Ocular Immunology and Inflammation

ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/ioii20

Safety and Efficacy of CLS-TA by Anatomic Location of Inflammation: Results from the Phase 3 PEACHTREE Clinical Trial

Milan Shah, Thomas Albini, Quan Nguyen, Charles Wykoff, Mark Barakat, Rahul N. Khurana, Barry Kapik & Thomas A. Ciulla

To cite this article: Milan Shah, Thomas Albini, Quan Nguyen, Charles Wykoff, Mark Barakat, Rahul N. Khurana, Barry Kapik & Thomas A. Ciulla (2024) Safety and Efficacy of CLS-TA by Anatomic Location of Inflammation: Results from the Phase 3 PEACHTREE Clinical Trial, Ocular Immunology and Inflammation, 32:8, 1556-1563, DOI: 10.1080/09273948.2023.2262015

To link to this article: https://doi.org/10.1080/09273948.2023.2262015

Published online: 09 Jan 2024.

OCULAR IMMUNOLOGY AND INFLAMMATION
2024, VOL. 32, NO. 8, 1556–1563
https://doi.org/10.1080/09273948.2023.2262015

Taylor & Francis
Taylor & Francis Group

ORIGINAL ARTICLE

Safety and Efficacy of CLS-TA by Anatomic Location of Inflammation: Results from the Phase 3 PEACHTREE Clinical Trial

Milan Shah, MD[a], Thomas Albini, MD[b], Quan Nguyen, MD MSc[c], Charles Wykoff, MD, PhD[d], Mark Barakat, MD[e], Rahul N. Khurana, MD[f,g], Barry Kapik, MS[h], and Thomas A. Ciulla, MD, MBA[h]

[a]Ophthalmology, Midwest Eye Institute, Carmel, Indiana, USA; [b]Ophthalmology, Bascom Palmer Eye Institute, Miami, Florida, USA; [c]Byers Eye Institute, Stanford University School of Medicine, Palo Alto, California, USA; [d]Retina Consultants of Texas, Blanton Eye Institute, Houston Methodist Hospital, Houston, TX, USA; [e]Ophthalmology, Retina Consultants of Arizona, Phoenix, Arizona, USA; [f]Northern California Retina-Vitreous Associates, Mountain View, California, USA; [g]Ophthalmology, University of California, San Francisco, CA, USA; [h]Clearside Biomedical, Inc, Alpharetta, Georgia, USA

ABSTRACT

Purpose: To explore the efficacy of CLS-TA, a proprietary suprachoroidal injectable suspension of triamcinolone acetonide, in noninfectious uveitis (NIU) with macular edema (ME), categorized by anatomic subtype.
Methods: Patients diagnosed with ME associated with NIU of any etiology and anatomic subtype were eligible for the phase 3 PEACHTREE trial of CLS-TA. Post-hoc analyses were performed, stratified by discrete anatomic subtype of uveitis (anterior, intermediate, posterior, and panuveitis.)
Results: Across all anatomic subtypes at 24 weeks, patients receiving CLS-TA at baseline and week 12 demonstrated mean increases in BCVA ranging from +12.1 to +15.9 letters, mean central subfield thickness (CST) improvement ranging from −120.1 µm to −189.0 µm, and IOP changes ranging from +0.5 to +3.1 mmHg. Overall, reports of adverse events were similar among subtypes.
Conclusions: Irrespective of the uveitic anatomic subtype among patients treated for ME associated with NIU, a clinical benefit in participants treated with CLS-TA was demonstrated, with a comparable safety profile.

ARTICLE HISTORY
Received 5 March 2023
Revised 5 September 2023
Accepted 16 September 2023

KEYWORDS
Non-infectious uveitis; uveitic macular edema; suprachoroidal injection; triamcinolone acetonide

Uveitis is a heterogeneous collection of inflammatory ocular conditions and a leading cause of vision loss globally. Non-infectious uveitis (NIU) accounts for up to 90% of cases, affecting approximately 350,000 patients in the United States.[1] NIU can be divided into subtypes based on the anatomic location of inflammation; anterior uveitis affects the iris and ciliary body; intermediate uveitis affects the vitreous and pars plana region; posterior uveitis affects the retina and the choroid; and panuveitis can affect all parts of the uvea. Periocular and intravitreal corticosteroids are often utilized in the treatment of uveitis but can be associated with the development of cataract and intraocular pressure (IOP) elevations.

