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The Multicenter Uveitis Steroid Treatment (MUST) Trial: Rationale, Design and Baseline Characteristics

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Abstract

Purpose—To describe the design and methods of the Multicenter Uveitis Steroid Treatment (MUST) Trial, and the baseline characteristics of enrolled patients.

Design—Baseline data from a 1:1 randomized, parallel treatment design clinical trial at 23 clinical centers comparing systemic corticosteroid therapy (and immunosuppression when indicated) to fluocinolone acetonide implant placement.

Methods—Eligible patients have active or recently active non-infectious intermediate, posterior, or panuveitis. The study design had 90% power (two-sided type I error rate=0.05) to detect a 7.5 letter (1.5 line) difference between groups in the mean visual acuity change between baseline and two years. Secondary outcomes include ocular and systemic complications of therapy and quality of life. Baseline characteristics include demographic and clinical characteristics, quality of life, and reading center gradings of lens and fundus photos, optical coherence tomography images, and fluorescein angiograms.

Results—Over three years, 255 patients were enrolled (481 eyes with uveitis). At baseline, 50% of eyes with uveitis had best-corrected visual acuity worse than 20/40 (16% worse than 20/200), with a similar distribution of reduced visual acuity for intermediate uveitis and posterior or panuveitis

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cases. Structural complications, including macular edema (36%) and epiretinal membrane (48%), were common.

Conclusions—The MUST Trial will compare fluocinolone acetonide implant versus systemic therapy for management of intermediate, posterior and panuveitis. Patients with intermediate, posterior, or panuveitis enrolled in the trial had a high burden of reduced visual acuity, cataract, macular edema and epiretinal membrane; overall quality of life was lower than expected based on visual acuity.

Keywords

Uveitis; fluocinolone acetonide implant; corticosteroid; immunosuppressive drug therapy; clinical trial

Introduction

Uveitis, or intraocular inflammation, is an important cause of visual loss in the developed world,¹⁻³ reported as causing 10% of cases of blindness in the United States,² and as being the fifth, sixth, or seventh leading cause of blindness in various studies.^{3,4} Uveitis has a disproportionately high impact in terms of years of potential vision lost and economic effects because it often strikes at a younger age than common age-related eye disorders such as cataract, age-related macular degeneration, and glaucoma.¹ The proportion of blindness caused by uveitis may be declining,³ presumably because of improving treatment. However, most patients managed in tertiary clinics experience visual loss at some point during their clinical course.⁵

On the basis of clinical examination, uveitis can be classified into anterior, intermediate, posterior, or panuveitis—based on which portion of the eye is inflamed.^{6,7} The risk of vision loss is progressively higher along this spectrum.^{5,8} In developed countries, such as the United States, the majority of intermediate uveitis and panuveitis cases, and about one-half the posterior uveitis cases presenting for care to uveitis practices, are presumed to be “autoimmune,” with no evidence of infection, and a salutary response to corticosteroid and other anti-inflammatory therapies.⁹⁻²⁰

Non-infectious uveitides encompass a wide variety of specific syndromes, each with specific diagnostic features. However, for non-infectious cases, corticosteroids are the mainstay of treatment in most instances, regardless of the specific syndrome diagnosed.²¹⁻²³ Use of systemic corticosteroids—with immunosuppressive drugs when indicated—historically has been the primary method advocated for control of severe cases of intermediate, posterior and panuveitis.²² The fluocinolone acetonide implant (0.59 mg, Bausch & Lomb, Inc., Tampa, FL),^{24,25} introduced in 2005, is designed to be effective in controlling uveitis for 2.5-3 years,²⁶ and thus offers an alternative paradigm for the medium- or long-term management of these cases of uveitis. The relative efficacy and side effect profiles of these alternatives have not been compared.

In order to provide evidence on the relative effectiveness and safety of systemic therapy with respect to fluocinolone acetonide implant therapy, we have undertaken a randomized, controlled clinical trial directly comparing these alternatives for the management of non-infectious intermediate, posterior, or panuveitis. This report describes the design of the trial, and the baseline characteristics of the patients enrolled into the trial, providing new information about the demographic and clinical characteristics of intermediate, posterior and panuveitis patients managed in tertiary uveitis practices.

