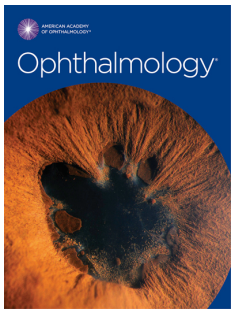
Journal Pre-proof



Long-Term Safety and Efficacy of Adalimumab in Patients With Noninfectious Intermediate Uveitis, Posterior Uveitis, or Panuveitis

Eric B. Suhler, MD, MPH, Glenn J. Jaffe, MD, Eric Fortin, MD, Lyndell L. Lim, MBBS, FRANZCO, Pauline T. Merrill, MD, Andrew D. Dick, MBBS, MD, Antoine P. Brezin, MD, PhD, Quan Dong Nguyen, MD, MSc, Jennifer E. Thorne, MD, PhD, Joachim Van Calster, MD, Luca Cimino, MD, Alfredo Adan, MD, PhD, Hiroshi Goto, MD, Toshikatsu Kaburaki, MD, Michal Kramer, MD, Albert T. Vitale, MD, Martina Kron, PhD, Alexandra P. Song, MD, MPH, Jianzhong Liu, MD, Sophia Pathai, MBBS, PhD, Kevin M. Douglas, MD, Ariel Schlaen, MD, PhD, Cristina Muccioli, MD, MBA, Mirjam E.J. Van Velthoven, MD, PhD, Manfred Zierhut, MD, PhD, James T. Rosenbaum, MD

PII: S0161-6420(20)31038-1

DOI: https://doi.org/10.1016/j.ophtha.2020.10.036

Reference: OPHTHA 11537

To appear in: *Ophthalmology*

Received Date: 21 November 2019

Revised Date: 7 October 2020

Accepted Date: 29 October 2020

Please cite this article as: Suhler EB, Jaffe GJ, Fortin E, Lim LL, Merrill PT, Dick AD, Brezin AP, Nguyen QD, Thorne JE, Van Calster J, Cimino L, Adan A, Goto H, Kaburaki T, Kramer M, Vitale AT, Kron M, Song AP, Liu J, Pathai S, Douglas KM, Schlaen A, Muccioli C, Van Velthoven MEJ, Zierhut M, Rosenbaum JT, Long-Term Safety and Efficacy of Adalimumab in Patients With Noninfectious Intermediate Uveitis, Posterior Uveitis, or Panuveitis, *Ophthalmology* (2020), doi: https://doi.org/10.1016/j.ophtha.2020.10.036.

Long-Term Safety and Efficacy of Adalimumab in Patients With Noninfectious Intermediate Uveitis, Posterior Uveitis, or Panuveitis

Authors:
Eric B. Suhler, MD, MPH,[1] Glenn J. Jaffe, MD,[2] Eric Fortin, MD,[3] Lyndell L. Lim, MBBS, FRANZCO,[4] Pauline T. Merrill, MD,[5] Andrew D. Dick, MBBS, MD,[6] Antoine P. Brezin, MD, PhD,[7] Quan Dong Nguyen, MD, MSc,[8] Jennifer E. Thorne, MD, PhD,[9] Joachim Van Calster, MD,[10] Luca Cimino, MD,[11] Alfredo Adan, MD, PhD,[12] Hiroshi Goto, MD,[13] Toshikatsu Kaburaki, MD,[14] Michal Kramer, MD,[15] Albert T. Vitale, MD,[16] Martina Kron, PhD,[17] Alexandra P. Song, MD, MPH,[18] Jianzhong Liu, MD,[18] Sophia Pathai, MBBS, PhD,[19] Kevin M. Douglas, MD,[18] Ariel Schlaen, MD, PhD,[20] Cristina Muccioli, MD, MBA,[21] Mirjam E. J. Van Velthoven, MD, PhD,[22] Manfred Zierhut, MD, PhD,[23] James T. Rosenbaum, MD[24]

Affiliations:
[1]Oregon Health & Science University, Casey Eye Institute, OHSU-PSU School of Public Health, and VA Portland Health Care System, Portland, OR, USA; [2]Duke University, Durham, NC, USA; [3]University of Montreal, Montreal, QC, Canada; [4]Centre for Eye Research Australia, Royal Victorian Eye and Ear Hospital, East Melbourne, VIC, Australia; [5]Rush University Medical Center, Chicago, IL, USA; [6]University of Bristol, Bristol Eye Hospital, Bristol, UK, and National Institute for Health Research (NIHR) Biomedical Research Centre at Moorfields Eye Hospital and University College London, Institute of Ophthalmology, London, UK; [7]Université Paris Descartes, Hôpital Cochin, Paris, France; [8]Byers Eye Institute, Stanford University, Palo Alto, CA, USA; [9]Department of Ophthalmology, Wilmer Eye Institute, Johns Hopkins University School of Medicine, and Department of Epidemiology, Center for Clinical Trials, Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD, USA; [10]University Hospitals Leuven, Leuven, Belgium; [11]Ocular Immunology Unit, Azienda USL IRCCS, Reggio Emilia, Italy; [12]Hospital Clinic de Barcelona, Barcelona, Spain; [13]Tokyo Medical University, Tokyo, Japan; [14]University of Tokyo, Tokyo, Japan; [15]Rabin Medical Center, Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel; [16]John A. Moran Eye Center, University of Utah, Salt Lake City, UT, USA; [17]AbbVie Deutschland GmbH & Co KG, Ludwigshafen, Germany; [18]AbbVie Inc., North Chicago, IL, USA; [19]Johnson & Johnson Vision, Singapore; [20]Austral University, Buenos Aires, Argentina; [21]Federal University of São Paulo, São Paulo, SP, Brazil; [22]Rotterdam Eye Hospital, Rotterdam, Netherlands; [23]University of Tübingen, Tübingen, Germany; [24]Departments of Ophthalmology and Medicine, Oregon Health & Science University and Legacy Devers Eye Institute, Portland, OR, USA

Article type: Full-length article

Financial support: This study was sponsored by AbbVie Inc. (North Chicago, IL, USA). The sponsor participated in study design and conduct; data management, analysis, and interpretation; and manuscript preparation, review, and approval.

Disclosures:

EBS has served on the AbbVie steering committee; as a consultant for AbbVie, Clearside, EyeGate, EyePoint, Eyevensys, Gilead, Inotek, Mallinckrodt, Santen, and XOMA; and has received research support from AbbVie, Aldeyra, Bristol-Myers Squibb, Clearside, EyeGate, EyePoint, Genentech, and Novartis.

GJJ has served as a consultant for AbbVie, EyePoint Pharmaceuticals, and Eyevensys.

EF has served on advisory boards and as consultant for AbbVie, Alcon, and Allergan and has received grants from AbbVie, Allergan, and Gilead.

LLL has served on advisory boards and as a consultant for AbbVie, Allergan, and Bayer and has received research support from Bayer.

PTM has served on the steering committee for the VISUAL studies; has received research support from AbbVie, Clearside, Gilead, and Santen; and has served as a consultant and on advisory boards for Alimera, Allergan, EyePoint, and Santen.

ADD has served on advisory boards for AbbVie.

APB has served on advisory boards and as a consultant for AbbVie.

QDN has served on the scientific advisory boards for AbbVie, Bausch & Lomb, Santen, and XOMA and serves as chairman of the steering committee for the VISUAL studies.

JET has served on scientific advisory boards for AbbVie, Clearside, and Santen; received grant funding from Allergan; and has served as a consultant for Gilead and Nightstarx.

JVC has received research support from Novartis; personal fees from AbbVie, Allergan, Bayer, DORC, MSD, Novartis, Santen, and Zeiss; and has received non-financial support from AbbVie, Allergan, Bayer, DORC, and Novartis.

LC has served as consultant for AbbVie and Santen.

AA has served on advisory boards for AbbVie, Allergan, and Santen.

HG has served on advisory boards for AbbVie.

TK has served on advisory boards for AbbVie.

M Kramer has served as a consultant for AbbVie.

ATV has served as consultant for AbbVie and Roche.