Macular edema (ME) affects approximately one-third of uveitic patients and is the leading cause of uveitis vision loss, for which there has historically been no specifically approved treatment.[2] However, in October 2021, XIPERE® (CLS-TA triamcinolone acetonide injectable suspension) for suprachoroidal (SC) use was approved by the United States Food and Drug Administration (FDA), becoming the first such treatment specifically approved for ME associated with uveitis. The approval was based on the successful phase 3 PEACHTREE trial results (ClinicalTrials.gov Identifier NCT02595398) using suprachoroidal CLS-TA to treat ME associated with NIU.[3] PEACHTREE was a 6-month, randomized, multicenter, double-masked, sham-controlled study in patients with ME associated with anterior-, intermediate-, posterior-, or pan-uveitis.

In PEACHTREE, patients were treated at baseline and week 12, and there was a clinically meaningful gain of 15 letters or more from baseline in Early Treatment of Diabetic Retinopathy Study (ETDRS) best corrected visual acuity (BCVA) for 47% of patients treated with CLS-TA, along with a clinically meaningful 153 µm reduction of central subfield thickness (CST) at 24 weeks among all patients in the Active arm.[3] Suprachoroidal injection of CLS-TA is thought to result in more targeted delivery of drug to the affected chorioretinal tissues while relatively sparing the anterior segment, resulting in lower risk of corticosteroid associated adverse events (AEs), such as cataract formation and IOP elevations.[4,5] In PEACHTREE, elevated IOP occurred in 11.5% and 15.6% of the CLS-TA and control groups, respectively, while cataract adverse event rates were comparable (7.3% and 6.3%, respectively).[3]

In addition, PEACHTREE demonstrated clinically and statistically significant resolution of anterior and posterior segment inflammation in approximately 70% of patients.[3] However, while PEACHTREE enrolled patients with ME associated with various anatomic subtypes (anterior, intermediate, posterior, or panuveitis), there has been limited information on outcomes stratified by these anatomic locations. The POINT study, a comparative study evaluating three arms of corticosteroid treatments for uveitic ME, analyzed OCT reduction in CST and visual acuity gains; however, these endpoints

CONTACT Milan Shah, MD mlnshah@yahoo.com Ophthalmology, Midwest Eye Institute, 10300 N. Illinois St., Carmel, Indiana 46290, USA
Prior Presentations: This data has been presented at: AAO 2022, October 032022, Chicago, IL.
This article has been corrected with minor changes. These changes do not impact the academic content of the article.

were not examined with respect to anatomic subtypes of uveitis among subjects.[6] Consequently, the primary objective of this post hoc analysis was to determine if there were differences in efficacy and safety outcomes based on the discrete uveitic anatomic subtype in patients receiving suprachoroidal CLS-TA compared to the Control.

Methods

Study participants

The study design and main findings from PEACHTREE have been previously reported in Yeh et al.[3] Eligible patients had a diagnosis of ME secondary to NIU of any etiology, defined as having intraretinal or subretinal fluid along with CST of 300 µm or more as measured by Spectral-Domain Optical Coherence Tomography (SD-OCT). The study eye of patients was required to have a BVCA between 5 and 70 letters, inclusively, or a Snellen equivalent between 20/800 and 20/40. Eligible patients were not required to have signs of inflammation in the study eye and were allowed to be receiving systemic corticosteroids of ≤20 mg/day for oral prednisone or equivalent, nonsteroidal anti-inflammatory drugs and immunomodulatory therapies at study entry provided they were on a stable dose for at least 2 weeks prior to enrollment and no increase in dosing was anticipated for the duration of the study. Administrations of masked study drug occurred at Day 0 and Week 12.