Methods

The Multicenter Uveitis Steroid Treatment (MUST) Trial is a randomized, partially masked, comparative multicenter clinical trial comparing the effectiveness and safety of local therapy with the fluocinolone acetonide implant (Bausch & Lomb, Inc., Rochester, New York) versus systemic therapy with oral corticosteroids and immunosuppressive drugs when indicated²² for patients with severe non-infectious intermediate uveitis, posterior uveitis, or panuveitis. The specific aims of the trial are:

- To compare visual outcomes between implant therapy and systemic therapy
- To compare effectiveness of two treatment strategies for controlling uveitis and avoiding the accumulation of complications thereof over time
- To compare rates of both ocular and systemic side effects
- To compare quality of life between treatment strategies

Cost-effectiveness analysis²⁷ also will be conducted. The overall goal is to ascertain the relative benefits and risks of the alternative therapies, and the incremental cost-effectiveness, of the two treatment approaches.

A detailed description of the study methods—including the rationale for the specific methodologies and treatment approaches selected—is provided as supplemental text (available online at www.AJO.com). In brief, the MUST Trial is designed to detect a difference between randomly assigned treatment groups of 7.5 letters (1.5 lines) in mean (eye-specific) change in logMAR visual acuity from baseline to follow-up at 2 years. Sample size calculations estimated that enrollment of 250 patients would provide 90% power to detect this difference, allowing for a type 1 error probability of 0.05, assuming 10% losses to follow-up. Eligible patients had active or recently active (within 60 days) intermediate, posterior or panuveitis that was judged to require systemic corticosteroid therapy (eligibility criteria are given in Supplemental Table 1). These are the forms of uveitis for which the fluocinolone acetonide implant therapy is indicated, and are forms of uveitis for which systemic therapy as studied in the trial is commonly indicated.²²

Because one of the alternative treatments is systemically administered, and the goal of the trial was to compare alternative treatment strategies at the level of the patient (including quality of life analysis), patients (rather than eyes) were randomized to the alternative treatments. Random treatment assignments to implant or systemic therapy (allocation ratio 1:1) were stratified by clinical center. Within each clinical center, randomization also was stratified by the type of uveitis (intermediate uveitis vs. posterior or panuveitis) because visual acuity outcomes likely differ between these disease categories⁸ (see Supplemental Figure 1).

Implant therapy (see Supplemental Figure 2) consisted of treatment with the commercially available fluocinolone acetonide 0.59 mg implant (Retisert, Bausch & Lomb, Inc, Rochester, New York) in each eye with uveitis of sufficient severity to justify treatment with systemic corticosteroids. After quieting of the anterior chamber to less than grade 1+ of anterior chamber cells,⁷ implantation was performed by a study-certified surgeon using a standard technique²⁵ within 28 days of randomization. When applicable, the second eye was implanted within 28 days thereafter using the same approach. Eyes initially receiving systemic corticosteroid or immunosuppressive therapy were tapered off of such therapy following implant placement, generally within several weeks, but slowly enough to avoid complications related to adrenal suppression from corticosteroid therapy. Eyes developing a reactivation of uveitis following implantation were re-implanted using the same approach; the choice to remove or leave in place a pre-existing implant is left to the best medical judgment of the treating surgeon.

Systemic therapy consisted of oral corticosteroid therapy—supplemented when indicated by immunosuppression—in accordance with expert panel recommendations.²² Patients with active uveitis at baseline were started on prednisone 1 mg/kg/day up to a maximum adult oral dose of 60 mg/day (see Supplemental Figure 3), which was continued until the uveitis was controlled, or until the patient had been on this dose of prednisone for four weeks. Once suppression of uveitis was achieved, oral corticosteroids were tapered, according to specified guidelines. Patients whose uveitis already had been controlled within the 60 days prior to enrollment started at their current prednisone dose, and tapered their prednisone dose in the same manner. When immunosuppressive therapy was indicated (see Supplemental Figure 3 and Supplemental Text), the choice of which immunosuppressive drug to use was not dictated by the trial, in order to permit selection of the agent with the best side effect profile for an individual patient. However, the treatments selected was administered in accordance with expert panel guidelines, including laboratory monitoring for potential toxicities.²²

Many additional treatment protocol details are given in the Supplemental Text (available at www.AJO.com).