M Kron is an employee of AbbVie Deutschland GmbH & Co KG.

APS, JL, and KMD are employees of AbbVie.

SP is a former employee of AbbVie.

AS has served on advisory boards for AbbVie.

CM has served as a consultant for AbbVie.

MEJVV has served as a lecturer for AbbVie Netherlands, Bayer Netherlands, and Novartis Netherlands and has received travel reimbursements from Allergan Europe.

MZ has served on scientific advisory boards for AbbVie and Santen.

JTR was a consultant for AbbVie, Celldex, Corvus, Eyevensys, Genentech, Gilead, Horizon, Janssen, Novartis, Regeneron, Roche, Santen, Topivert, and UCB; has received financial support from Pfizer; and has received royalties from UpToDate.

Running head: Adalimumab in patients with noninfectious uveitis

Corresponding author information:
Name: Eric B. Suhler, MD, MPH
Affiliation: Oregon Health & Science University, Casey Eye Institute
Address: 3375 SW Terwilliger Blvd, Portland, OR 97239-4197 USA
Telephone: 503-494-5023
Fax: 503-494-7233
Email: suhlere@ohsu.edu

Tables/figures: 5 tables/5 figures/2 supplementary figures

This article contains additional online-only material. The following should appear online-only: Supplemental Figures 1 and 2.

Manuscript: 2612 words

Keywords: adalimumab, uveitis

Abbreviations:
AE=adverse event
BCVA=best corrected visual acuity
CNS=central nervous system
E=event
ETDRS=Early Treatment Diabetic Retinopathy Study
ITT=intent to treat
logMAR=logarithm of the minimum angle of resolution
MedDRA=Medical Dictionary for Regulatory Activities
MRI=magnetic resonance imaging
OCT=optical coherence tomography
PY=patient-years
SAE=serious AE
TEAE=treatment-emergent AE
TNF=tumor necrosis factor

Abstract

Purpose: To evaluate long-term efficacy and safety of extended treatment with adalimumab in patients with noninfectious intermediate, posterior, or panuveitis.

Design: Open-label, multicenter, phase 3 extension study (VISUAL III).

Participants: Adults who had completed a randomized, placebo-controlled phase 3 parent trial (VISUAL I or II) without treatment failure (inactive uveitis) or discontinued after meeting treatment failure criteria (active uveitis).

Methods: Patients received subcutaneous adalimumab 40 mg every other week. Data were collected for ≤362 weeks. Adverse events (AEs) were recorded until 70 days after the last dose of study drug.

Main Outcome Measures: Main outcome measures were long-term safety and quiescence; other efficacy variables included inflammatory lesions, anterior chamber cell and vitreous haze grade, macular edema, visual acuity, and dose of uveitis-related corticosteroids.

Results: Of 424 patients enrolled, 67% (283/424) had active uveitis and 33% (141/424) had inactive uveitis at study entry; 60 patients subsequently met exclusion criteria, and 364 patients were included in the intent-to-treat analysis. Efficacy variables were analyzed through week 150 when approximately 50% of patients (214/424) remained in the study. The percentage of patients in quiescence increased from 34% (122/364) at week 0 to 85% (153/180) at week 150. Corticosteroid-free quiescence was achieved by 54% (66/123) and 89% (51/57) of patients with active or inactive uveitis at study entry, respectively, by week 150. Mean daily dose of corticosteroids was reduced from 9.4±17.1 mg/day at week 0 (n=359) to 1.5±3.9 mg/day at week 150 (n=181). The percentage of patients who achieved other efficacy variables increased over time for those with active uveitis at study entry and was maintained for those with inactive uveitis. The most frequently reported treatment-emergent AEs of special interest for

adalimumab were infections (n=275; 78.7 events/100 patient-years); AEs and serious AEs occurred at a rate of 396 events/100 patient-years and 15 events/100 patient-years, respectively.

Conclusions: Long-term treatment with adalimumab led to quiescence and reduced corticosteroid use for patients who entered VISUAL III with active uveitis and maintenance of quiescence for those with inactive uveitis. AEs were comparable to those reported in the parent trials and consistent with the known safety profile of adalimumab.

148

149 Introduction

150 Noninfectious uveitis is one of the most common causes of vision loss or blindness in many
151 population-based studies.[1] Recurrent inflammation in patients with uveitis leads to potentially sight-
152 threatening ocular complications; however, long-term corticosteroid use for treatment of inflammation
153 can also cause potentially serious systemic and ocular toxicity.[2-5] Biologic therapies, such as tumor
154 necrosis factor (TNF)-α antagonists that target immune-mediated pathways, may provide effective
155 steroid-sparing treatment of uveitis.[7,8]

156 Adalimumab (Humira®; AbbVie Inc., North Chicago, IL, USA) is a human monoclonal antibody
157 to TNF-α that is approved to treat noninfectious uveitis.[9] VISUAL I and II were phase 3 randomized
158 clinical trials of adalimumab efficacy and safety to treat active or inactive uveitis, respectively.[10,11] In
159 these studies, treatment with adalimumab was associated with lower risk of uveitis recurrence or visual
160 acuity loss compared with placebo during and after corticosteroid taper.[10,11] Adverse events (AEs)
161 reported in the VISUAL studies were consistent with the safety profile established across the approved
162 indications of adalimumab, with the exception of events associated with the underlying condition of
163 noninfectious uveitis, such as demyelination and sarcoidosis.

164 VISUAL III was an open-label extension study of VISUAL I and II that evaluated long-term
165 efficacy and safety of extended treatment with adalimumab in patients with noninfectious intermediate,
166 posterior, or panuveitis. Interim results from VISUAL III reported efficacy and safety through 78 weeks
167 of adalimumab treatment.[12] This study reports final efficacy results through 150 weeks and safety results
168 up to 362 weeks of treatment under conditions similar to “real-world” clinical practice.

169

170 Methods

Study Design

This open-label, multicenter, phase 3 extension study (VISUAL III, registered at clinicaltrials.gov, trial ID NCT01148225, and clinicaltrialsregister.eu, EudraCT number 2009-016196-29) was conducted at 85 study sites in 21 countries in Europe, North and South America, Australia, and Japan. Study visits occurred at weeks 0, 2, 4, 8, 12, and 18, and every 12 weeks thereafter until the final visit. The study was conducted in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use guidelines and complied with the ethical principles of the Declaration of Helsinki. Protocol approval was obtained from appropriate review boards before study initiation, and all patients gave informed consent before study enrollment.

Patients

Full inclusion and exclusion criteria were published previously.[12] Briefly, eligible adults with noninfectious intermediate, posterior, or panuveitis could enroll in VISUAL III if they had successfully completed VISUAL I or II without treatment failure (inactive uveitis) or discontinued the parent study having met treatment failure criteria (active uveitis). Patients with active uveitis status determined at the final visit of the parent study could have been in quiescence at VISUAL III study entry because the week-0 visit in VISUAL III could have occurred ≤28 days later, during which time the patient's disease status may have changed.

Treatment

All patients received subcutaneous adalimumab 40 mg every other week. Patients with active disease at study entry could receive concomitant corticosteroid and/or immunosuppressive therapy as permitted in the parent study, and all patients were permitted to continue, taper, and/or discontinue

concomitant corticosteroid and/or immunosuppressive therapy at investigator discretion. Patients were allowed ≤2 periocular corticosteroid injections per eye per year.

Outcome Measures

The main outcome measure was quiescence, defined as no new active inflammatory chorioretinal and/or inflammatory retinal vascular lesions, and anterior chamber cell grade and vitreous haze grade ≤0.5+ in both eyes relative to baseline. Efficacy variables were measured as described previously[12] and included inflammatory chorioretinal and/or inflammatory retinal vascular lesions, anterior chamber cell grade ≤0.5+, vitreous haze grade ≤0.5+, evidence of macular edema assessed by changes in central retinal thickness, proportion of patients without worsening of BCVA by ≥15 letters on the ETDRS chart, and dose of uveitis-related corticosteroids and immunomodulators.

