entered into the study with active versus inactive uveitis. For subjects who had active uveitis when they entered the study, the efficacy analyses will start at Week 8. For subjects who had inactive uveitis when they entered the study, the efficacy analyses will start at Week 0. Continuous variables will be summarized by the number of non-missing observations, mean, standard deviation, median, quartiles, minimum and maximum. Categorical variables will be summarized by counts and percentages.

8.1.5 Analysis of Safety

Treatment-emergent AEs will be summarized using descriptive statistics. Treatment-emergent AEs are defined as events with an onset date on or after the first study drug administration until 70 days following the last study drug administration. In case of increasing severity of an existing AE, the worsening will be considered as a new AE with a new onset date.

AEs will be tabulated by system organ class and preferred term whereby the most current implemented MedDRA dictionary will be used. Also, summaries by severity and relationship to study drug will be done. Certain AEs, like serious or severe, leading to premature withdrawal, will be listed and described in detail. AEs of special interest for treatment with biologics will be defined in the SAP and analyzed separately.

Other safety variables like laboratory data and vital signs will be described by descriptive statistics as mentioned before. In addition, shift tables and listings will be provided for abnormal values whereby the normal range of the analyzing laboratory will be used.

The IDMC will undertake a comprehensive review and assessment of the cumulative safety data until the completion of Study M10-877 and Study M10-880. Please refer to Section 5.5.5.1 for additional information regarding IDMC review.

8.2 Determination of Sample Size

The sample size of this study will depend on how many subjects rollover into the extension study, who have either discontinued from M10-877 or M10-880 due to a "Treatment Failure" or have successfully completed M10-877 or M10-880.

9.0 Ethics

9.1 Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

Good Clinical Practice (GCP) requires that the clinical protocol, any protocol amendments, the Investigator's Brochure, the informed consent and all other forms of subject information related to the study (e.g., advertisements used to recruit subjects) and any other necessary documents be reviewed by an IEC/IRB. The IEC/IRB will review the ethical, scientific and medical appropriateness of the study before it is conducted. IEC/IRB approval of the protocol, informed consent and subject information and/or advertising, as relevant, will be obtained prior to the authorization of drug shipment to a study site.

Any amendments to the protocol will require IEC/IRB approval prior to implementation of any changes made to the study design. The Investigator will be required to submit, maintain and archive study essential documents according to ICH GCP.

Any serious adverse events that meet the reporting criteria, as dictated by local regulations, will be reported to both responsible Ethics Committees and Regulatory

Agencies, as required by local regulations. During the conduct of the study, the Investigator should promptly provide written reports (e.g., ICH Expedited Reports, and any additional reports required by local regulations) to the IEC/IRB of any changes that affect the conduct of the study and/or increase the risk to subjects. Written documentation of the submission to the IEC/IRB should also be provided to AbbVie.

9.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, ICH guidelines, applicable regulations and guidelines governing clinical study conduct and the ethical principles that have their origin in the Declaration of Helsinki, and all applicable local regulations. Responsibilities of the clinical investigator are specified in Appendix A.

9.3 Subject Information and Consent

The Investigator or his/her representative will explain the nature of the study to the subject, and answer all questions regarding this study. Prior to any study-related Baseline procedures being performed on the subject, the informed consent statement will be reviewed and signed and dated by the subject, the person who administered the informed consent, and any other signatories according to local requirements. A copy of the signed and dated informed consent form will be given to the subject and the original will be placed in the subject's medical record. An entry must also be made in the subject's dated source documents to confirm that informed consent was obtained prior to any study-related procedures and that the subject received a signed copy.

For subjects that complete or terminate early from the study, but are within the 70-day follow-up window: if an updated informed consent form is approved these subjects will not be required to return to the study site for the purposes of signing the updated informed consent form, provided the subject is contacted regarding the changes and there is documentation of the contact in the subject's source documents.

If the parent studies are prematurely stopped based upon the recommendation of the IDMC, and this recommendation is based on safety concerns, subjects will be required to return for their Final/Early Termination visit in Study M11-327.

10.0 Source Documents and Case Report Form Completion

10.1 Source Documents

Source documents are defined as original documents, data and records. This may include hospital records, clinical and office charts, laboratory data/information, subjects' diaries or evaluation checklists, pharmacy dispensing and other records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, and/or x-rays. Data collected during this study must be recorded on the appropriate source documents.

The investigator(s)/institution(s) will permit study-related monitoring, audits, IEC/IRB review, and regulatory inspection(s), providing direct access to source data documents.

The following assessments that will be completed by the subject or physician will be considered source documentation:

- NEI Visual Functioning Questionnaire (VFQ-25)
- EuroQol-5D Questionnaire (EQ-5D)
- Health Resource Utilization Questionnaire (HRU)
- Work Productivity and Activity Impairment, Questionnaire: Specific Health Problem Questionnaire (WPAI-SHP)

The adverse event eCRF data segments of: alternate etiology, severity, frequency and relationship to study drug, may also be used as source and will require an Investigator approval on the eCRF as verification of the accuracy of the information.

10.2 Case Report Forms

Electronic case report forms (eCRF) must be completed for each subject screened/enrolled in this study. These forms will be used to transmit information collected during the study to AbbVie and regulatory authorities, as applicable. The eCRF data for this study are being collected with an electronic data capture (EDC) system called Rave® provided by the technology vendor Medidata Solutions Incorporated, NY, USA. The EDC system and the study-specific electronic Case Report Forms (eCRFs) will comply with Title 21 CFR Part 11. The documentation related to the validation of the EDC system is available through the vendor, Medidata, while the validation of the study-specific eCRFs will be conducted by AbbVie and will be maintained in the Trial Master File at AbbVie.

The Investigator will document subject data in his/her own subject files. These subject files will serve as source data for the study. All eCRF data required by this protocol will be recorded by investigative site personnel in the EDC system. All data entered into the eCRF will be supported by source documentation. The central laboratory will send hard copies of laboratory results to sites which must be reviewed by the Investigator and filed as source data.

The Investigator or an authorized member of the Investigator's staff will make any necessary corrections to the eCRF. All change information, including the date and person performing the corrections, will be available via the audit trail, which is part of the EDC system. For any correction, a reason for the alteration will be provided. The eCRFs will be reviewed periodically for completeness, legibility, and acceptability by AbbVie personnel (or their representatives). AbbVie (or their representatives) will also be allowed access to all source documents pertinent to the study in order to verify eCRF entries. The Principal Investigator will review the eCRFs for completeness and accuracy and provide his or her electronic signature and date to eCRFs as evidence thereof.

Medidata will provide access to the EDC system for the duration of the trial through a password-protected method of internet access. Such access will be removed from investigator sites at the end of the site's participation in the study. Data from the EDC

system will be archived on appropriate data media (CD-ROM, etc.) and provided to the Investigator at that time as a durable record of the site's eCRF data. It will be possible for the Investigator to make paper printouts from that media.

The site will complete the VFQ-25 and HRU questionnaires via interview. The remaining questionnaires listed below will be completed by the subject, except when subjects with impaired vision cannot complete the questionnaires on their own, the site may administer the questionnaire. Except for the HRU which will be entered into EDC by the site, the subjects and site will enter responses on paper Case Report Forms provided by AbbVie and forwarded to AbbVie CDM for double data entry.

Any corrections to the questionnaires can only be made by the original respondent. All changed information, including the date and person performing the corrections, will be available via the audit trail.