Because the primary goal of therapy for uveitis is to preserve vision, the primary outcome by which success is judged in the MUST Trial is best-corrected visual acuity, as measured by standard logarithmic (ETDRS) visual acuity charts.³⁸ Other outcomes evaluated pertain to control of intraocular inflammation, the occurrence of ocular complications of uveitis or of therapy, the occurrence of systemic complications of therapy, and self-reported quality of life. Imaging studies employed and the representative features evaluated by them include: lens photography (cataract), fundus photography (macular edema, epiretinal membranes, optic nerve morphology, chorioretinal lesions, vascular occlusions), Stratus Optical Coherence Tomography (macular edema, vitreoretinal interface abnormalities including epiretinal membrane), and fluorescein angiography (macular edema, vascular leakage, perfusion abnormalities, choroidal neovascularization). Health-related quality of life data also are assessed, including health utility as measured by the EuroQol 5-dimension and Visual Analog Scale scores,³⁹⁻⁴⁰ general health-related quality of life as measured by the SF-36,⁴¹⁻⁴² and vision-related quality of life as measured by the 25-item NEI-VFQ.⁴³ Masking is applied to the determination of visual acuity (beginning six months after randomization, to avoid unmasking by visible post-operative changes), those outcomes based on photographic reading, and diagnosis of glaucoma by an outcomes committee. Because sham surgery is not performed, masking during ascertainment of the other outcomes is not feasible.

Statistical Methods for Baseline Analysis

Patient, ocular and imaging characteristics at randomization were summarized for the population as a whole and stratified by uveitis type at enrollment based on data collected as of 1 October 2009. For patient characteristics, differences between the strata were compared using the Wilcoxon rank-sum test for continuous variables and the χ^2 test—or Fisher's Exact Test if appropriate—for categorical variables. When the unit of analysis was the eye, linear, logistic or multinomial regression models were used to compare strata after adjusting for the excess correlation between eyes from the same individual using generalized estimating equations³⁵—derived methods for continuous, binary, and multinomial outcomes, respectively.

Results

Between December 6, 2005 and December 9, 2008, 255 patients were enrolled at 23 clinical centers, and randomized to implant (129 patients) or systemic (126 patients) therapy. Ninety-seven patients (180 eyes with uveitis) were enrolled in the intermediate uveitis stratum, and 158 (301 eyes with uveitis) enrolled in the posterior or panuveitis stratum (see Table 1). The

age and sex distributions were similar between groups, but the race/ethnicity distribution differed significantly in that Hispanic persons were more likely to have posterior or panuveitis than intermediate uveitis. EuroQol visual analog scale⁴⁰ health utility scores were similar between groups—the mean overall score (74.1, 95% CI: 71.6 to 76.6) was reduced with respect to normative population values⁵⁹ (normative score=80.0 (standardized to the MUST population for age group and sex)). Eighty-nine per cent of patients had bilateral uveitis, with a similar proportion in both strata. In total, 21% of patients had a systemic inflammatory disease in association with uveitis, 15% in the intermediate uveitis group vs. 25% in the posterior or panuveitis group ($p=0.05$). Patients with posterior or panuveitis were substantially more likely to have Behçet's Disease than patients with intermediate uveitis (5% vs 0%, $p=0.03$). Osteoporosis, defined as a T score less than -2.5 on DEXA scanning of the spine (L2-L4) and left femoral neck,³⁷ was present among 8% of patients in both groups at baseline.

Among 481 eyes with uveitis, 180 (37%) were in the intermediate uveitis stratum, and 301 (63%) in the posterior/panuveitis stratum (see Table 2). The distributions of severity of vitreous haze and vitreous inflammatory cells were similar at baseline between the two groups. Intraocular pressure also was similar in the two groups, with most patients having average intraocular pressure at baseline; patients with high intraocular pressures and uncontrolled glaucoma had been excluded from enrollment (see Supplemental Table 1). Approximately half of eyes with uveitis had low vision (best-corrected visual acuity worse than 20/40), and approximately 16% were legally blind (best corrected visual acuity of 20/200 or worse), with a similar distribution across intermediate uveitis vs. posterior or panuveitis cases. Considering the better eye of each patient—including eyes without uveitis—31% had low vision, and 5% were legally blind at baseline. As expected, visual field reductions were more extensive in the posterior or panuveitis group than the intermediate uveitis group (average Humphrey mean deviations of -8.7 vs -6.4 respectively, $p<0.01$). Overall, 75% of patients had a mean deviation of -3.0 or worse.