Safety Evaluations

All enrolled patients who received ≥1 dose of adalimumab were included in the safety analysis. Safety was monitored through collection of AEs that were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 19.0. Treatment-emergent AEs (TEAEs) were defined as events with an onset or worsening date on or after first study drug administration and until 70 days after last study drug administration. AEs were rated by severity and relationship to study drug. The AE described by the MedDRA preferred term of "uveitis" corresponded to worsening of a patient's underlying uveitis.

Statistical Analyses

Efficacy data were analyzed through week 150; the sample size of available data after week 150 was too small for meaningful analysis. Efficacy analyses were performed with ITT data set and were stratified by patients who entered the study with active versus inactive uveitis. Changes were calculated relative to week 0 or week 8 for patients who entered the study with inactive or active uveitis, respectively. Efficacy was analyzed descriptively as observed to reflect real-world practice conditions. AEs were reported as number of events and as events per 100 patient-years (E/100 PY). A separate analysis was performed for AEs of special interest. Uveitis-related events were also analyzed separately and adjudicated by the sponsor (AbbVie) based on a list of preferred terms to be either related or not related to uveitis.

Results

Patients

A total of 424 patients were enrolled and received ≥1 dose of study drug; the ITT set included 364 patients (**Figure 1**). At study entry, 67% of patients (283/424) had active uveitis, and 33% (141/424) had inactive uveitis. Demographics are reported in **Table 1**. During the study, 37 patients (10%; active uveitis, 31/240; inactive uveitis, 6/124) started immunomodulators and 74 (20%; active uveitis, 56/240; inactive uveitis, 18/124) started systemic corticosteroids. Six patients received periocular corticosteroid injections.

Outcomes

Quiescence

Consistent with results from the interim analysis,[12] quiescence was maintained beyond week 78 in both active and inactive groups; 80% of patients in the active group (98/123) and 96% in the inactive group (55/57) were in quiescence at week 150 (**Figure 2**).

At week 150, 54% (66/123) of patients with active uveitis at study entry and 89% (51/57) of patients with inactive uveitis achieved corticosteroid-free quiescence. For patients with active uveitis at study entry who were in quiescence at week 150 and receiving corticosteroids, most were receiving ≤7.5 mg/day (**Figure 3A**); only 3 of the 55 patients in quiescence in the inactive group were receiving corticosteroids (**Figure 3B**). Of patients receiving corticosteroids to control active uveitis at study entry (n=141), 68 remained in the study at week 150; 44% of those (30/68) were in corticosteroid-free quiescence at week 150. Of the 9 patients with inactive uveitis receiving corticosteroids at study entry, the 2 patients remaining in the study at week 150 were in corticosteroid-free quiescence.

Of patients with active uveitis at study entry, 68% (157/232) had ≥1 uveitis recurrence between week 8 and final visit, and 9% (21/232) discontinued from the study because of recurrence. Of patients with inactive uveitis at study entry, 39% (48/124) experienced ≥1 uveitis recurrence between week 0 and final visit, and 0.8% (1/124) discontinued because of recurrence.

Other Efficacy Variables

Overall, the trends observed for quiescence (ie, improvement in patients with active uveitis at study entry and maintenance in those with inactive uveitis) were similar for other efficacy variables, including the proportion of patients with no active inflammatory lesions (**Figure 4A**), anterior chamber cell grade ≤0.5+ (**Figure 4B**), vitreous haze grade ≤0.5+ (**Figure 4C**), central retinal thickness

(**Supplemental Figure 1;** available at www.aaojournal.org), and visual acuity. Mean binocular BCVA at baseline versus week 150 was 0.27 versus 0.14 logMAR, respectively, in patients with active uveitis at study entry and 0.05 versus 0.02 logMAR, respectively, in patients with inactive uveitis at study entry; **Supplemental Figure 2**.

Corticosteroid and Immunomodulator Use

The mean daily dose of corticosteroids was reduced from 9.4±17.1 mg/day at week 0 (n=359) to 1.5±3.9 mg/day at week 150 (n=181) for all patients (**Figure 5**). Of patients who received immunomodulators at baseline, 64% (23/36) and 85% (17/20) of patients with active and inactive uveitis at study entry, respectively, still received immunomodulators at week 150. However, at week 150, mean changes from baseline of −36% and −29% were observed in the dose of immunomodulators in patients with active and inactive uveitis at study entry, respectively.

Safety

Adverse events

For all patients enrolled in VISUAL III (N=424), the mean total number of doses of adalimumab received was 69.2 (min–max, 1–180 doses), and the mean exposure to adalimumab was 140.4 weeks (min–max, 2–362 weeks), corresponding to a total exposure of 1141.9 PY. Overall, 398 patients (94%; 396 E/100 PY) had ≥1 TEAE (**Tables 2 and 3**). Of these patients, 226 (53%; 80 E/100 PY) experienced ≥1 TEAE that was considered by the investigator to be possibly/probably related to study drug (**Table 3**). Most TEAEs (78%) were mild or moderate in severity. Four patients reported a severe TEAE of "blindness" (the MedDRA preferred term for loss of visual acuity): 1 patient with corneal edema in the right eye had a 30-letter vision loss and received a cornea transplant; 1 patient with pupillary membrane

fibrosis experienced vision loss of ≥30 letters; 1 patient experienced uveitis recurrence with 12- and 21-letter vision loss from best in the right and left eyes, and received 80 mg prednisone; 1 patient experienced angle closure glaucoma with vision loss of 48 letters from baseline in the right eye and received laser peripheral iridotomy. All severe TEAEs of blindness were determined by the investigator to be not related to adalimumab and related to uveitis or long-term complications of uveitis.

A total of 101 patients (24%; 15 E/100 PY; **Table 2**) experienced ≥1 serious AE (SAE); 29 patients (7%; 3.4 E/100 PY) experienced ≥1 SAE that was considered by the investigator to be possibly/probably related to study drug. After adjudication by the sponsor, 51% of patients were reported to have ≥1 uveitis-related TEAE, including uveitis (30%) and cystoid macular edema (10%).

Adverse events of special interest for treatment with adalimumab

The most frequently reported TEAEs of special interest were infections, reported in 275 patients (65%; 79 E/100 PY; **Table 4**). One patient with cytomegalovirus chorioretinitis and 1 patient with *Aspergillus* infection discontinued study drug.

Injection site reactions were reported in 52 patients (12%; 11 E/100 PY); all were considered by the investigator to be mild or moderate in severity. Allergic reactions were reported in 28 patients (7%; 3.0 E/100 PY), were non-serious, and mild to moderate in severity. Two patients discontinued study drug because of allergic reactions (1 event of urticaria; 1 event of drug eruption).

Seven patients had ≥1 positive tuberculosis test result at baseline. During the study, 20 patients (5%; 1.8 E/100 PY) reported treatment-emergent tuberculosis-related events, including 1 active case and 19 latent cases; of these, 6 were patients with ≥1 positive tuberculosis test result at baseline. Of the 19 patients who discontinued the study drug because of tuberculosis-related events, 4 events were considered serious.

Thirteen patients (3%; 1.3 E/100 PY) reported treatment-emergent malignancies (**Table 4**). One patient developed B-cell lymphoma (0.2%; 0.09 E/100 PY) that resulted in death, determined by the investigator to be probably not related to adalimumab. Six patients had 8 events of non-melanoma skin cancer (1.4%; 0.7 E/100 PY); of these, 4 events were considered by the investigator to be possibly related to the study drug and 3 events were SAEs. Six patients developed other malignancies (metastatic pancreatic carcinoma, rectal adenocarcinoma, lymphoproliferative disorder, colon adenocarcinoma, lobular breast carcinoma in situ, and colorectal cancer), all of which were considered not related or probably not related to study drug; of these patients, 5 discontinued study drug.