- NEI Visual Functioning Questionnaire (VFQ-25)
- EuroQol-5D Questionnaire (EQ-5D)
- Health Resource Utilization Questionnaire (HRU)
- Work Productivity and Activity Impairment, Questionnaire: Specific Health Problem Questionnaire (WPAI-SHP)

11.0 Data Quality Assurance

Prior to the initiation of the study, a meeting will be held with AbbVie personnel, the Investigators and appropriate site personnel. This meeting will include a detailed discussion of the protocol, performance of study procedures, eCRF, Subject Questionnaires and Subject Diary completion, and specimen collection methods.

The AbbVie CRA will monitor each site throughout the study.

Source document verification will be performed.

All data entered in the database will be verified at AbbVie. Any discrepancies will be reviewed. The data will be reviewed and computer logic checks will be run to identify items such as inconsistent study dates. A manual review of selected line listings also will be performed at the end of the study. Queries will be generated in the EDC system. Any necessary corrections will be made to the eCRF.

The data from the central laboratory analyses will be electronically transferred from the central laboratory to the study database. A final review of all laboratory results will be conducted by a physician and clinical review team at AbbVie.

12.0 Use of Information and Publication

12.1 Use of Information

All information concerning adalimumab and AbbVie operations, such as AbbVie patent applications, formulas, manufacturing processes, basic scientific data, or formulation information, supplied by AbbVie and not previously published is considered confidential information.

The information developed during the conduct of this clinical trial is also considered confidential and will be used by AbbVie in connection with the development of adalimumab. This information may be disclosed as deemed necessary by AbbVie to other clinical Investigators, other pharmaceutical companies, to the FDA and to other government agencies. To allow for the use of the information derived from this clinical trial and to ensure complete and thorough analysis, the Investigator is obligated to provide AbbVie with complete test results and all data developed in this study and to provide direct access to source data/documents for trial-related monitoring, audits, IEC/IRB review, and regulatory inspection.

This confidential information shall remain the sole property of AbbVie, shall not be disclosed to others without the written consent of AbbVie, and shall not be used except in the performance of this study.

The Investigator will maintain a confidential subject identification code list of all subjects enrolled in the study (by name and subject number). This list will be maintained at the site and will not be retrieved by AbbVie.

Information regarding this study may be posted on various internet web sites and will maximally include study name, number, general population to be enrolled, entrance qualifications, brief description of the study, study objectives, doses, accruing Investigators (upon their approval) and number of subjects to be enrolled.

Please refer to your Investigator site contract for information related to publication practices.

13.0 Completion of the Study

The investigator will conduct the study in compliance with the protocol and complete the study within the timeframe specified in the contract between the investigator (Director of the Site in Japan) and AbbVie. Continuation of this study beyond this date must be mutually agreed upon in writing by both the investigator (Director of the Site in Japan) and AbbVie. The investigator will provide a final report to the IEC/IRB following conclusion of the study, and will forward a copy of this report to AbbVie or their representative.

The investigator (Director of the Site in Japan) must retain any records related to the study according to local requirements. If the investigator (Director of the Site in Japan) is not able to retain the records, he/she must notify AbbVie to arrange alternative archiving options.

AbbVie will select the signatory investigator from the investigators who participate in the study. Selection criteria for this investigator will include level of participation as well as significant knowledge of the clinical research, investigational drug and study protocol. The signatory investigator for the study will review and sign the final study report in accordance with the European Medicines Agency (EMA) Guidance on Investigator's Signature for Study Reports.

The end-of-study is defined as the date of the last subject's last scheduled visit or the actual date of follow-up contact, whichever is later.

AbbVie may terminate this study prematurely, for reasonable cause, provided that written notice is submitted a reasonable time in advance of the intended termination. Advance notice is not required if the study is stopped due to safety concerns.

14.0 Investigator's Agreement

1. I have received and reviewed the Investigator's Brochure for adalimumab.
2. I have read this protocol and agree that the study is ethical.
3. I agree to conduct the study as outlined and in accordance with all applicable regulations and guidelines.
4. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.
5. I agree that all electronic signatures will be considered the equivalent of a handwritten signature and will be legally binding.

Protocol Title:	A Multicenter Open-Label Study of the Long-term Safety and Efficacy of the Human Anti-TNF Monoclonal Antibody Adalimumab in Subjects with Non-infectious Intermediate-, Posterior-, or Pan-uveitis – VISUAL III
Protocol Date:	04 June 2015

Signature of Principal Investigator	Date
Name of Principal Investigator (printed or typed)	

15.0 Reference List

1. Mazurek GH, Jereb J, Vernon A, et al. Updated guidelines for using Interferon Gamma Release Assays to detect Mycobacterium tuberculosis infection – United States, 2010. MMWR Recomm Rep. 2010 Jun 25;59(RR-5):1-25.
2. Yanoff M, Duker JS, editors. Yanoff and Duker: Ophthalmology, 3rd ed. Elsevier Health Sciences; 2009.
3. Jabs DA, Nussenblatt RB, Rosenbaum JT. The standardization of uveitis nomenclature (SUN) working group. Standardization of uveitis nomenclature for reporting clinical data. Results of the First International Workshop. Am J Ophthalmol. 2005;140(3):509-16.
4. Rothova A, Suttorp-van Schulten MS,Treffers WF, Kijlstra A. Causes and frequency of blindness in patients with intraocular inflammatory disease. Br J Ophthalmol. 1996;80(4):332-6.
5. Wakefield D, Chang JH. International Ophthalmology Clinics. 2005 Spring 45(2):1-13.
6. Jabs DA, Rosenbaum JT, Foster CS, Holland GN, Jaffe GJ, Louie JS, 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):492-513.
7. Cervantes-Castaneda RA, Jawed N, Foster CS. Immunosuppressive therapy for noninfectious uveitis. Retinal Physician. 2007;March:30-8.
8. Becker MD, Smith JR, Max R, Fiehn C. Management of sight-threatening uveitis: new therapeutic options. Drugs. 2005;65(4):497-519.
9. Smith JR, Rosenbaum JT. Management of Uveitis: A rheumatologic perspective. Arthritis Rheum. 2002;46(2):309-18.
10. Nussenblatt R. The natural history of uveitis. Int Ophthalmology. 1990;14:303-8.
11. Retisert (fluocinolone acetonide intravitreal implant [Package Insert]. Rochester, NY: Bausch & Lomb; 2007.

12. Jaffe GJ, Martin D, Callanan D, Pearson PA, Levy B. Fluocinolone acetonide implant (Retisert) for noninfectious posterior uveitis: Thirty-four-week results of a multicenter randomized clinical study. Ophthalmology. 2006;113:1020-7.
13. Callanan DG, Jaffe GJ, Martin DF, Pearson PA, Comstock TL. Treatment of posterior uveitis with a fluocinolone acetonide implant: Three-year clinical trial results. Arch Ophthalmol. 2008;126(9):1191-1201.
14. Caspi RR, Sun B, Agarwal RK. T cell mechanisms in experimental autoimmune uveoretinitis: susceptibility is a function of the cytokine response profile. Eye. 1997;11:209-12.
15. Murphy CC, Duncan L, Forrester JV, Dick AD. Systemic CD4+ T cell phenotype and activation status in intermediate uveitis. Br J Ophthalmol. 2004;88:412-6.
16. Deschenes J, Char DH, Kaleta S. Activated T lymphocytes in uveitis. Br J Ophthalmol. 1988;72:83-7.
17. Dick AD, Forrester JV, Liversidge J, Cope AP. The role of tumour necrosis factor (TNF-a) in experimental autoimmune uveoretinitis (EAU). Progress in Retinal and Eye Research. 2004;23:617-37.
18. Okada AA, Sakai J, Usui M, Mizuguchi J. Intraocular cytokine quantification of experimental autoimmune uveoretinitis in rats. Ocular Immunology and Inflammation. 1998;6(2):111-20.
19. Sartani G, Silver PB, Rizzo LV, Chan C, Wiggert B, Mastorakos G, et al. Anti-tumor necrosis factor alpha therapy suppresses the induction of experimental autoimmune uveoretinitis in mice by inhibiting antigen priming. Invest Ophthalmol Vis Sci. 1996;37:2211-8.
20. Dick AD, Duncan L, Hale G, Waldmann H, Isaacs J. Neutralizing TNF-alpha activity modulates T-cell phenotype and function in experimental autoimmune uveoretinitis. J of Autoimmunity. 1998;11:255-64.
21. Callejas-Rubio JL, Sánchez-Cano D, García Serrano JL, Ortego-Centeno N. Letter to the Editor: Adalimumab therapy for refractory uveitis: A pilot study. J Ocul Pharmac Ther. 2008;24(6):613-4.