The trial did not limit inclusion by anatomic subtype or primary site of inflammation. Thus, all eligible patients with either anterior (iris and ciliary body) uveitis, intermediate (vitreous and peripheral retina) uveitis, posterior (retina or choroid) uveitis, pan-uveitis (iris, ciliary body, vitreous, retina, or choroid), or any combination of these subtypes were enrolled in Peachtree.

Study design

This post hoc study involved analysis of previously collected, de-identified trial data from the PEACHTREE trial. Approval was obtained by an institutional review board (IRB) and/or independent ethics committee at each study site. Additionally, the clinical trial was performed in compliance with the provisions of the Declaration of Helsinki, International Conference on Harmonization Good Clinical Practice guidelines, and applicable local regulations.

Efficacy and safety endpoint assessments

In this post hoc analysis, efficacy endpoints included: the proportion of patients with ≥15-letter improvement from baseline in ETDRS BCVA, the proportion of patients with CST <300 µm as measured using SD-OCT and masked central reading center evaluation, mean change from baseline in BCVA letter score, mean change from baseline in CST, the proportion of patients receiving rescue therapy, and the proportion of patients with resolution of clinical indicators of inflammation. In PEACHTREE, pre-defined criteria were established for the administration of rescue therapy, with the timing and choice of rescue therapy administered at the investigator's discretion. Inflammatory activity was determined by slit-lamp examinations of anterior chamber cells and flare using a standardized grading scale (SUN criteria),[7] and ophthalmoscopic examination of vitreous haze using a standardized photographic grading scale in Nussenblatt[8] as modified by Lowder.[9] These standardized scales each assigned a score of 0 to represent "no sign of inflammation."

Safety endpoints included the incidence of serious adverse events (SAEs) and treatment-emergent adverse events (AEs) reported during the entire 24-week study period, mean change from baseline in IOP, the proportion of patients with IOP-related events, including IOP ≥30 mmHg, IOP increases from baseline of 10 mmHg or more, and the use of IOP-lowering medications and/or procedures, as well as cataract formation.

Statistical analysis

Efficacy and safety endpoints were evaluated in the subset of patients from the PEACHTREE study's intent-to-treat (all randomized patients) and safety (all patients receiving any study drug) populations, respectively, who were diagnosed with NIU of a single, discrete anatomical subtype. However, patients diagnosed with a combination of anterior uveitis and posterior uveitis were categorized as having panuveitis for the purpose of this statistical analysis. Subjects with other various overlaps in anatomic subtypes were excluded. Descriptive statistics were used to summarize continuous variables, while counts and percentages were used to summarize nominal and categorical variables. Demographic and baseline characteristics were evaluated in order to assess for clinically important imbalances in study subpopulations.

The number and percentage of patients with an improvement from a baseline of 15 letters or more in BCVA, a CST less than 300 µm, need for rescue therapy, and resolution of inflammation were summarized. Resolution of inflammation, a composite endpoint, was defined as a grade of 0 on anterior chamber cells, anterior chamber flare, and vitreous haze. Statistical testing was performed in a pair-wise fashion in which comparisons between the two treatment groups (Active vs. Control) were made within each anatomic subtype. Differences between treatments in proportions within each subgroup based on anatomic subtype were tested using a Cochran-Mantel-Haenszel chi-square test, stratified by country. For mean changes from baseline in BCVA and CST, the estimate of the between-treatment difference, 95% confidence interval, and P-value were calculated based on an analysis of variance model with fixed effects for treatment group and country.

Outcomes based on the assessment of treatment-emergent adverse events, serious adverse events, and IOP-related events were summarized with counts and percentages. Adverse events starting after studying drug administration or worsening from the pre-treatment state were considered to be treatment-emergent.

In the intent-to-treat population, values for missing data and for all data points after rescue medication had been administered were imputed using the method of last

observation carried forward. An alpha level of 0.050 was used for declaring statistical significance. No adjustments were made to the alpha level to account for multiple comparisons. Statistical analysis was conducted using SAS software version 9.4 (SAS Institute, Cary, NC). All tests were two-sided.