Six patients (1.4%; 0.5 E/100 PY) each reported treatment-emergent demyelinating events, including demyelination (n=2), multiple sclerosis (n=2), and optic neuritis (n=2); 5 of these discontinued adalimumab (**Table 5**). Four patients (0.9%; 0.4 E/100 PY), all with a medical history of sarcoidosis, reported treatment-emergent sarcoidosis. One of the 2 uveitis-related sarcoidosis events was an SAE occurring in a patient with posterior uveitis. All other sarcoidosis events occurred in patients with panuveitis and were considered non-serious. Each event was judged not related to study drug. Two patients (0.5%; 0.2 E/100 PY) reported lupus-like syndrome. Both events were moderate in severity and considered by the investigator to be probably related to study drug. One event led to discontinuation.

Four deaths (0.4 E/100 PY) were reported, caused by B-cell lymphoma, metastatic pancreatic carcinoma, trauma, and brain abscess. Of these, only the brain abscess was considered by the investigator to be possibly related to study drug.

Discussion

In this study, patients with noninfectious intermediate, posterior, or panuveitis who participated in the VISUAL I and II trials were observed for up to 7 years (median, 2.8 years) while receiving open-

label adalimumab. Efficacy outcomes were consistent with interim results,[12] suggesting that long-term adalimumab therapy increased the likelihood of achieving and maintaining disease control and provided corticosteroid-sparing effects through week 150. Key long-term safety data showed that the majority of AEs were mild or moderate in severity. The types and incidence rates of AEs were similar to those reported for adalimumab in the parent trials[10,11] and in studies of adalimumab for other approved indications.[9]

AEs of special interest included serious infections in 8% of patients (3.5 E/100 PY), similar to the rate reported in patients with inactive uveitis controlled with corticosteroids (VISUAL II[11]; 3.2 E/100 PY) and lower than the rate reported in patients with active uveitis (VISUAL I[10]; 8.0 E/100 PY). Furthermore, the rate of serious infections in VISUAL III was within the range reported for other indications of adalimumab (1.4–6.7 E/100 PY; N=23,458).[13] Rates of active and latent tuberculosis reported here (1.8 E/100 PY) were similar to rates reported in patients with active uveitis in VISUAL I (1.6 E/100 PY)[10]; in contrast, no cases of active tuberculosis were reported in patients with inactive uveitis in VISUAL II,[11] but a rate of 3.2 E/100 PY was observed for latent tuberculosis. In the current study, the rate of active tuberculosis (0.1 E/100 PY) was within the range reported for other indications of adalimumab (0–0.3 E/100 PY),[13] and the rate of latent cases (1.7 E/100 PY) aligned with the rate reported in VISUAL I (1.6 E/100 PY).[10]

Other AEs of special interest included malignancy (1.3 E/100 PY), which was lower or comparable to the rate reported in the parent trials.[10,11] Malignancy rates in VISUAL III were also similar to the rates reported for other indications of adalimumab[13] (malignancies excluding lymphoma and non-melanoma skin cancer, 0.0–0.9/100 PY; lymphoma, 0.0–0.2/100 PY; non-melanoma skin cancer [serious events only], 0.0–0.3/100 PY).

Uveitis, particularly intermediate uveitis, is associated with demyelinating disorders such as multiple sclerosis.[14-18] Over the last few decades, the prevalence of demyelinating diseases has been increasing in many regions of the world.[19] In this study, demyelinating disorders were observed in 6 patients (3 with intermediate uveitis); the observed rate of demyelinating disorders was comparable to that reported for patients with uveitis not receiving adalimumab (data on file; AbbVie Inc., North Chicago, IL, USA). Caution is recommended in the prescribing information for use of adalimumab in patients with preexisting or recent onset of central or peripheral nervous system demyelinating disorders.[9]

Although this study evaluated a relatively large number of patients, a key limitation was the decreasing number of patients with available data after week 78 because of sites closing upon regulatory/reimbursement approval. Other limitations included the lack of a comparator group and the permitted use of other immunosuppressive agents and local corticosteroid therapy, as discussed previously.[12]

In summary, long-term, real-world use of adalimumab led to disease control in patients with active uveitis and maintenance in patients with inactive disease. The long-term safety profile of adalimumab in adults with noninfectious intermediate, posterior, and panuveitis in VISUAL III was consistent with the safety profile established in the parent studies (VISUAL I and II)[10,11] and in studies of adalimumab for other indications[13]; no new safety signals were identified.

Acknowledgments

Medical writing support was provided by Catherine DeBrosse, PhD, of ICON (North Wales, PA, USA), and was funded by AbbVie Inc. The authors acknowledge Dr. Ilse De Schryver for her valuable contributions as a study site investigator.

Data Sharing

AbbVie is committed to responsible data sharing regarding the clinical trials we sponsor. This includes access to anonymized, individual and trial-level data (analysis data sets), as well as other information (eg, protocols and Clinical Study Reports), as long as the trials are not part of an ongoing or planned regulatory submission. This includes requests for clinical trial data for unlicensed products and indications.

These clinical trial data can be requested by any qualified researchers who engage in rigorous, independent scientific research and will be provided following review and approval of a research proposal and Statistical Analysis Plan (SAP) and execution of a Data Sharing Agreement (DSA). Data requests can be submitted at any time, and the data will be accessible for 12 months, with possible extensions considered. For more information on the process, or to submit a request, visit the following link: https://www.abbvie.com/our-science/clinical-trials/clinical-trials-data-and-information-sharing/data-and-information-sharing-with-qualified-researchers.html.

References

1. Dick AD, Tundia N, Sorg R, et al. Risk of ocular complications in patients with noninfectious intermediate uveitis, posterior uveitis, or panuveitis. *Ophthalmology* 2016;123:655-62.
2. Sen HN, Vitale S, Gangaputra SS, et al. Periocular corticosteroid injections in uveitis: effects and complications. *Ophthalmology* 2014;121:2275-86.
3. Miloslavsky EM, Naden RP, Bijlsma JW, et al. Development of a Glucocorticoid Toxicity Index (GTI) using multicriteria decision analysis. *Ann Rheum Dis* 2017;76:543-6.
4. Stanbury RM, Graham EM. Systemic corticosteroid therapy--side effects and their management. *Br J Ophthalmol* 1998;82:704-8.
5. Durrani OM, Tehrani NN, Marr JE, et al. Degree, duration, and causes of visual loss in uveitis. *Br J Ophthalmol* 2004;88:1159-62.
6. Dick AD, Rosenbaum JT, Al-Dhibi HA, et al. Guidance on Noncorticosteroid Systemic Immunomodulatory Therapy in Noninfectious Uveitis: Fundamentals Of Care for UveitiS (FOCUS) Initiative. *Ophthalmology* 2018.
7. Suhler EB, Lowder CY, Goldstein DA, et al. Adalimumab therapy for refractory uveitis: results of a multicentre, open-label, prospective trial. *Br J Ophthalmol* 2013;97:481-6.
8. Lindstedt EW, Baarsma GS, Kuijpers RW, van Hagen PM. Anti-TNF-alpha therapy for sight threatening uveitis. *Br J Ophthalmol* 2005;89:533-6.
9. HUMIRA® (adalimumab). Full Prescribing Information, AbbVie Inc., North Chicago, IL, USA, 2016.
10. Jaffe GJ, Dick AD, Brezin AP, et al. Adalimumab in patients with active noninfectious uveitis. *N Engl J Med* 2016;375:932-43.