Regarding structural ocular abnormalities associated with inflammation, as ascertained by image grading, 41% of eyes were pseudophakic at baseline in each group, and 39% of the remainder were judged to have a lens opacity at baseline (see Table 3). The mean macular thickness tended to be greater in the intermediate uveitis group than the posterior or panuveitis group (288 vs 256 μm , $p=0.09$). Cystoid edema was present in the central macula in 38% of eyes, with a similar distribution across intermediate uveitis and posterior/panuveitis cases. Fluorescein angiographic grading demonstrated a similar degree of macular leakage in the two groups, with a mean of 3.5 ± 5.3 disc areas. By grading of color photographs, epiretinal membranes were significantly more common in the intermediate uveitis group than the posterior or panuveitis group (57% vs 42%, $p=0.01$), although the difference arose from a greater frequency of subtle epiretinal membranes in the former group, whereas both groups had a similar proportion with “definite” epiretinal membrane (11% vs 13%, $p=0.63$). Macular pigmentary disturbances were more common in posterior/panuveitis cases than intermediate uveitis cases (39% vs 16%, $p<0.01$). Subretinal fibrosis (6% vs. 1%, $p=0.05$) and disk swelling (6% vs 1%, $p = 0.03$) were infrequent, but more common in the posterior/panuveitis than the intermediate uveitis group.

Discussion

The 2005 introduction of the fluocinolone implant, which is effective for controlling severe posterior segment ocular inflammation over long periods of time,^{24,25} raised questions about the relative merits of local therapy with the fluocinolone acetonide implant versus systemic therapy for intermediate, posterior, and panuveitis. Implant therapy is expected to be highly effective for control of inflammation while the implant continues to deliver drug, but is expected to result in a high incidence of cataract and intraocular pressure elevation requiring

treatment.^{24,25,28} Systemic therapy is likely to have more systemic side effects²² and more relapses of inflammation—as the minimum suppressive prednisone dose is determined by iterative tapering—but is likely to result in a lower incidence of local complications of corticosteroid therapy^{60,61} and may have systemic or ocular benefits by addressing more comprehensively the autoimmunity that likely underlies many of these cases. The MUST Trial is designed to provide guidance as to whether one of these paradigms is superior.

Given that the proportion of eyes with bilateral uveitis and the number of patients actually enrolled was higher than expected (see Supplemental Text, available at www.ajo.com), the trial will have greater statistical power than originally estimated, and therefore is expected to answer the questions of interest effectively. The trial is designed to evaluate both the benefits and the side effects (local and systemic) of the alternative treatments. Because local side effects are expected to be more frequent in the implant group,^{24,25,28} and systemic side effects in the systemic therapy group,²² quality of life results may be highly informative regarding the merits of the alternative treatments. Cost and cost-effectiveness analyses²⁷ will be performed, to determine the relative costs of each treatment approach, and the incremental cost of each incremental gain in benefit with the superior treatment. Enrollment of the trial was completed in December, 2008 and the primary results at the two-year follow-up point can be expected shortly after that follow-up point is reached (early 2011).

In baseline observations from the MUST Trial, intermediate uveitis was diagnosed in a lower proportion of Hispanic persons than Caucasian or African-American persons; because clinical trial patients are not necessarily sampled in manner representative of the general population, it is unclear whether this difference in the distribution of site of inflammation by race/ethnicity is meaningful. The results also suggest that systemic inflammatory disease is less commonly associated with intermediate uveitis than with posterior or panuveitis, confirming clinical impressions. Nearly 10% of patients had osteoporosis at baseline, emphasizing the importance of following bone mineral density testing and providing appropriate preventive and remedial treatment in patients for whom systemic corticosteroid therapy will be used.^{22,37}

At enrollment, patients/eyes had a high prevalence of reduced visual acuity and of ocular complications of uveitis, and reported a substantially reduced quality of life, emphasizing the significant adverse consequences of intermediate, posterior, and panuveitis. Using a time tradeoff methodology, the losses of health utility associated with a reduction of vision to the 20/60-20/100 range and to 20/200 or worse have been estimated as being a 28% and a 39% reduction in the quality of life respectively.⁶² Our patients were observed to have health utility similar to that associated with visual acuity in the 20/60-20/100 range, even though only 5% had low vision in their better eye, suggesting that uveitis may have additional health impact over and above its effect on vision, perhaps via symptoms of inflammation unmeasured by visual acuity, side effects of treatment, and/or the impact of associated systemic disease.