22. Mushtaq B, Saeed T, Situnayake RD, Murray PI. Adalimumab for sight-threatening uveitis in Behcet's disease. Eye. 2007;21:824-5.

23. Diaz-Llopis M, Garcia-Delpech S, Salom D, Udaondo P, Hernandez-Garfella M, Bosch-Morell F, et al. Adalimumab therapy for refractory uveitis: A pilot study. J Ocul Pharmacol Ther. 2008;24:351-61.

24. Vazquez-Cobian LB, Flynn T, Lehman TJA. Adalimumab therapy for childhood uveitis. J Pediatr. 2006;149:572-5.

25. Tognon S, Graziani G, Marcolongo R. Anti-TNF-Therapy in seven patients with Behcet's uveitis: advantages and controversial aspects. Ann. N.Y. Acad. Sci. 2007;1110:474-84.

26. Saurenmann RK, Levin AV, Rose JB, Parker S, Rabinovitch T. Tumour necrosis factor a inhibitors in the treatment of childhood uveitis. Rheumatology. 2006;45:982-9.

27. Niccoli L, Nannini C, Benucci M, Chindamo C, Cassara E. Long-term efficacy of infliximab in refractory posterior uveitis of Behcet's disease: a 24-month follow-up study. Rheumatology. 2007;46:1161-4.

28. Lindstedt EW, Baarsma GS, Kuijpers RWAM, van Hagen PM. Anti-TNF-a therapy for sight threatening uveitis. Br J Ophthalmol. 2005;89:533-6.

29. Suhler EB, Smith JR, Wertheim MS, Lauer AK, Kurz DE. A prospective trial of infliximab therapy for refractory uveitis. Arch Ophthalmol. 2005;123:903-12.

30. Suhler EB, Smith JR, Giles TR, Lauer AK, Wertheim MS. Infliximab therapy for refractory uveitis: 2-year results of a prospective trial. Arch Ophthalmol. 2009;127(6):819-22.

31. Schmeling H, Horneff G. Etanercept and uveitis in patients with juvenile idiopathic arthritis. Rheumatology. 2005;44:1008-11.

32. Foster CS, Tufail F, Waheed NK, Chu D, Miserocchi E. Efficacy of etanercept in preventing relapse of uveitis controlled by methotrexate. Arch Ophthalmol. 2003;121(4):437-40.

33. Jakob E, Reuland MS, Mackensen F, Harsch N, Fleckenstein M, Lorenz HM, et al. Uveitis subtypes in a german interdisciplinary uveitis center – analysis of 1916 patients. J Rheumatol. 2009;36(1):127-36.

34. Biester S, Deuter C, Michels H, Haefner R, Kuemmerle-Deschner J, Doycheva D, et al. Adalimumab in the therapy of uveitis in childhood. Br J Ophthalmol. 2007;91:319-24.

35. Rudwaleit M, Rodevand E, Holck P, Vanhoof J, Kron M, Kary S, et al. Adalimumab effectively reduces the rate of anterior uveitis flares in patients with active ankylosing spondylitis. Ann Rheum Dis. 2009;68:696-701.

36. Suhler EB, Goldstein DA, Lowder CY, Giles TR, Liesegang TL. Adalimumab (Humira) for the treatment of refractory uveitis: preliminary results of a multicenter prospective phase II clinical trial. Oral Presentation, Association of Research in Vision and Ophthalmology annual meeting. Fort Lauderdale, FL. 2009.

37. The Age-Related Eye Diseases Study Group. The age-related eye disease study (AREDS) system for classifying cataracts from photographs: AREDS report no. 4. Am J Ophthalmol. 2001 Feb;131(2):167-75.

38. Chew EY, Kim J, Sperduto R, Datiles MB III, Coleman H, Smith J, et al. Evaluation of the Age-Related Eye Disease Study (AREDS) Clinical Lens Grading System. Accepted for publication in Ophthalmology.

39. Nussenblatt RB, Palestine AG, Chan C, Roberge F. Standardization of vitreal inflammatory activity in intermediate and posterior uveitis. Ophthalmology. 1985;92:467-71.

40. Nussenblatt RB, Peterson JS, Foster CS, Rao NA, See RF. Initial Evaluation of Subcutaneous Daclizumab Treatments for Noninfectious Uveitis. Ophthalmology. 2005;112:764-770.

41. Díaz-Llopis M, Salom D, Garcia-de-Vicuña C, et al. Treatment of refractory uveitis with adalimumab: a prospective multicenter study of 131 patients. Ophthalmology. 2012;119(8):1575-81.

Appendix A. Responsibilities of the Clinical Investigator

Clinical research studies sponsored by AbbVie are subject to the Good Clinical Practices (GCP) and local regulations and guidelines governing the study at the site location. In signing the Investigator Agreement in Section 14.0 of this protocol, the Investigator is agreeing to the following:

1. Conducting the study in accordance with the relevant, current protocol, making changes in a protocol only after notifying AbbVie, except when necessary to protect the safety, rights or welfare of subjects.
2. Personally conducting or supervising the described investigation(s).
3. Informing all subjects, or persons used as controls, that the drugs are being used for investigational purposes and complying with the requirements relating to informed consent and ethics committees [e.g., independent ethics committee (IEC) or institutional review board (IRB)] review and approval of the protocol and amendments.
4. Reporting adverse experiences that occur in the course of the investigation(s) to AbbVie and the site director.
5. Reading the information in the Investigator's Brochure/safety material provided, including the instructions for use and the potential risks and side effects of the investigational product(s).
6. Informing all associates, colleagues, and employees assisting in the conduct of the study about their obligations in meeting the above commitments.
7. Maintaining adequate and accurate records of the conduct of the study, making those records available for inspection by representatives of AbbVie and/or the appropriate regulatory agency, and retaining all study-related documents until notification from AbbVie.
8. Maintaining records demonstrating that an ethics committee reviewed and approved the initial clinical investigation and all amendments.

9. Reporting promptly, all changes in the research activity and all unanticipated problems involving risks to human subjects or others, to the appropriate individuals (e.g., coordinating Investigator, institution Director) and/or directly to the ethics committees and AbbVie.

10. Following the protocol and not making any changes in the research without ethics committee approval, except where necessary to eliminate apparent immediate hazards to human subjects.

Appendix B. List of Protocol Signatories

Name	Title	Functional Area
[redacted]		Clinical
		Clinical
		Statistics
		Clinical

Appendix C. Non-Drug Materials Provided to the Study Sites

Study sites will receive the following supplies prior to or during the study:

- Tote Bags
- Coolers
- Sharps Containers
- Ice Packs
- Subject Dosing Diary

Appendix D. Day 70 Follow-up (Phone Call or Clinic Visit)

Site Name/Number: _____/_____

Subject Number: _____

Please contact all subjects approximately 70 days following last study drug administration.