11. Nguyen QD, Merrill PT, Jaffe GJ, et al. Adalimumab for prevention of uveitic flare in patients with inactive non-infectious uveitis controlled by corticosteroids (VISUAL II): a multicentre, double-masked, randomised, placebo-controlled phase 3 trial. *Lancet* 2016;388:1183-92.
12. Suhler EB, Adan A, Brezin AP, et al. Safety and efficacy of adalimumab in patients with noninfectious uveitis in an ongoing open-label study: VISUAL III. *Ophthalmology* 2018;125:1075-87.
13. Burmester GR, Panaccione R, Gordon KB, et al. Adalimumab: long-term safety in 23 458 patients from global clinical trials in rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, psoriasis and Crohn's disease. *Ann Rheum Dis* 2013;72:517-24.
14. Zein G, Berta A, Foster CS. Multiple sclerosis-associated uveitis. *Ocul Immunol Inflamm* 2004;12:137-42.
15. Le Scanff J, Seve P, Renoux C, et al. Uveitis associated with multiple sclerosis. *Mult Scler* 2008;14:415-7.
16. Boskovich SA, Lowder CY, Meisler DM, Gutman FA. Systemic diseases associated with intermediate uveitis. *Cleve Clin J Med* 1993;60:460-5.
17. Jakob E, Reuland MS, Mackensen F, et al. Uveitis subtypes in a German interdisciplinary uveitis center--analysis of 1916 patients. *J Rheumatol* 2009;36:127-36.
18. Messenger W, Hildebrandt L, Mackensen F, et al. Characterisation of uveitis in association with multiple sclerosis. *Br J Ophthalmol* 2015;99:205-9.
19. Global, regional, and national burden of multiple sclerosis 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol* 2019;18:269-85.

FIGURE LEGENDS

Figure 1. Study design. Patients who prematurely discontinued study drug were counted under each reason given for discontinuation; therefore, the sum of the counts given for the reasons may be greater than the overall number of discontinuations. Reasons for discontinuation from the study recorded as "other" included any reason for discontinuation, excluding adverse event (AE), lack of efficacy, withdrawal of consent, and lost to follow-up. *Safety outcomes through last drug date plus 70 days of follow-up were assessed in the safety set. †Efficacy outcomes were assessed in the intent-to-treat (ITT) set. ‡Discontinuations were cumulative through last study visit.

Figure 2. Percentage of patients achieving quiescence stratified by disease activity at baseline. Data are presented as percentage ± exact 95% Clopper-Pearson CI. *Light bars,* active uveitis; *dark bars,* inactive uveitis. The number of observed patients is indicated within the base of the bar.

Figure 3. Percentage of patients achieving quiescence according to concomitant dose of corticosteroids for patients who entered the study with (A) active uveitis and (B) inactive uveitis. Data are presented as observed. Doses of uveitis-related systemic corticosteroids were converted into prednisone equivalents; 4 patients in the active uveitis group received corticosteroids that could not be transferred into prednisone equivalents and were excluded from analysis.

Figure 4. Percentage of patients with (A) no active inflammatory lesions, (B) anterior chamber cell grade ≤0.5+, and (C) vitreous haze grade ≤0.5+ in both eyes, stratified by disease activity at baseline. Data are presented as percentage ± exact 95% Clopper-Pearson CI. *Light bars,* active uveitis; *dark bars,* inactive uveitis. The number of observed patients is indicated within the base of the bar.

Figure 5. Mean daily dose of uveitis-related corticosteroids.

Table 1. Patient Demographics and Baseline Disease Characteristics (ITT Set)

	Active Uveitis N=240	Inactive Uveitis N=124	Total N=364
Age, y			
Mean ± SD	42.3±14.3	42.3±13.1	42.3±13.9
Range	19.0–80.0	19.0–81.0	19.0–81.0
Sex, n (%)			
Female	134 (56)	76 (61)	210 (58)
Male	106 (44)	48 (39)	154 (42)
Race, n (%)			
White	170 (71)	100 (81)	270 (74)
Asian	37 (15)	8 (6.5)	45 (12)
Black or African American	17 (7.1)	7 (5.6)	24 (6.6)
American Indian or Alaska Native	2 (0.8)	0	2 (0.5)
Multiracial	3 (1.3)	0	3 (0.8)
Other	11 (4.6)	9 (7.3)	20 (5.5)
Type of uveitis, n (%)			
Panuveitis	133 (55)	54 (44)	187 (51)
Posterior	50 (21)	51 (41)	101 (28)
Intermediate	55 (23)	18 (15)	73 (20)
Intermediate/posterior	2 (0.8)	1 (0.8)	3 (0.8)
Diagnosis, n (%)			
Idiopathic disease	90 (38)	29 (23)	119 (33)
Vogt-Koyanagi-Harada disease	48 (20)	23 (19)	71 (20)
Sarcoidosis	34 (14)	17 (14)	51 (14)
Birdshot chorioretinopathy	23 (10)	26 (21)	49 (13)
Behçet disease	11 (4.6)	16 (13)	27 (7.4)
Multifocal choroiditis and panuveitis	11 (4.6)	3 (2.4)	14 (3.8)
Other	23 (10)	10 (8.1)	33 (9.1)
Duration of uveitis, mo			
Mean ± SD	62.4±73.3	62.0±52.6	62.3±66.9
Range	2.8–558.4	4.5–260.3	2.8–558.4
Immunomodulator use at baseline, n (%)	66 (28)	50 (40)	116 (32)
Azathioprine	8 (3.3)	8 (6.5)	16 (4.4)
Cyclosporine	11 (4.6)	12 (9.7)	23 (6.3)
Methotrexate	23 (9.6)	17 (14)	40 (11)
Mycophenolate mofetil (or equivalent)	23 (9.6)	13 (10)	36 (9.9)
Uveitis-related corticosteroid use at baseline, n (%)	141 (59)	9 (7.3)	150 (41)
Oral	116 (48)	7 (5.6)	123 (34)
Topical	59 (25)	3 (2.4)	62 (17)
Other	7 (2.9)	0	7 (1.9)

ITT=intent to treat.

Table 2. Summary of AEs

Category	Adalimumab N=424 n (%)	Adalimumab PY=1142 E (E/100 PY)
TEAE	398 (94)	4516 (396)
TEAE at least possibly adalimumab related[a]	226 (53)	916 (80)
Severe TEAE[b]	85 (20)	158 (14)
SAE[c]	101 (24)	176 (15)
SAE at least possibly adalimumab related[a]	29 (6.8)	39 (3.4)
TEAE leading to discontinuation of adalimumab[d]	77 (18)	91 (8.0)
TEAE leading to death	4 (0.9)	4 (0.4)
Uveitis-related TEAE by investigator	241 (57)	719 (63)
Uveitis-related TEAE by adjudication	218 (51)	520 (46)
Deaths[e]	4 (0.9)	4 (0.4)

AE=adverse event; E=event; PY=patient-years; SAE=serious AE; TEAE=treatment-emergent AE.

[a]As assessed by investigator.

[b]Severe TEAEs reported in >2 patients included hypertension (n=5; 1.2%); blindness, reduced visual acuity, and urinary tract infection (n=4 each; 0.9%); and uveitis, vitreous hemorrhage, and arthralgia (n=3 each; 0.7%).

[c]SAEs reported in ≥3 patients included cataract in 7 patients (1.7%; 0.96 E/100 PY); uveitis and urinary tract infection in 5 patients each (1.2%; 0.44 E/100 PY); and retinal detachment, vitreous hemorrhage, cholelithiasis, pneumonia, and obesity in 3 patients each (0.7%; 0.26 E/100 PY).

[d]TEAEs leading to discontinuation of adalimumab occurring in >5 patients included positive *Mycobacterium tuberculosis* complex test result (n=10; 2.4%), positive tuberculin test result (n=7; 1.7%), and cystoid macular edema (n=6; 1.4%).

[e]Non–treatment-emergent deaths.