Among eyes with uveitis, visual acuity was similar in the intermediate and the posterior/panuveitis groups. Overall visual sensitivity as measured by automated visual field testing was reduced in both groups—likely reflecting the impact of macular edema and other complications of uveitis—but was significantly lower in the posterior/panuveitis group, probably reflecting the additional impact of chorioretinal lesions. Lens opacities were very common in both groups, with 80% either pseudophakic or with lens opacity at enrollment, indicating that there is a high risk of cataract in severe uveitis cases, though likely in part reflecting a greater willingness to consider randomization to implant treatment in pseudophakic or cataractous eyes, given that implant therapy is expected to cause cataract in nearly all phakic eyes.^{25,63} Eyes with intermediate uveitis tended to have a higher prevalence of macular edema and epiretinal membrane, which may reflect a practice pattern of using the occurrence of such events as an

indication for more aggressive anti-inflammatory therapy. Other complications of posterior segment inflammation were unusual in both groups.

In addition to addressing the clinical questions regarding treatment approaches, the MUST Trial will provide the first large, prospective data set of long-term, longitudinal observations on the outcomes of patients with severe uveitis, potentially yielding information regarding the clinical epidemiology of complications of uveitis. The large number of patients at baseline with reduced visual acuity, and other uveitis-related problems such as macular edema and epiretinal membrane, suggests that the study will provide substantial power to evaluate several important open questions for severe cases of these types of uveitis, including the risk of both improvement in and loss of visual acuity, the incidence of posterior segment complications of uveitis, and the incidence of ocular surgery, among others.

Limitations of the study design arise primarily from heterogeneity of the forms of uveitis involving the posterior segment. Posterior and panuveitis particularly consist of a wide variety of inflammatory entities, which could potentially be heterogeneous in their response to one or both of the treatments. Results from the Bausch & Lomb BLP 415-001 trial of the fluocinolone acetonide implant suggest that implant therapy is highly effective across a broad array of uveitis patients,^{24,25} suggesting that heterogeneity is not likely to be relevant for the implant arm. The benefits of systemic anti-inflammatory therapy have been indicated in several specific disease states,^{61,64-66} also suggesting a broad utility of this therapeutic approach. Because patients are being enrolled at tertiary uveitis centers, where treatments of this nature often are administered, it is likely that more severe cases were enrolled than might have been enrolled at less specialized centers. However, because qualitative treatment-disease severity interactions are unlikely, the relative risk of change in vision likely also should be sufficiently generalizable to be useful in determining which treatment approach is best in a less specialized setting. Finally, because patients enrolled in clinical trials usually are not typical patients, the experience of MUST Trial patients may differ in some ways from that of future patients. However, the strengths of the randomized clinical trial methodology with respect to alternative designs outweigh this limitation, leaving the clinical trial approach as the most favorable design available for evaluating the relative merits of alternative treatments for specified disease diagnoses.

In summary, the MUST Trial is a phase 4 effectiveness trial which aims to evaluate whether fluocinolone acetonide implant therapy or systemic corticosteroid therapy (supplemented when indicated by use of immunosuppressive drugs) is superior for the management of non-infectious intermediate, posterior, and panuveitis. Enrollment was completed in December, 2008, and the primary two year follow-up results can be expected in early 2011. Observations from the baseline characteristics of the MUST patients suggest that these patients have a high prevalence of visual loss, cataract or pseudophakia, macular edema, and epiretinal membrane, and a reduced overall quality of life greater in degree than would be expected based on loss of visual acuity alone.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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including the study design and the collection, management, analysis, and interpretation of the data, as well as in the review and approval of this manuscript.

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c. Contributions of the Authors in each of these areas: design and conduct of the study (MUST Research Group; writing committee: JHK, MMA, JTH, DAJ); collection, management, analysis, and interpretation of the data (MUST Research Group; writing committee: JHK, MMA, JTH, DAJ, EAS); and preparation, review, or approval of the manuscript (MUST Research Group; writing committee: JHK, MMA, JTH, DAJ, EAS).

d. Statement about Conformity with Author Information: The study has been registered on clinicaltrials.gov (identifier NCT00132691), and was approved by the governing IRB's of all centers listed in the Credit Roster.