Results

Demographics and baseline characteristics

PEACHTREE randomized and treated 160 patients (96, Active; 64, Control).[3] In the current post-hoc analysis, the number of patients in the Active and Control arms, respectively, diagnosed with uveitis of a single anatomic subtype included anterior (13 vs 7), intermediate (21 vs 15), posterior (20 vs 11), and panuveitis (30 vs 24). All patients completed the study, except for two patients diagnosed exclusively with intermediate uveitis (1 Active, noncompliance; 1 Control, withdrew consent), and two patients with panuveitis (1 Active, withdrew consent, 1 Active, lost to follow-up).

Demographic and baseline characteristics appeared generally balanced across treatments and anatomic subtype (Table 1). The mean age was approximately 50 years. Across anatomical subtypes, mean BCVA and CST in the study eye ranged from 49.2 to 59.0 letters and from 457.4 to 525.3 µm, respectively. BCVA and CST ranged from 49.8 to 59.7 letters and from 483.7 to 544.9 µm, respectively, for patients in the Control arm. An imbalance in the time since uveitis diagnosis was noted between the Active and Control arms across all anatomic locations with the greatest disparities among patients diagnosed with anterior (150.9 weeks, Active; 48.9 weeks, Control) and intermediate (177.5 weeks, Active; 55.9 weeks, Control) uveitis. The concurrent use of oral corticosteroids and/or immunosuppressants at baseline entry was higher in patients diagnosed with panuveitis (50.0%, Active; 41.7%, Control) as compared to the other uveitic subgroups (ranging from 4.8% to 38.5%).

Efficacy

The percentage of patients with an improvement from baseline of ≥15 letters in BCVA at Week 24 ranged from 42.9% to 55.0% among patients in the Active arm and from 0% to 28.6% among patients in the Control arm (Figure 1A). These results reached statistical significance only in patients diagnosed exclusively with posterior uveitis (55.0%, Active; 0%, Control; $P = 0.005$) and panuveitis (43.3%, Active; 12.5%, Control; $P = 0.020$).

As compared to baseline, at week 24 patients in the Active arm showed mean improvements in BCVA ranging across anatomic subtype from 12.1 to 15.9 letters, compared to changes ranging from loss of 1.6 to gain of 9.1 letters in Control patients (Figure 2). Although BCVA gains were realized across all treatment arms, inter-treatment difference vs. control was statistically significant for patients diagnosed exclusively with posterior uveitis (15.9 letters, Active; 2.8 letters, Control; $P = 0.024$) and panuveitis (12.1 letters, Active; −1.6 letters, Control; $P = 0.015$).

Across all four anatomic subtypes, the percentage of patients with CST< 300 µmat Week 24 ranged from 40.0% to 65.0% among patients in the Active arm and from 6.7% to 18.2% among patients in the Control arm (Figure 1B). Statistically significant differences between the two treatment arms were detected in patients exclusively diagnosed with intermediate uveitis (65.0%, Active; 6.7%, Control; $P < 0.001$) and posterior uveitis (65.0%, Active; 18.2%, Control; $P = 0.009$).

Mean reductions in CST at Week 24 ranged from 120.1 to 189.0 µm among Active patients across anatomic subtype compared to mean changes among Control patients ranging from an increase of 10.2 µm to a reduction of 20.3 µm (Figure 2). The differences in CST among the two treatment arms within each anatomic location subgroup were statistically significant ($P \leq 0.014$), in favor of the Active arm, except for patients diagnosed with anterior uveitis.

Rescue therapy, permitted at any time during the study based on pre-defined criteria, was used at a higher rate among patients in the Control arm, ranging from 66.7% to 85.7% of patients compared to 7.7% to 20.0% of patients in the Active arm (Figure 1C). The difference between the two treatment arms within each anatomic subtype was statistically significant ($P \leq 0.002$).

There was a significant reduction in inflammatory signs by week 24 in the CLS-TA-treated group with (60.0% to 76.2%) exhibiting no inflammation across anatomic subtypes compared with (0% to 63.6%) of patients with resolved inflammation in the Control arm. (Figure 1D) Statistical significance was noted only among patients diagnosed with anterior uveitis (69.2%, CLS-TA; 0%, Control; $P = 0.005$) and intermediate

Table 1. Demographics and baseline characteristics.