Table 3. Most Frequently Reported TEAEs in Patients Receiving Adalimumab

	Adalimumab	
MedDRA Preferred Term	**TEAEs Occuring in ≥5.0% of Patients N=424 n (%)**	**TEAEs at Least Possibly Related to Study Drug N=424 n (%)**
Patients with TEAE	398 (94)	226 (53)
Uveitis	128 (30)	16 (3.8)
Nasopharyngitis	105 (25)	37 (8.7)
Arthralgia	74 (17)	22 (5.2)
Headache	63 (15)	10 (2.4)
Urinary tract infection	52 (12)	24 (5.7)
Upper respiratory tract infection	43 (10)	13 (3.1)
Cystoid macular edema	43 (10)	3 (0.7)
Cough	42 (9.9)	6 (1.4)
Bronchitis	38 (9.0)	15 (3.5)
Cataract	37 (8.7)	1 (0.2)
Fatigue	36 (8.5)	16 (3.8)
Influenza	36 (8.5)	9 (2.1)
Sinusitis	35 (8.3)	35 (8.3)
Nausea	32 (7.5)	8 (1.9)
Oropharyngeal pain	32 (7.5)	6 (1.4)
Visual acuity reduced	32 (7.5)	2 (0.5)
Dry eye	30 (7.1)	N/A
Diarrhea	28 (6.6)	N/A
Hypertension	28 (6.6)	2 (0.5)
Back pain	26 (6.1)	3 (0.7)
Eye pain	25 (5.9)	N/A
Intraocular pressure increased	24 (5.7)	N/A
Macular edema	24 (5.7)	2 (0.5)
Pain in extremity	24 (5.7)	N/A
Pyrexia	24 (5.7)	6 (1.4)
Rash	24 (5.7)	7 (1.7)
Iridocyclitis	22 (5.2)	2 (0.5)
Aspartate aminotransferase increased	21 (5.0)	10 (2.4)
Conjunctivitis allergic	21 (5.0)	N/A
Vitreous floaters	21 (5.0)	1 (0.2)

MedDRA=Medical Dictionary for Regulatory Activities; TEAE=treatment-emergent adverse event.

Table 4. Overview of TEAEs of Special Interest (≥2 Patients) and Infections

	AE of Special Interest Category	Adalimumab	
		N=424 n (%)	PY=1141.9 E (E/100 PY)
Infection	275 (65)	899 (79)	
Serious infection[a]	33 (7.8)	40 (3.5)	
Tuberculosis	20 (4.7)	20 (1.8)	
Latent tuberculosis	19 (4.5)	19 (1.7)	
Active tuberculosis	1 (0.2)	1 (0.09)	
Injection site reaction	52 (12)	125 (11)	
Allergic reaction, including angioedema, anaphylaxis	28 (6.6)	34 (3.0)	
Hematologic disorders including pancytopenia	15 (3.5)	17 (1.5)	
Malignancy	13 (3.1)	15 (1.3)	
Non-melanoma skin cancer	6 (1.4)	8 (0.70)	
Lymphoma[b]	1 (0.2)	1 (0.09)	
Other malignancy[c]	6 (1.4)	6 (0.53)	
Liver failure and other liver events	9 (2.1)	10 (0.88)	
Vasculitis	6 (1.4)	8 (0.70)	
Non-cutaneous vasculitis	6 (1.4)	8 (0.70)	
Demyelinating disorder	6 (1.4)	6 (0.53)	
Diverticulitis	4 (0.9)	5 (0.44)	
Opportunistic infection[d]	4 (0.9)	5 (0.44)	
Worsening and new onset of psoriasis	5 (1.2)	5 (0.44)	
Parasitic infection/infestation	4 (0.9)	4 (0.35)	
Sarcoidosis	4 (0.9)	4 (0.35)	

Cerebrovascular accident	2 (0.5)	2 (0.18)
Congestive heart failure	2 (0.5)	2 (0.18)
Lupus-like reaction and systemic lupus erythematosus	2 (0.5)	2 (0.18)
Myocardial infarction	2 (0.5)	2 (0.18)

Infections Reported in ≥10.0% of Patients MedDRA preferred terms	**N=424 n (%)**
Patients with a treatment-emergent infection	275 (65)
Nasopharyngitis	105 (25)
Urinary tract infection	52 (12)
Upper respiratory tract infection	43 (10)

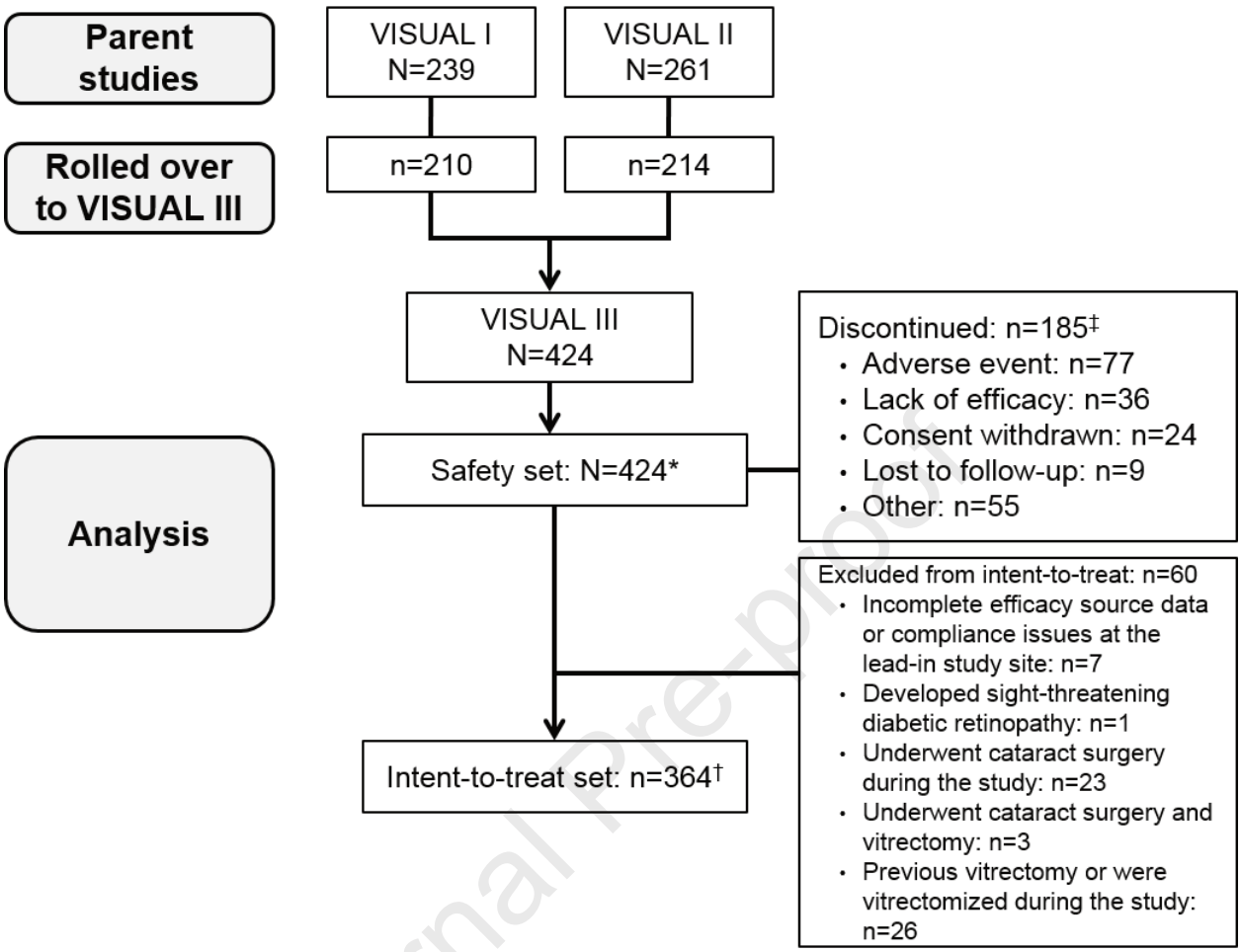
AE=adverse event; E=event; PY=patient-years; TEAE=treatment-emergent AE.
[a]Serious infections in >1 patient included urinary tract infection in 5 patients (1%); pneumonia in 3 patients (0.7%); and diverticulitis, sinusitis, and pyelonephritis in 2 patients each (0.5%).
[b]The observed case of lymphoma was B-cell lymphoma.
[c]Excluding lymphoma, hepatosplenic T-cell lymphoma, leukemia, non-melanoma skin cancer, and melanoma.
[d]Excluding oral candidiasis and tuberculosis.