e. Other Acknowledgments: None

Appendix

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Table 1

Characteristics of patients with uveitis at randomization

	Disease Stratum			
	Total	Intermediate	Posterior or Panuveitis	p-value*
Participants: N (%)	255	97 (38%)	158 (62%)	
Demographics:				
Age at enrollment (yrs)				
Mean ± SD	46.3 ± 15.0	45.4 ± 15.0	46.9 ± 15.0	0.46
Median (25 th -75 th %-tile)	47 (34 to 56)	46 (33 to 55)	47 (35 to 58)	
Male: N (%)	64 (25%)	28 (29%)	36 (23%)	0.28
Race/Ethnicity: N (%)				
White	142 (56%)	60 (62%)	82 (52%)	< 0.01
Hispanic or Latino (any Race)	33 (13%)	5 (5%)	28 (18%)	
Black	66 (26%)	29 (30%)	37 (23%)	
Other	14 (5%)	3 (3%)	11 (7%)	
Quality of life				
Health utility** (0 to 100)				
Mean ± SD	74.1± 20.0	72.1 ± 21.0	75.3 ± 19.4	0.20
Median (25 th -75 th %-tile)	80 (67 to 90)	75 (60 to 87)	80 (70 to 90)	
Missing	3 (1%)	2 (2%)	1 (1%)	
Clinical characteristics:				
Uveitis: N (%)				
Bilateral	226 (89%)	83 (86%)	143 (91%)	0.23
Unilateral	29 (11%)	14 (14%)	15 (9%)	
Time since diagnosis (yrs)				
Mean ± SD	6.1 ± 7.2	6.0 ± 5.0	6.2 ± 8.2	0.07
Median (25 th -75 th %-tile)	3.8 (1.2 to 8.0)	5.0 (2.0 to 8.8)	3.4 (0.9 to 7.9)	
Missing	4 (2%)	1 (1%)	3 (2%)	
Systemic disease: N (%)				
None	198 (79%)	82 (85%)	116 (75%)	0.05
Present	52 (21%)	14 (15%)	38 (25%)	
Behçet’s disease	8 (3%)	0 (0%)	8 (5%)	0.03 §
Sarcoidosis	26 (10%)	7 (7%)	19 (12%)	0.29§
Multiple sclerosis	4 (2%)	3 (3%)	1 (1%)	0.16§
Juvenile idiopathic arthritis	5 (2%)	2 (2%)	3 (2%)	> 0.99§
Missing	5(2%)	1 (1%)	4 (3%)	
Bone density [†] : N (%)				
Normal	132 (53%)	53 (56%)	79 (51%)	0.61
Osteopenia	96 (39%)	33 (35%)	63 (41%)	
Osteoporosis	21 (8%)	9 (9%)	12 (8%)	
Missing	6 (2%)	2 (1%)	4 (2%)	

* Unless otherwise specified, p-values compare the distribution of all primary categories except for 'Missing' for the two strata.

§ P-value indicates a comparison of a single category across strata.

** Health utility reflects the EuroQol visual analog scale score,⁴⁰ where 0 reflects death, and 100 reflects perfect health.

† Osteopenia is defined as a T score between -1 and -2.49 inclusive at the spine or femoral neck (whichever is worse). Osteoporosis is defined as a T score of -2.5 or worse at the spine and/or femoral neck.³⁷