Date of Call/Visit: _____

☐ Lost to Follow-up (Please check this box if subject was not willing to provide any follow-up information or you were unable to speak to the subject following at least two phone call attempts and one certified letter).

☐ No Events Reported

List any Adverse Events (AE) and/or Serious Adverse Events (SAE) that occurred since the subject's last study drug administration. Please document all adverse events on a 500 AE CRF in the EDC system. (Please report all SAEs to AbbVie within 24 hours of being made aware of the event). **In addition, please note stop dates to any adverse events that were ongoing at the last study visit. If an adverse event is determined to be ongoing at the 70 day call/visit, please note in source documents and in EDC.**

_____	_____
_____	_____
_____	_____
_____	_____

Name of person completing form (printed): _____

Signature of person completing form: _____

Date: _____

Please fax this form to AbbVie at [redacted]

Subject Injection Instructions

0.8 mL dose

(Administered as a single dose-pre-filled syringe)

Protocol M11-327

Table of Contents

Dosing Schedule

General Information and Supplies

Injection Procedures

Dosing Diary
Adalimumab

Instructions: To be completed for every study dose. Study medication should be taken at about the same time of day, on the same day of the week as directed by your study doctor. Please refer to the Self Injection Instructions provided to you for additional dosing information. Call the doctor's office if you are having problems administering your study medication.

Appendix F. AREDS 2008 Clinical Lens Opacity Grading Procedures

AREDS Study Group

- Dilate pupils to at least 5 mm diameter
- Use slit lamp with ~10× magnification
- Use brightest beam intensity
- Nuclear opacity
  - Orient beam at 45° to viewing axis
  - Adjust slit beam to standard parameters: 8 mm height and 0.3 mm width
  - Compare opalescence of nucleus with that in standard photos
- Cortical and PSC opacities
  - Select wide slit beam setting optimum for retro-illumination of lens
  - Visualize lens opacities against red fundus reflex background
  - Count only opacities definitely visible against red reflex
  - Mentally combine all cortical opacities into one contiguous area
  - Compare total opacity area with that in standard photos
- Classify each opacity with scale defined by 3 standard photos
- Select nearest half-step
  - Similar to standard or between two standards
  - Obviously less than mildest standard or greater than most severe

3. How much of the time do you worry about your eyesight?
(Circle One)

READ CATEGORIES:		
	None of the time	1
	A little of the time	2
	Some of the time	3
	Most of the time	4
	All of the time?	5

4. How much pain or discomfort have you had in and around your eyes (for example, burning, itching, or aching)? Would you say it is:
(Circle One)

READ CATEGORIES:		
	None	1
	Mild	2
	Moderate	3
	Severe, or	4
	Very severe?	5

PART 2 - DIFFICULTY WITH ACTIVITIES

The next questions are about how much difficulty, if any, you have doing certain activities wearing your glasses or contact lenses if you use them for that activity.

5. How much difficulty do you have reading ordinary print in newspapers? Would you say you have:
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

6. **How much difficulty do you have doing work or hobbies that require you to see well up close, such as cooking, sewing, fixing things around the house, or using hand tools? Would you say:**
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

7. **Because of your eyesight, how much difficulty do you have finding something on a crowded shelf?**
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

8. **How much difficulty do you have reading street signs or the names of stores?**
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

9. **Because of your eyesight, how much difficulty do you have going down steps, stairs, or curbs in dim light or at night?**

(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

10. Because of your eyesight, how much difficulty do you have noticing objects off to the side while you are walking along?
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

11. Because of your eyesight, how much difficulty do you have seeing how people react to things you say?
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

12. **Because of your eyesight, how much difficulty do you have picking out and matching your own clothes?**
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

13. **Because of your eyesight, how much difficulty do you have visiting with people in their homes, at parties, or in restaurants ?**
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

14. **Because of your eyesight, how much difficulty do you have going out to see movies, plays, or sports events?**
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

15. Now, I'd like to ask about driving a car. Are you currently driving, at least once in a while?

(Circle One)

Yes	1	*Skip To Q 15c*
No	2	

15a. IF NO, ASK: Have you never driven a car or have you given up driving?

(Circle One)

Never drove	1	*Skip To Part 3, Q 17*
Gave up	2	

15b. IF GAVE UP DRIVING: Was that mainly because of your eyesight, mainly for some other reason, or because of both your eyesight and other reasons?

(Circle One)

Mainly eyesight	1	*Skip To Part 3, Q 17*
Mainly other reasons	2	*Skip To Part 3, Q 17*
Both eyesight and other reasons	3	*Skip To Part 3, Q 17*

15c. IF CURRENTLY DRIVING: How much difficulty do you have driving during the daytime in familiar places? Would you say you have:

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4

For each of the following statements, please tell me if it is definitely true, mostly true, mostly false, or definitely false for you or you are not sure.

(Circle One On Each Line)

	Definitely True	Mostly True	Not Sure	Mostly False	Definitely False
20. I stay home most of the time because of my eyesight.	1	2	3	4	5
21. I feel frustrated a lot of the time because of my eyesight.	1	2	3	4	5
22. I have much less control over what I do, because of my eyesight.	1	2	3	4	5
23. Because of my eyesight, I have to rely too much on what other people tell me...	1	2	3	4	5
24. I need a lot of help from others because of my eyesight.	1	2	3	4	5
25. I worry about doing things that will embarrass myself or others, because of my eyesight.	1	2	3	4	5

That's the end of the interview. Thank you very much for your time and your help.

Appendix H. EuroQol-5D Questionnaire (EQ-5D)

EQ-5D

Health Questionnaire

(English version for the US)

By placing a checkmark in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about	☐
I have some problems in walking about	☐
I am confined to bed	☐

Self-Care

I have no problems with self-care	☐
I have some problems washing or dressing myself	☐
I am unable to wash or dress myself	☐

Usual Activities (*e.g., work, study, housework, family or leisure activities*)

I have no problems with performing my usual activities	☐
I have some problems with performing my usual activities	☐
I am unable to perform my usual activities	☐

Pain/Discomfort

I have no pain or discomfort	☐
I have moderate pain or discomfort	☐
I have extreme pain or discomfort	☐

Anxiety/Depression

I am not anxious or depressed	☐
I am moderately anxious or depressed	☐
I am extremely anxious or depressed	☐

Appendix I. Health Resource Utilization Questionnaire (HRU)

Since the last study visit has the subject had any visits for their uveitis other than the protocol required visit?

YES: ____
NO: ____
If YES, please provide the following:

1. Since the last protocol required visit, has the subject been seen by a health care professional for their uveitis?

   YES: ____
   NO: ____
   If YES, how many times: ____

2. Since the last protocol required visit, has the subject been seen in the Emergency Room for their uveitis?

   YES: ____
   NO: ____
   If YES, how many times: ____

3. Since the last protocol required visit, has the subject been admitted to the hospital due to their uveitis?

   YES: ____
   NO: ____

   If YES, please list the ADMISSION DATE: __ __/___ ___ ___/ ___ ___ ___ __
   DD MMM YYYY

   DISCHARGE DATE: __ __/___ ___ ___/ ___ ___ ___ __
   DD MMM YYYY

Appendix J. Work Productivity and Activity Impairment, Questionnaire: Specific Health Problem Questionnaire V2.0 (WPAI-SHP)

The following questions ask about the effect of your UVEITIS on your ability to work and perform regular activities. *Please fill in the blanks or circle a number, as indicated.*

1. Are you currently employed (working for pay)? _____ NO ___ YES
   If NO, check "NO" and skip to question 6.

The next questions are about the **past 7 days**, not including today.