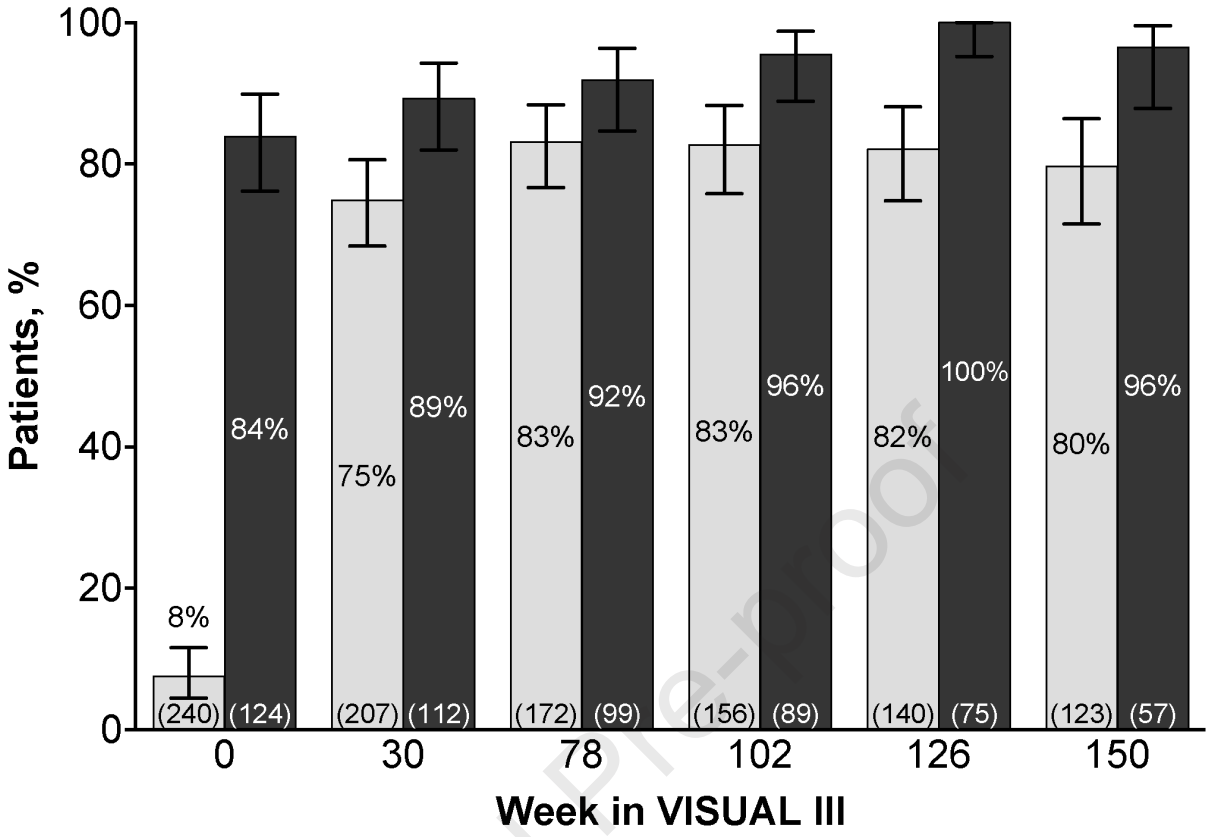
Table 5. Summary of 6 Treatment-Emergent Demyelinating Events

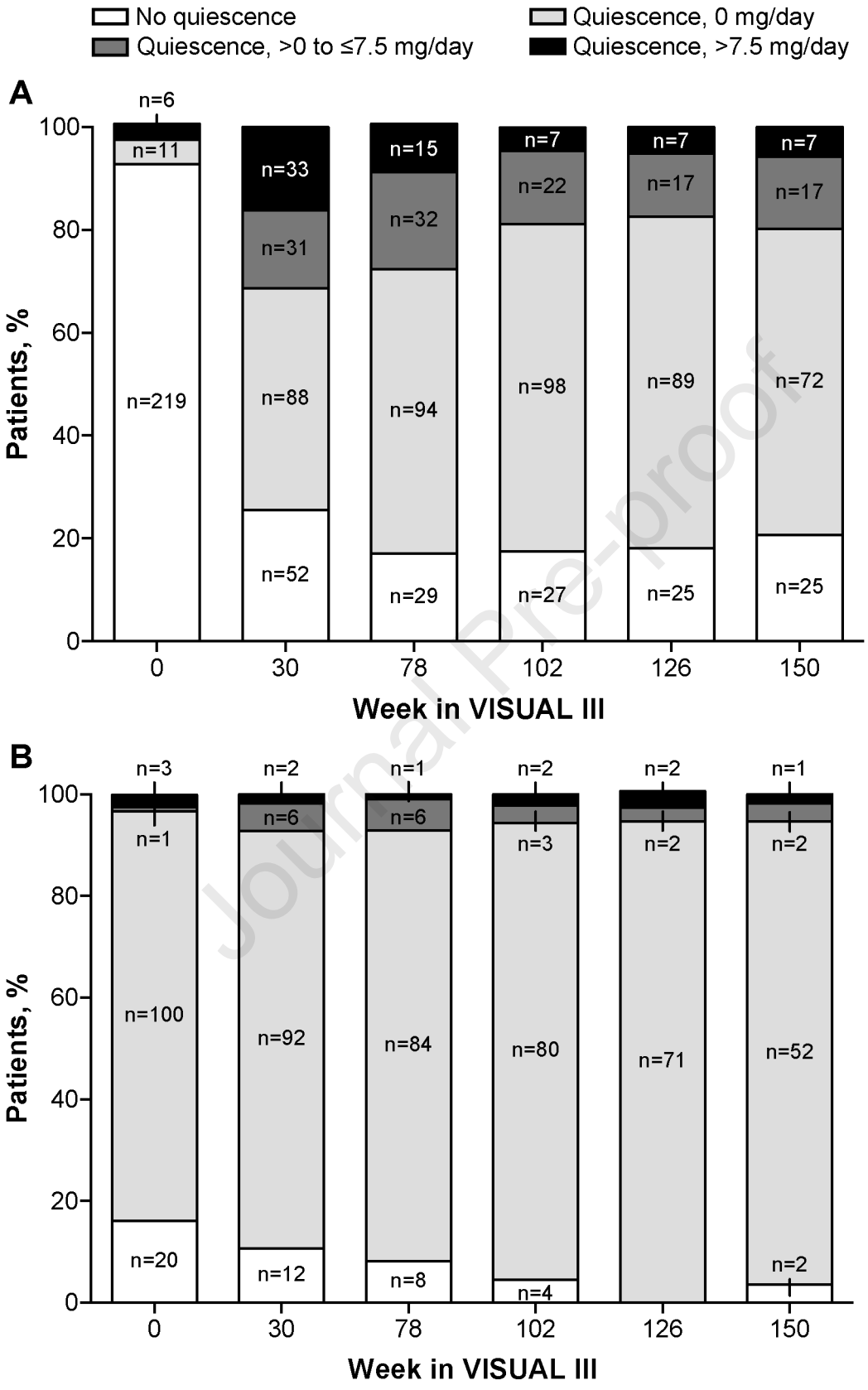
MedDRA-Reported Term	Type of Uveitis	Severity	Serious (Y/N)	Relation to Adalimumab	MRI Finding/Confirmation	Discontinuation of Adalimumab (Y/N)
Demyelination	Panuveitis	Moderate	Y	Possibly related	MRI showed an alternate etiology of periventricular demyelinating brain lesions	Y
Demyelination	Intermediate	Mild	N	Possibly related	MRI confirmed demyelinating event	Y
Multiple sclerosis	Intermediate	Mild	Y	Possibly related	Alternate etiology of nervous system inflammation reported	Y
Multiple sclerosis	Intermediate	Moderate	Y	Probably related	Initial MRI did not show cerebral demyelinating lesions; follow-up, confirmed diagnosis of multiple sclerosis approximately 5 months after end of the study	N
Optic neuritis[a]	Posterior	Severe	N	Not related	No demyelination detected with MRI	Y
Optic neuritis	Posterior	Severe	N	Possibly related	MRI showed multiple white matter lesions that may have been vascular or related to demyelination; subsequent neurology consult confirmed diagnosis of optic neuritis and found no evidence of clinical demyelinating disease	Y