Table 2
Ocular characteristics of eyes with uveitis at baseline

	Disease Stratum			p-value*
	Total	Intermediate	Post/Pan	
Participants: N	255	97	158	
Eyes with uveitis at enrollment: N (%)	481	180 (37%)	301 (63%)	
Vitreous haze[†] (Grade 0-4⁺): N (%)				
0	141 (31%)	49 (29%)	92 (32%)	0.26
1 ⁺	205 (45%)	71 (42%)	134 (47%)	
2 ⁺	77 (17%)	36 (21%)	41 (14%)	
3 ⁺	20 (4%)	9 (5%)	11 (4%)	
4 ⁺	4 (1%)	0 (0%)	4 (1%)	
Cannot Assess	8 (2%)	6 (3%)	2 (1%)	
Missing	26 (5%)	9 (5%)	17 (6%)	
Anterior vitreous cells[§] : N (%)				
0	75 (17%)	29 (17%)	46 (16%)	0.82
0.5+	109 (24%)	34 (20%)	75 (27%)	
1+	146 (32%)	61 (36%)	85 (30%)	
2+	90 (20%)	35 (21%)	55 (19%)	
3+	25 (6%)	6 (4%)	19 (7%)	
4+	6 (1%)	3 (2%)	3 (1%)	
Cannot Assess	28 (6%)	12 (7%)	16 (5%)	
Missing	2 (1%)	0 (0%)	2 (1%)	
IOP (mm Hg):				
Mean ± SD	14.0 ± 4.7	13.7 ± 4.0	14.3 ± 5.0	0.14
Median (25 th -75 th %-tile)	14.0 (11.5 to 17.0)	14.0 (11.5 to 16.0)	14.5 (12.0 to 17.0)	
Missing	4 (0%)	0 (0%)	4 (1%)	
Visual acuity				
Eyes with uveitis at enrollment				
Mean ± SD	61.4 ± 26.4	61.8 ± 25.8	61.2 ± 26.9	0.92
Median (25 th -75 th %-tile)	70.1 (49.1 to 80.1)	69.1 (49.1 to 81.1)	70.1 (50.1 to 80.1)	
Worse than 20/40: N (%)	237 (50%)	94 (53%)	143 (48%)	0.34 [‡]
Worse than 20/200: N (%)	74 (15%)	27 (15%)	47 (16%)	0.88 [‡]
Missing	6 (1%)	1 (1%)	5 (2%)	
Better eyes[‡]				
Mean ± SD	73.4 ± 18.0	73.5 ± 19.6	73.4 ± 16.9	0.48
Median (25 th -75 th %-tile)	78.1 (66.1 to 86.1)	80.1 (64.1 to 87.1)	77.1 (66.1 to 85.1)	
Worse than 20/40: N (%)	79 (31%)	32 (33%)	47 (30%)	0.68 [‡]
Worse than 20/200: N (%)	12 (5%)	5 (5%)	7 (4%)	0.77 [‡]
Missing	1 (0.3%)	0 (0%)	1 (1%)	
Worse eyes[‡]				

	Disease Stratum			p-value [*]
	Total	Intermediate	Post/Pan	
Mean $\pm$ SD	50.5 $\pm$ 30.5	52.2 $\pm$ 29.2	49.5 $\pm$ 31.4	0.58
Median (I25 th -75 th %-tile)	59.1 (30.1 to 75.1)	61.1 (35.1 to 75.1)	57.1 (29.1 to 75.1)	
Worse than 20/40: N (%)	165 (65%)	64 (66%)	101 (64%)	0.89
Worse than 20/200: N (%)	67 (26%)	24 (25%)	43 (27%)	0.66
Missing	1 (0.3%)	0 (0%)	1 (1%)	
Visual field automated perimetry:				
Mean deviation				
Mean $\pm$ SD	-7.8 $\pm$ 7.5	-6.4 $\pm$ 6.5	-8.7 $\pm$ 8.0	< 0.01
Median (25 th -75 th %-tile)	-5.2 (-9.5 to -3.0)	-4.0 (-7.6 to -2.8)	-5.8 (-11.2 to -3.2)	
Missing	22 (5%)	6 (3%)	16 (5%)	

[†] Vitreous haze measurements are based upon the scale developed by Nussenblatt and coworkers, and affirmed by the SUN Working group.

[§] Anterior vitreous cell measurements are based upon the following scale, based on cells present in a 1 $\times$ 0.5 mm beam: 0=no cells; 0.5+=1-5 cells; 1+=6-10 cells; 2+=11-20 cells; 3+=21-50 cells; 4+= 51 or more cells.

[‡] Visual acuity for better and worse eyes are calculated based upon all eyes, whether or not they have uveitis.

^{*} P-values are calculated using linear, logistic or multinomial regression adjusting for multiple measurements per individual with robust standard errors when appropriate. Unless otherwise indicated, the p-value represents the comparison between strata across all categories except for 'Missing' or 'Cannot Assess'.

[¥] P-value indicates a comparison of a single category across strata.