2. During the past 7 days, how many hours did you miss from work because of problems associated with your UVEITIS? Include hours you missed on sick days, times you went in late, left early, etc., because of your UVEITIS. Do not include time you missed to participate in this study.

   _____HOURS

3. During the past seven days, how many hours did you miss from work because of any other reason, such as vacation, holidays, time off to participate in this study?

   _____HOURS

4. During the past seven days, how many hours did you actually work?
   _____HOURS *(If "0," skip to question 6.)*

5. During the past 7 days, how much did your UVEITIS affect your productivity <u>while you were working</u>?

Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as usual. If UVEITIS affected your work only a little, choose a low number. Choose a high number if UVEITIS affected your work a great deal.

Consider only how much UVEITIS affected productivity while you were working.

UVEITIS had no effect on my work	0	1	2	3	4	5	6	7	8	9	10	UVEITIS completely prevented me from working

CIRCLE A NUMBER

6. During the past 7 days, how much did your UVEITIS affect your ability to do your regular daily activities, other than work at a job?

By regular activities, we mean the usual activities you do, such as work around the house, shopping, childcare, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could do and times you accomplished less than you would like. If UVEITIS affected your activities only a little, choose a low number. Choose a high number if UVEITIS affected your activities a great deal.

Consider only how much UVEITIS affected your ability to do your regular daily activities, other than work at a job.

UVEITIS had no effect on my daily activities	0	1	2	3	4	5	6	7	8	9	10	UVEITIS completely prevented me from doing my daily activities

CIRCLE A NUMBER

WPAI:SHP V2.0 (US English)

Appendix K. Japan Appendix

In Japan only, the above protocol is to be followed except where indicated in the sections below. It is anticipated that approximately 400 adult subjects with non-infectious intermediate-, posterior-, or pan-uveitis will be enrolled at up to 102 investigational sites in the United States, Canada, Europe, Israel, Latin America, Japan and Australia.

5.3.1 Efficacy and Safety Measurements Assessed and Flow Chart

Safety data will be collected in the form of adverse events, physical examinations, vital signs and laboratory tests throughout the treatment period. Adverse events will also be collected up to 70 days after the last injection in this study. The 70-day follow-up phone call will not be required for any subject that initiates commercial adalimumab after the end of study participation.

The visit window for all scheduled visits is ±7 days for all visits. If a subject has an out of window visit, the next visit should occur as originally scheduled based on the first date of study drug administration (Baseline visit).

Study procedures will be performed per the main protocol as summarized in the visit schedule presented in Table 1 except where indicated in the sections below.

Table 1. Study Activities - Japan Only

Activity	Baseline[J1]	Week 2	Week 4	Week 8	Week 12	Week 18	Week 30	Week 42	Week 54	Week 66	Every 12 Weeks Following Week 66[r]	Final/Early Termination Visit	Unscheduled Visit	70-Day Follow-up
Chest X-ray	X							X				X	X	

These footnotes only pertain to the Japan portion of the study and do not replace any procedures in the main protocol.

J1. The chest x-ray does not need to be repeated even if the Baseline visit occurs greater than (>) 14 days after the Final/Early Termination visit of the parent study.

5.3.1.1 Study Procedures

Chest X-ray (CXR)

For Japan only, all subjects will undergo a standard CXR (posterior-anterior [PA] and lateral views) at the Baseline visit, which will be conducted as part of the Final/Early Termination visit in the parent study, and at the Final/Early Termination visit of Study M11-327 to ensure safety of the subjects. In the assessment of the CXR, a radiologist and/or physician for respiratory medicine must note the presence or absence of calcified granulomas and/or pleural scarring/thickening and/or signs of active TB. The Principal Investigator will indicate the clinical significance of any findings and will sign and date the report. In the absence of abnormal findings the Principal Investigator should sign and date the report to indicate review of the report. The CRA will monitor this documentation. Subjects can have a repeat CXR at any time during the study as warranted based on the opinion of the Investigator and/or CXR is inconclusive.

If a subject has a positive TB test at Baseline or Week 42, 90, 138, 186, 234, 282, or 330, subjects will undergo a standard CXR (posterior-anterior [PA] and lateral views) to rule out the presence of TB or other clinically relevant findings.

In addition, other diagnostic imaging tests may be performed as needed if pulmonary involvement is suspected based on the investigator's clinical assessment.

Dispense Study Drug

Study drug will be administered to subjects by study site medical staff, by himself/herself or by a designee (family member or health care professional) throughout the study.

Subjects in Japan will be administered the study drug at the investigative site throughout the study when the dose of prednisone or prednisone equivalent is > 10 mg/day to secure the safety of the subjects.

Subjects or a designated family member will be trained to administer study medication during the first visit or several times, if appropriate. This training must be documented in the subject's source document.

Subjects or a trained designated family member or a Health Care Professional will administer the injections of the study medication in the subject's home or in the clinic during the weeks the subjects are not in the office for scheduled study visits.

Subjects will maintain a log for all study medication administered outside of the study visit (i.e., at home). The dosing records will be reviewed and verified for compliance at each clinic visit. All relevant dosing information will be retained by study personnel. Additionally, any discernible departure from the protocol regarding study drug administration will be documented appropriately. A sample of the Subject Dosing Diary is presented in Appendix E.

For subjects that cannot/will not self-administer study drug or do not have adequate support (family member) at home, administration will occur in the clinic.

At all office visits, subjects should be observed after study drug administration until judged clinically stable by the study personnel. If an anaphylactic reaction or other serious allergic reaction occurs, administration of study medication should be discontinued immediately and appropriate therapy initiated. When dosing at home, subjects should be instructed to contact the site immediately with any signs or symptoms of a reaction.

For subjects who deviate from the dosing schedule, every effort should be made to bring the subject back to the original dosing schedule as soon as possible.

The subject must be instructed to return study drug at each clinic visit for the purpose of compliance assessment and drug accountability as detailed in Section 5.5.6.1.

6.5 Adverse Event Reporting

In Japan, the Principal Investigator will provide documentation of all serious adverse events to the Director of the investigative site and the Sponsor.

7.0 Protocol Deviations

In Japan, the Investigator will record all protocol deviations in the appropriate medical records at site.

9.3.1 Informed Consent Form and Explanatory Material

In Japan, the Principal Investigator will prepare the consent form and explanatory material required to obtain subject's consent to participate in the study in cooperation with the sponsor and will revise these documents as required. The prepared or revised consent forms and explanatory material will be submitted to the sponsor. Approval of the IRB will be obtained prior to use in the study.

9.3.2 Revision of the Consent Form and Explanatory Material

In Japan, when important new information related to the subject's consent becomes available, the Principal Investigator will revise without delay the consent form and explanatory material based on the information and will obtain the approval of the IRB prior to use in the study. The Investigator will provide the information, without delay, to each subject already participating in the study, and will confirm the intention of each subject to continue in the study or not. The Investigator will also provide further explanation using the revised consent form and explanatory material and will obtain written consent from each subject of their own free will to continue participation in the study.

13.0 Completion of the Study

The Investigator will conduct the study in compliance with the protocol and complete the study within the timeframe specified in the contract between the Investigator (Director of

the Site in Japan) and AbbVie. Continuation of this study beyond this date must be mutually agreed upon in writing by both the Investigator (Director of the Site in Japan) and AbbVie. The Investigator will provide a final report to the IEC/IRB following conclusion of the study, and will forward a copy of this report to AbbVie or their representative.