	Anterior Uveitis		Intermediate Uveitis		Posterior Uveitis		Panuveitis	
Demographic	Active	Control	Active	Control	Active	Control	Active	Control
No. of Patients	13	7	21	15	20	11	30	24
Mean age (Std Err), yrs	51.2 (4.06)	48.4 (5.02)	47.8 (3.54)	44.2 (3.04)	50.0 (2.76)	55.5 (4.61)	49.7 (2.71)	52.0 (3.71)
Women, no. (%)	7 (53.8)	3 (42.9)	14 (66.7)	7 (46.7)	7 (35.0)	7 (63.6)	19 (63.3)	14 (58.3)
Mean duration of uveitis diagnosis (Std Err), wks	150.9 (55.74)	48.9 (19.36)	177.5 (47.90)	55.9 (21.05)	155.9 (67.44)	135.5 (46.32)	191.4 (41.80)	142.8 (25.32)
Mean BCVA (Std Err), letters	54.9 (2.96)	59.7 (3.66)	59.0 (3.20)	49.8 (3.95)	49.2 (3.35)	51.7 (3.96)	53.8 (2.43)	54.8 (2.56)
Mean CST (Std Err), µm	464.0 (47.94)	483.7 (51.36)	492.8 (25.46)	544.9 (43.00)	457.4 (35.70)	538.8 (44.71)	525.3 (31.03)	504.2 (35.04)
Oral Therapy, n (%)[a]	5 (38.5)	1 (14.3)	1 (4.8)	1 (6.7)	5 (25.0)	2 (18.2)	15 (50.0)	10 (41.7)

Std Err = standard error of the mean.
[a]Oral therapy included systemic corticosteroids and/or immunosuppressants.