Table 3
Image characteristics in eyes with uveitis at enrollment

	Disease Stratum			p-value [‡]
	Total	Intermediate	Post/Pan	
Participants: N	255	97	158	
Eyes with uveitis at enrollment: N(%)	481	180	301	
Lens images: N	464	180	284	
Lens opacities: N(%)				
Absent	134 (61%)	56 (67%)	78 (57%)	0.21 [§]
Present	87 (39%)	27 (33%)	60 (43%)	
Aphakic/pseudophakic	191 (41%)	75 (41%)	116 (41%)	
Cannot grade [*]	52 (11%)	22 (12%)	30 (10%)	
Optical coherence tomography: N	454	171	283	
Retinal thickness at center (μm)				
Mean ± SD	268.0 ± 185.0	288.2 ± 188.8	256.0 ± 181.9	0.09
Median (25 th -75 th %-tile)	198.5 (162.0 to 296.5)	211.0 (168.0 to 334.0)	192.0 (158.0 to 270.0)	
≤ 200	223 (51%)	71 (44%)	152 (56%)	0.05
201-239	57 (12%)	26 (15%)	31 (11%)	
≥ 240	156 (36%)	66 (41%)	90 (33%)	
Cannot Grade [*]	18 (4%)	8 (4%)	10 (3%)	
Cystoid spaces: N(%)				
Absent	265 (62%)	97 (61%)	168 (62%)	0.81
Definite	166 (38%)	63 (39%)	102 (38%)	
Not at center	58 (13%)	15 (9%)	43 (16%)	
At center	108 (25%)	48 (30%)	60 (22%)	
Cannot Grade [*]	23 (5%)	11 (6%)	12 (4%)	
Color fundus images: N	436	165	271	
Epiretinal membrane: N (%)				
Absent	198 (52%)	60 (42%)	138 (57%)	0.01
Present	185 (48%)	82 (58%)	103 (43%)	
Cellophane reflex/subtle	139 (36%)	66 (46%)	73 (30%)	
Definite	46 (12%)	16 (11%)	30 (13%)	
Cannot grade [*]	53 (12%)	23 (14%)	30 (11%)	
Subretinal fibrosis: N (%)				
Absent	367 (96%)	141 (99%)	226 (94%)	0.05
Definite	17 (4%)	2 (1%)	15 (6%)	
Not at center	14 (4%)	2 (1%)	12 (5%)	
At center	3 (1%)	0 (0%)	3 (1%)	
Cannot grade [*]	52 (12%)	22 (13%)	30 (11%)	
Cup-to-disc ratio (vertical)				
Mean ± SD	0.31 ± 0.12	0.29 ± 0.13	0.33 ± 0.11	0.10

	Disease Stratum			p-value [‡]
	Total	Intermediate	Post/Pan	
Median (IQR)	0.31 (0.21 to 0.39)	0.27 (0.19 to 0.37)	0.32 (0.24 to 0.40)	
Cannot grade [*]	82 (18%)	30 (18%)	52 (19%)	
Papillary Swelling				
Absent	378 (96%)	149 (99%)	229 (94%)	0.03
Definite	16 (4%)	1 (1%)	15 (6%)	
Cannot grade [*]	42 (10%)	15 (9%)	27 (10%)	
Pigment disturbance within the macular area ^{**}				
Absent	263 (69%)	117 (84%)	146 (61%)	< 0.01
Definite	116 (31%)	23 (16%)	93 (39%)	
Not at center	70 (19%)	15 (11%)	55 (23%)	
At center point	46 (12%)	8 (6%)	38 (16%)	
Cannot grade [*]	57 (13%)	25 (15%)	32 (12%)	
Fluorescein angiography: N	394	142	254	
Cystoid changes in the macula				
Absent	256 (70%)	80 (60%)	176 (76%)	<0.01
Present	109 (30%)	53 (40%)	56 (24%)	
Cannot grade [*]	31 (8%)	9 (6%)	22 (9%)	
Capillary loss within the macular area [*]				
Absent	197 (95%)	74 (96%)	123 (94%)	0.50
Present	11 (5%)	3 (4%)	8 (6%)	
Missing	188 (47%)	65 (46%)	123 (48%)	
Leakage within the macular area ^{**}				
Mean ± SD	3.5 ± 5.3	3.5 ± 5.0	3.6 ± 5.5	0.90
Median (IQR)	0.6 (0.0 to 4.9)	1.1 (0.0 to 4.9)	0.5 (0.0 to 4.6)	
Absent	148 (40%)	48 (36%)	100 (43%)	0.29
Present	218 (60%)	85 (64%)	133 (57%)	
Cannot grade [*]	30 (8%)	9 (6%)	21 (8%)	

* Cannot grade=Image quality insufficient to allow grading, usually because of ocular scarring preventing adequate imaging.

** The macular area refers to the 16 disk-area region centered on the fovea.

[‡] Unless otherwise specified, p-values are calculated to compare primary categorizations excluding 'Cannot grade', 'Missing' or central point involvement.

[§] P-value comparing 'Absent' and 'Present'.