The Investigator (Director of the Site in Japan) must retain any records related to the study according to local requirements. If the Investigator (Director of the Site in Japan) is not able to retain the records, he/she must notify AbbVie to arrange alternative archiving options.

16.0 Clinical Expense and Compensation

16.1 Expenditure of the Clinical Expense

The sponsor will pay the expenses related to this study to the investigative site in accordance with "Special Healthcare Expenditure." The expenses for screening test, etc. will be paid based on the contract agreed upon with each investigative site. To lighten the burden imposed on the subject with participation to the study, transportation expenses, etc. will be paid to the subjects via participating investigative site in accordance with the rules of the investigative site.

16.2 Compensation for Health Impairment and Insurance

1. If a subject suffers some sort of health impairment due to this study, the investigative site will provide treatment and other necessary measures. Among the expenses required for the treatment, the amount not covered by health insurance that the patient must pay directly will be borne by the sponsor only when the event is associated with the use of the study drug.
2. When a subject suffers health impairment during this study and a dispute occurs or might potentially occur between the investigative site and the subject, the investigative site will immediately report this to the sponsor and resolve it. The sponsor will work with the investigative site in resolving any issues or problems.

3. When the investigative site must compensate subject for any health impairment caused by this study, the compensation paid by the investigative site and the expenses related to any dispute will be borne in full by the sponsor, except in cases where the responsibility for the problem is attributed to the investigative site. This shall not apply to cases where the health impairment occurred because the investigative site performed the study with marked deviation from the GCP or the protocol or because of a deliberate action or a major error by the investigative site.
4. When a subject suffers health impairment during this study and liability for compensation arises, the sponsor will compensate in accordance with the SOP regarding the compensation prepared in advance.
5. The sponsor will obtain clinical study insurance and will take other necessary measures to cover the claims and compensation required in such cases.

17.0 Storage of Records

The directors of the investigative sites will retain the "Essential documents to be retained by study institutions" specified in the Section 4.9.5 of ICH guideline for the period specified in the following.

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents are no longer need to be retained.

18.0 Study Period

For Japan sub-study, the study will conclude immediately after study drug receives country regulatory approval for uveitis. The study will be discontinued approximately three months after discontinuation of the uveitis program due to study cancellation or non-approval by the regulatory agencies, if applicable. Subjects will be instructed to return for their next scheduled visit for a final visit at this time.

Investigator's Agreement - Japan

The Principal Investigator will agree to the following: 1) I have received and reviewed the Investigator's Brochure for Adalimumab I have read this protocol and agree that the study is ethical; 3) I agree to conduct the study as outlined and in accordance with all applicable regulations and guidelines; 4) I agree to maintain the confidentiality of all information received or developed in connection with this protocol and 5) I agree with the Sponsor about the contents of the protocol and CRFs and to comply with them.

Study Title:	A Multicenter Open-Label Study of the Long-term Safety and Efficacy of the Human Anti-TNF Monoclonal Antibody Adalimumab in Subjects with Non-infectious Intermediate-, Posterior-, or Pan-uveitis – VISUAL III
Protocol Number:	M11-327
Issue Date:	☐ Protocol: Version , / / ☐ CRF: Version , / /
Site–specific Change ☐ No ☐ Yes	Site Number: Contents of Change:

Investigator	Site: Title: Name: Date: / /	Seal
Trial Director	Sponsor: Title: Name: Date: / /	Seal

Appendix L. Protocol Amendment: List of Changes

The summary of changes is listed in Section 1.1.

Protocol Specific Changes:

Section 1.0 Title Page
"Sponsor/Emergency Contact:" previously read:

Sponsor/Emergency Contact:	**US, Canada, Latin America:** [redacted]	**Europe, Israel, and Australia:**
	Japan: [redacted]	

Has been changed to read:

Sponsor/Emergency Contact:	**US, Canada, Latin America:**	**Europe, Israel, and Australia:**
	[redacted]	
	Japan:	
	[redacted]	

Section 1.2 Synopsis
Subsection <u>Duration of Treatment:</u>
Previously read:

The entire study will be terminated in March 2016.

Has been changed to read:

The entire study will be terminated in March 2018.

Figure 1. Study Schematic
Figure note "*" previously read:

* Visits will occur every 12 weeks following Week 66 until the end of the study (not to exceed 15 March 2016).

Has been changed to read:

* Visits will occur every 12 weeks following Week 66 until the end of the study (not to exceed 15 March 2018).

Section 5.1 Overall Study Design and Plan: Description
Last paragraph previously read:

The entire study will be terminated in March 2016. Subjects who remain active in this clinical trial on 15 February 2016 should be contacted by the site to return for their study termination visit. Sites should complete the termination visit by 15 March 2016 for all of the remaining active subjects. These subjects will be considered as having completed the study.

Has been changed to read:

The entire study will be terminated in March 2018. Subjects who remain active in this clinical trial on 15 February 2018 should be contacted by the site to return for their study termination visit. Sites should complete the termination visit by 15 March 2018 for all of the remaining active subjects. These subjects will be considered as having completed the study.

Table 1. Study Activities
Table note "j.," "k.," and "r." previously read:

j. An annual TB test must be completed at the Week 42, 90, 138, 186, and 234 visits for all subjects. Please reference Section 5.3.1.1 Study Procedures for further information.
k. If the TB test is missed at the Week 42, 90, 138, 186, or 234 visits, the subject must be brought in within 30 days of the visit to have the test completed.
r. Subjects will have study visits every 12 weeks following Week 66 until the end of study (not to exceed 15 March 2016).

Has been changed to read:

j. An annual TB test must be completed at the Week 42, 90, 138, 186, 234, 282, or 330 visits for all subjects. Please reference Section 5.3.1.1 Study Procedures for further information.

k. If the TB test is missed at the Week 42, 90, 138, 186, 234, 282, or 330 visits, the subject must be brought in within 30 days of the visit to have the test completed.

r. Subjects will have study visits every 12 weeks following Week 66 until the end of study (not to exceed 15 March 2018).

Section 5.3.1.1 Study Procedures
First paragraph previously read:

Subjects will have clinic visits at Baseline, Week 2, Week 4, Week 8, Week 12, Week 18 and every 12 weeks thereafter until the final visit which should occur no later than March 2016.

Has been changed to read:

Subjects will have clinic visits at Baseline, Week 2, Week 4, Week 8, Week 12, Week 18 and every 12 weeks thereafter until the final visit which should occur no later than March 2018.

Section 5.3.1.1 Study Procedures
Third paragraph, first sentence previously read:

At Baseline (as part of the Final/Early Termination visit in the parent studies), Weeks 8, 18, 30, 42, 54, 66, every 12 weeks thereafter until the final visit which should occur no later than March 2016, and at the Final/Early Termination visit, the questionnaire assessments (to be completed in the following order: VFQ-25, EQ-5D, WPAI-SHP and the HRU) required for that visit should be completed first, followed by vital signs and eye exam assessments.

Has been changed to read:

At Baseline (as part of the Final/Early Termination visit in the parent studies), Weeks 8, 18, 30, 42, 54, 66, every 12 weeks thereafter until the final visit which should occur no later than March 2018, and at the Final/Early Termination visit, the questionnaire

assessments (to be completed in the following order: VFQ-25, EQ-5D, WPAI-SHP and the HRU) required for that visit should be completed first, followed by vital signs and eye exam assessments.

Section 5.3.1.1 Study Procedures
Subsection Clinical Laboratory Tests
Last paragraph previously read:

The central laboratory chosen for this study (ICON Central Laboratories) will provide instructions regarding the collection, processing and shipping of these samples.