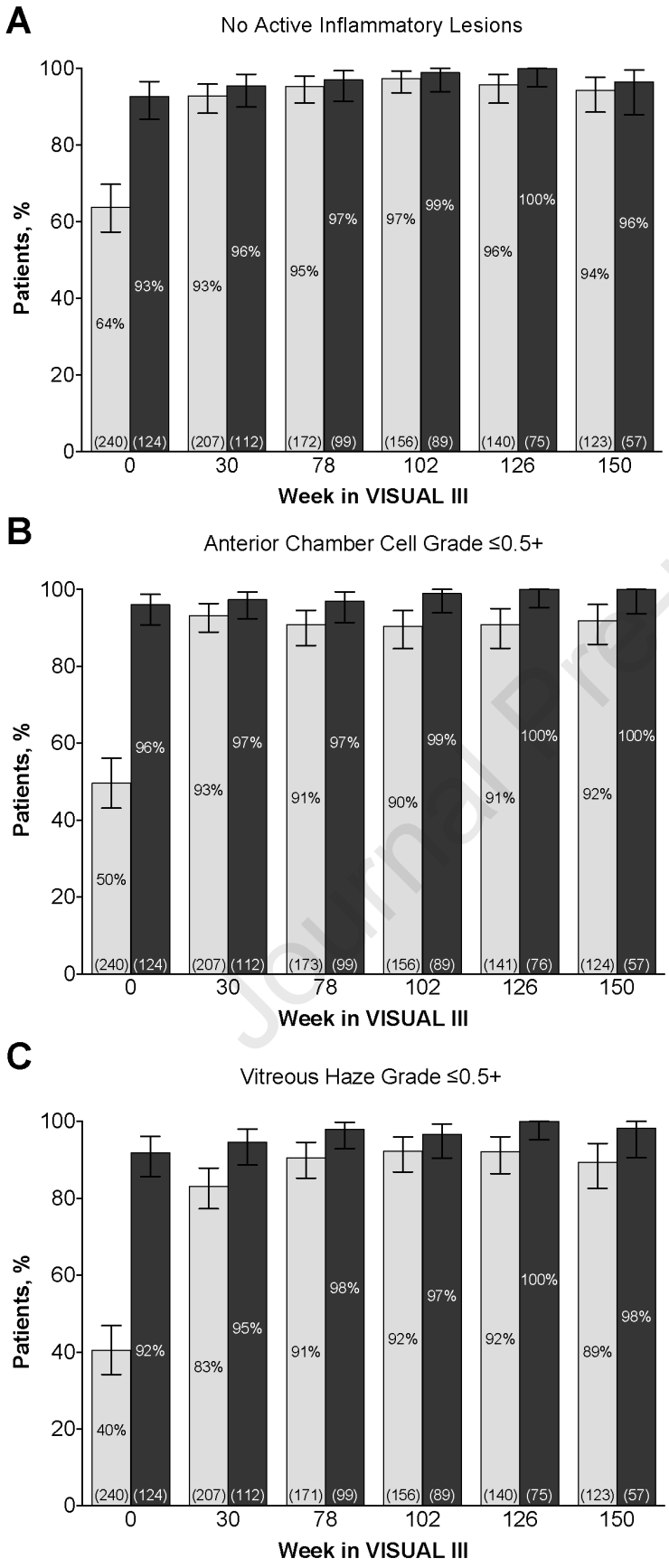
MedDRA=Medical Dictionary for Regulatory Activities; MRI=magnetic resonance imaging; N=no; Y=yes.

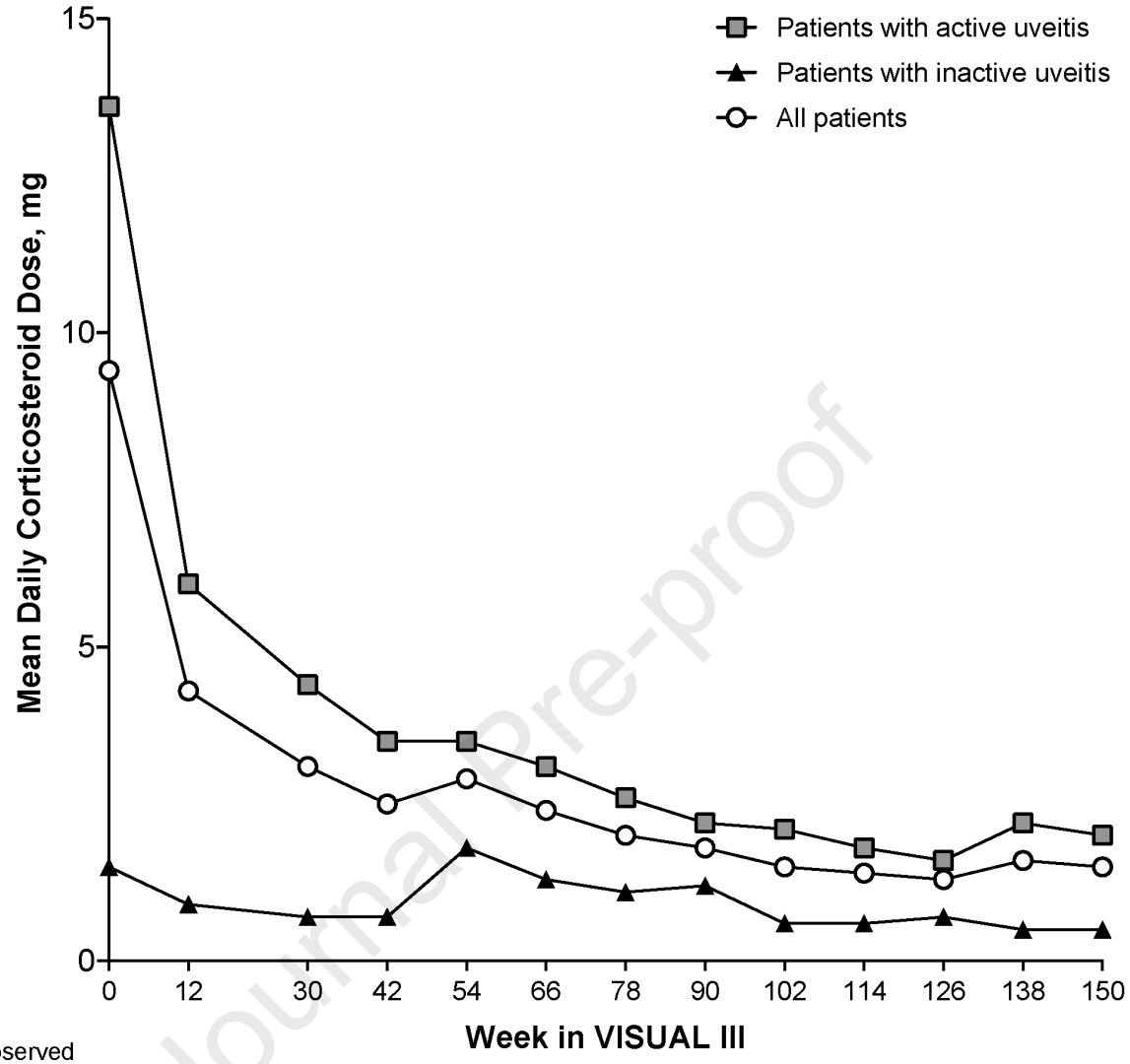
[a]Patient had a history of Behçet-associated disease at study entry; it was determined that the optic neuritis event may have had an underlying pathogenesis other than demyelinating disease.











n, as observed													
Active uveitis:	235	222	207	196	188	179	171	164	155	148	139	132	122
Inactive uveitis:	124	115	113	112	108	103	99	95	91	84	77	64	59
All patients:	359	337	320	308	296	282	270	259	246	232	216	196	181

Précis:

Patients with noninfectious uveitis responded well to long-term treatment with adalimumab and achieved disease quiescence with lower doses of corticosteroids. Adverse events occurred at the rate expected for treatment with biologics.