Has been changed to read:

The central laboratory chosen for this study (ICON Laboratory Services) will provide instructions regarding the collection, processing and shipping of these samples.

Section 5.3.1.1 Study Procedures
Subsection TB Screening
Third paragraph, first, second and third sentence previously read:

For the TB Screening, either a PPD skin test (alternatively, also known as tuberculin skin test) must be placed or the QuantiFERON®-TB Gold test (or IGRA equivalent) must be performed during the Baseline visit and Week 42, 90, 138, 186, and 234 visits for all subjects. The same type of TB test should be done at Weeks 42, 90, 138, 186, and 234 that was done at Baseline. For subjects with a positive PPD skin test in the parent protocol, a QuantiFERON®-TB Gold test (or IGRA equivalent) must be performed at the Baseline and Week 42, 90, 138, 186, and 234 visits.

Has been changed to read:

For the TB Screening, either a PPD skin test (alternatively, also known as tuberculin skin test) must be placed or the QuantiFERON®-TB Gold test (or IGRA equivalent) must be performed during the Baseline visit and Week 42, 90, 138, 186, 234, 282, and 330 visits for all subjects. The same type of TB test should be done at Weeks 42, 90, 138, 186, 234, 282 and 330 that was done at Baseline. For subjects with a positive PPD skin test in the

parent protocol, a QuantiFERON®-TB Gold test (or IGRA equivalent) must be performed at the Baseline and Week 42, 90, 138, 186, 234, 282, and 330 visits.

Section 5.3.1.1 Study Procedures
Subsection Chest X-ray (CXR)
First paragraph previously read:

If a subject has a positive TB test at Baseline or Weeks 42, 90, 138, 186, or 234, subjects will undergo a standard CXR (posterior anterior [PA] and lateral views) to rule out the presence of TB or other clinically relevant findings.

Has been changed to read:

If a subject has a positive TB test at Baseline or Weeks 42, 90, 138, 186, 234, 282, or 330, subjects will undergo a standard CXR (posterior anterior [PA] and lateral views) to rule out the presence of TB or other clinically relevant findings.

Section 5.3.1.1 Study Procedures
Subsection Dispense Study Drug
Fourth paragraph, last sentence previously read:

A sample of the Subject Dosing Diary is presented in 0.

Has been changed to read:

A sample of the Subject Dosing Diary is presented in Appendix E.

Section 5.4.1 Discontinuation of Individual Subjects
Sixth bullet following second paragraph previously read:

Subject has positive PPD test or positive (or indeterminate re-test) QuantiFERON®-TB Gold test (or IGRA equivalent) result at Baseline, Week 42, 90, 138, 186, or 234.

Has been changed to read:

Subject has positive PPD test or positive (or indeterminate re-test) QuantiFERON®-TB Gold test (or IGRA equivalent) result at Baseline, Week 42, 90, 138, 186, 234, 282, or 330.

Section 5.4.1 Discontinuation of Individual Subjects
Last paragraph previously read:

The entire study will be terminated in March 2016. Subjects who remain active in this clinical trial on 15 February 2016 should be contacted by the site to return for their study termination visit. Sites should complete the termination visit by 15 March 2016 for all of the remaining active subjects. These subjects will be considered as having completed the study.

Has been changed to read:

The entire study will be terminated in March 2018. Subjects who remain active in this clinical trial on 15 February 2018 should be contacted by the site to return for their study termination visit. Sites should complete the termination visit by 15 March 2018 for all of the remaining active subjects. These subjects will be considered as having completed the study.

Section 5.5.2.2 Storage and Disposition of Study Drugs
First paragraph, fifth sentence previously read:

The maximum, minimum and current temperature for both refrigerator and room temperature must be documented and reviewed for temperature excursions.

Has been changed to read:

The maximum, minimum and current temperature for refrigerator temperature must be documented and reviewed for temperature excursions.

Section 5.5.6 Treatment Compliance
Second paragraph, third sentence previously read:

In order to document compliance with the treatment regimen, the subject will be given a Subject Dosing Diary (0) to record all injection dates and times.

Has been changed to read:

In order to document compliance with the treatment regimen, the subject will be given a Subject Dosing Diary (Appendix E) to record all injection dates and times.

Section 5.6.4 Selection of Doses in the Study
Last paragraph previously read:

In total, adalimumab has now been tested in clinical studies in over 24,000 subjects representing more than 47,000 patient years, of which more than 90% of subjects were dosed with 40 mg eow at any given time.

Has been changed to read:

In total, adalimumab has now been tested in clinical studies in over 29,000 subjects representing more than 56,000 patient years.

Section 6.0 Complaints
Add: new section number and text

6.0 Complaints

A Complaint is any written, electronic, or oral communication that alleges deficiencies related to the physical characteristics, identity, quality, purity, potency, durability, reliability, safety, effectiveness, or performance of a product/device after it is released for distribution.

The investigational product in this trial contains both:

- Biologic compound(s) and
- Device component(s) (pre-filled syringe).

Complaints associated with any component of this investigational product must be reported to the Sponsor (Section 6.2.2). For adverse events, please refer to Sections 6.1 through 6.1.6. For product complaints, please refer to Section 6.2.

Section 6.0 through 6.6
Section number and title previously read:

6.0 Adverse Events

6.1 Definitions

6.1.1 Adverse Event

6.1.1.1 Uveitis-Related Events

6.1.2 Serious Adverse Events

6.2 Adverse Event Severity

6.3 Relationship to Study Drug

6.4 Adverse Event Collection Period

6.5 Adverse Event Reporting

Has been changed to read:

6.0 Complaints

6.1 Medical Complaints

6.1.1 Definitions

6.1.1.1 Adverse Event

6.1.1.1.1 Uveitis-Related Events

6.1.1.2 Serious Adverse Events

6.1.2 Adverse Event Severity

6.1.3 Relationship to Study Drug

6.1.4 Adverse Event Collection Period

6.1.5 Adverse Event Reporting

Section 6.5 Adverse Event Reporting
Previously read:

In the event of a serious adverse event, and additionally, any non-serious event of malignancy in subjects 30 years of age and younger, whether related to study drug or not, the physician will notify the AbbVie Immunology Clinical Safety Management Team within 24 hours of the physician becoming aware of the event by entering the serious adverse event or non-serious event of malignancy in subjects 30 years of age and younger data into the electronic data capture (EDC) system. Serious adverse events and non-serious events of malignancy in subjects 30 years of age and younger, that occur prior to the site having access to the Rave system should be faxed to the Immunology Clinical Safety Team within 24 hours of being made aware of the adverse event.

FAX to: [redacted]

For serious adverse event concerns, contact the Immunology Safety Team at:

Immunology Safety Team
Immunology Development
[redacted]
AbbVie
1 North Waukegan Road
North Chicago, IL 60064
USA

Fax:
Safety Hotline:
Email:
[redacted]

For any subject safety concerns, please contact the AbbVie Medical Monitors listed below:

For US, Canada, Latin America and Japan

[redacted]

For Europe, Israel and Australia

[redacted]

In the EU, the sponsor will be responsible for Suspected Unexpected Serious Adverse Reactions (SUSAR) reporting for the Investigational Medicinal Product (IMP) in accordance with Directive 2001/20/EC. The reference document used for SUSAR reporting in EU countries for adalimumab will be the most current version of the Investigator's Brochure.

Has been changed to read:

In the event of a serious adverse event, and additionally, any nonserious event of malignancy in subjects 30 years of age and younger, whether related to study drug or not, the investigator will notify Clinical Pharmacovigilance within 24 hours of the site being aware of the event by entering the serious adverse event or nonserious event of malignancy in subjects 30 years of age and younger data into the electronic data capture (EDC) system. Serious adverse events and nonserious events of malignancy in subjects 30 years of age and younger, that occur prior to the site having access to the RAVE system or if RAVE is not operable should be sent to Clinical Pharmacovigilance within 24 hours of site being made aware of the adverse event.

FAX to:	[redacted]
Email:	

For serious adverse event concerns, contact the Immunology Safety Team at:

Immunology Safety Team
Immunology Development
[redacted]
AbbVie
1 North Waukegan Road
North Chicago, IL 60064
USA

Fax:
Safety Hotline:
Email:
[redacted]

For any subject safety concerns, please contact the AbbVie Medical Monitors listed below:

For US, Canada, and Latin America:

[redacted]

For Europe, Israel, Australia and Japan:

[redacted]

Secondary Contact for Japan (Regional Medical Monitor):

[redacted]

[redacted] and [redacted] cover for each other. For any subject safety concerns or medical emergencies in which both medical monitors are unavailable, please call the following central back-up number:

Phone: [redacted]

In the EU, the sponsor will be responsible for Suspected Unexpected Serious Adverse Reactions (SUSAR) reporting for the Investigational Medicinal Product (IMP) in

accordance with Directive 2001/20/EC. The reference document used for SUSAR reporting in EU countries for adalimumab will be the most current version of the Investigator's Brochure.

Section 6.6 Pregnancy
Section number and title previously read:

6.6 Pregnancy

Has been changed to read:

6.1.6 Pregnancy

Section 6.2 Product Complaint
Add: new section and text, renumber subsequent sections

6.2 Product Complaint

6.2.1 Definition

A Product Complaint is any Complaint (see Section 6.0 for the definition) related to the biologic or drug component of the product or to the medical device component(s).

For a product this may include, but is not limited to, damaged/broken product or packaging, product appearance whose color/markings do not match the labeling, labeling discrepancies/inadequacies in the labeling/instructions (example: printing illegible), missing components/product, device not working properly, or packaging issues.

For medical devices, a product complaint also includes all deaths of a patient using the device, any illness, injury, or adverse event in the proximity of the device, an adverse event that could be a result of using the device, any event needing medical or surgical intervention including hospitalization while using the device and use errors.

Any information available to help in the determination of causality by the device to the events outlined directly above should be captured.

6.2.2 Reporting

Product Complaints concerning the investigational product and/or device must be reported to the Sponsor within 24 hours of the study site's knowledge of the event via the Product Complaint form. Product Complaints occurring during the study will be followed-up to a satisfactory conclusion. All follow-up information is to be reported to the Sponsor (or an authorized representative) and documented in source as required by the Sponsor. Product Complaints associated with adverse events will be reported in the study summary. All other complaints will be monitored on an ongoing basis.

Product Complaints may require return of the product with the alleged complaint condition (syringe). In instances where a return is requested, every effort should be made by the investigator to return the product within 30 days. If returns cannot be accommodated within 30 days, the site will need to provide justification and an estimated date of return.

The description of the complaint is important for AbbVie in order to enable AbbVie to investigate and determine if any corrective actions are required.

Section 7.0 Protocol Deviations
First paragraph previously read:

The Investigator should not implement any deviation from the protocol without prior review and agreement by the Sponsor and in accordance with the Independent Ethics Committee (IEC)/Independent Review Board (IRB) and local regulations, except when necessary to eliminate an immediate hazard to study subjects. When a deviation from the protocol is deemed necessary for an individual subject, the Investigator must contact the AbbVie Medical Monitor listed in Section 1.0 and Section 6.5.

Has been changed to read:

AbbVie does not allow intentional/prospective deviations from the protocol. The Principal Investigator is responsible for complying with all protocol requirements, and applicable global and local laws regarding protocol deviations. If a protocol deviation

occurs (or is identified) after a subject has been enrolled, the Principal Investigator is responsible for notifying Independent Ethics Committee (IEC)/Independent Review Board (IRB) regulatory authorities (as applicable), and the AbbVie Clinical Monitor(s) assigned to your site. Alternative contacts are as follows:

Alternate Contacts

North America, Latin America, and Japan	Europe, Israel, and Australia
[redacted]	

Such contact must be made as soon as possible to permit a review by AbbVie to determine the impact of the deviation on the subject and/or the study.

Section 7.0 Protocol Deviations
Delete: third paragraph

Such contact must be made as soon as possible to permit a review by AbbVie to determine the impact of the deviation on the subject and/or the study. Any significant protocol deviations affecting subject eligibility and/or safety must be reviewed and/or approved by the IEC/IRB and regulatory authorities, as applicable, prior to implementation.

Appendix B. List of Protocol Signatories
Previously read:

Name	Title	Functional Area
[redacted]		Clinical
		Clinical
		Statistics
		Clinical

Has been changed to read:

Name	Title	Functional Area
[redacted]		Clinical
		Clinical
		Statistics
		Clinical

Appendix E. Subject Dosing Diary
Last page of diary previously read:

M11-327

___-___ ___-___ ___-___ ___
Subject Identification Number

Adalimumab Dosing Diary

Date	Week #	Kit Number	Time of Study Drug Administration	Was the entire volume injected? (Y/N)	Initials of Person Administering Study Medication	Comments
19-Mar-13	EXAMPLE	101010	9:35	Y	MM	none
	Week 276					
	Week 278					
	Week 280					

20120312 Dosing Diary Uveitis
White Copy (site)

Abbott Laboratories

Adalimumab Dosing
Yellow Copy (diary)

Has been changed to read:

M11-327

___-___ ___-___ ___-___ ___
Subject Identification Number

Adalimumab Dosing Diary

Date	Week #	Kit Number	Time of Study Drug Administration	Was the entire volume injected? (Y/N)	Initials of Person Administering Study Medication	Comments
19-Mar-13	EXAMPLE	101010	9:35	Y	MM	none
	Week 276					
	Week 278					
	Week 280					
	Week 282					
	Week 284					
	Week 286					
	Week 288					
	Week 290					

20120312 Dosing Diary Uveitis
White Copy (site)

Abbott Laboratories

Adalimumab Dosing
Yellow Copy (diary)

Appendix F. AREDS 2008 Clinical Lens Opacity Grading Procedures
Delete: last paragraph

Website: http://eyephoto.ophth.wisc.edu/ResearchAreas.html

Appendix K. Japan Appendix
Section 5.3.1.1 Study Procedures
Subsection Chest X-ray (CXR)
Second paragraph previously read:

If a subject has a positive TB test at Baseline or Week 42, 90, 138, 186, or 234, subjects will undergo a standard CXR (posterior-anterior [PA] and lateral views) to rule out the presence of TB or other clinically relevant findings.

Has been changed to read:

If a subject has a positive TB test at Baseline or Week 42, 90, 138, 186, 234, 282, or 330, subjects will undergo a standard CXR (posterior-anterior [PA] and lateral views) to rule out the presence of TB or other clinically relevant findings.

Appendix K. Japan Appendix
Section 5.3.1.1 Study Procedures
Subsection Dispense Study Drug
Second paragraph previously read:

Subjects in Japan will be administered the study drug by the medical staff throughout the study when the dose of prednisone or prednisone equivalent is ≤ 10 mg/day to secure the safety of the subjects.

Has been changed to read:

Subjects in Japan will be administered the study drug at the investigative site throughout the study when the dose of prednisone or prednisone equivalent is > 10 mg/day to secure the safety of the subjects.