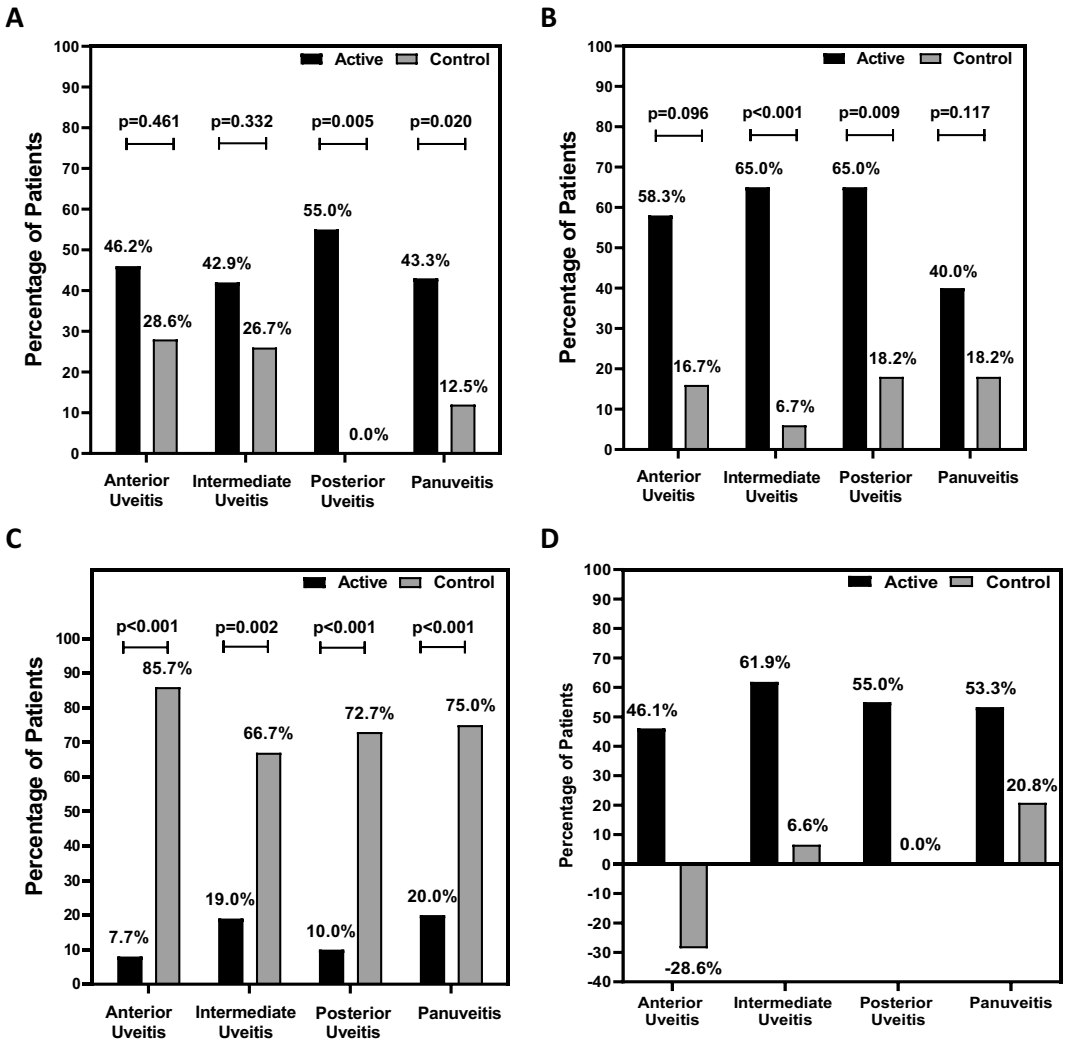

Figure 1. Efficacy summary by anatomic subtype. A, Percentage of patients with ≥15 letter improvement from baseline in best corrected visual acuity at week 24. P-values are based on a Cochran–Mantel–Haenszel (CMH) chi-square test stratified by country. B, Percentage of patients with central subfield retinal thickness <300 µm at week 24. P-values are based on a CMH chi-square test stratified by country. C, Percentage of patients receiving rescue therapy during the study. D, Difference between week 24 and baseline in the percentage of patients with complete resolution of signs of inflammation, defined as a grade of 0 for anterior chamber cells, anterior chamber flare and vitreous haze. A positive difference indicates an increase in % of patients with resolved inflammation. Analyses are based on the intent-to-treat population, defined as all randomized patients. Values for missing data and data post-rescue imputed using the method of last observation carried forward.

uveitis (76.2%, CLS-TA; 13.3%, Control; $P < 0.001$). Compared to baseline, the CLS-TA-treated group showed an improvement in the percentage of patients with resolved inflammation across all uveitis subgroups with an increase ranging from 46.1% to 61.9% (Figure 1D).

Safety

As reported in Yeh et al.[3] there were three serious adverse events reported during the study in three patients receiving CLS-TA including retinal detachment in the study eye of a patient diagnosed with intermediate uveitis, sialadenitis, and lumbar vertebral fracture. There were no meaningful imbalances between the treatment arms across the four anatomic subtypes with respect to adverse events in the study eye (Table 2, referenced online). The percentage of patients with one or more adverse events ranged across anatomic subtypes from 40.0% to 61.9% in the Active arm and from 50.0% to 66.7% in the Control arm. Patients experienced eye pain on the day of the SC injection at similar incidence rates between the treatment arms across anatomic subtypes with the exception of patients diagnosed with panuveitis (26.7%, Active; 4.2%, Control). Non-procedurally related adverse events reflecting elevations in IOP were also similar between the treatment groups.

None of the 20 patients diagnosed exclusively with anterior uveitis reported cataracts, while 5 patients with intermediate uveitis (4, Active; 1 Control), 3 with posterior uveitis (2, Active; 1 Control), and 3 with panuveitis (1, Active; 2, Control) developed a cataract or experienced cataract progression. One Control patient diagnosed with panuveitis underwent surgery to remove the cataract.

At Week 24, patients in the Active arm showed mean increases from baseline in IOP ranging across anatomic subtypes from 0.5 to 3.1 mmHg, compared to changes ranging from a reduction of 1.2 mmHg to an increase of 1.7 mmHg in

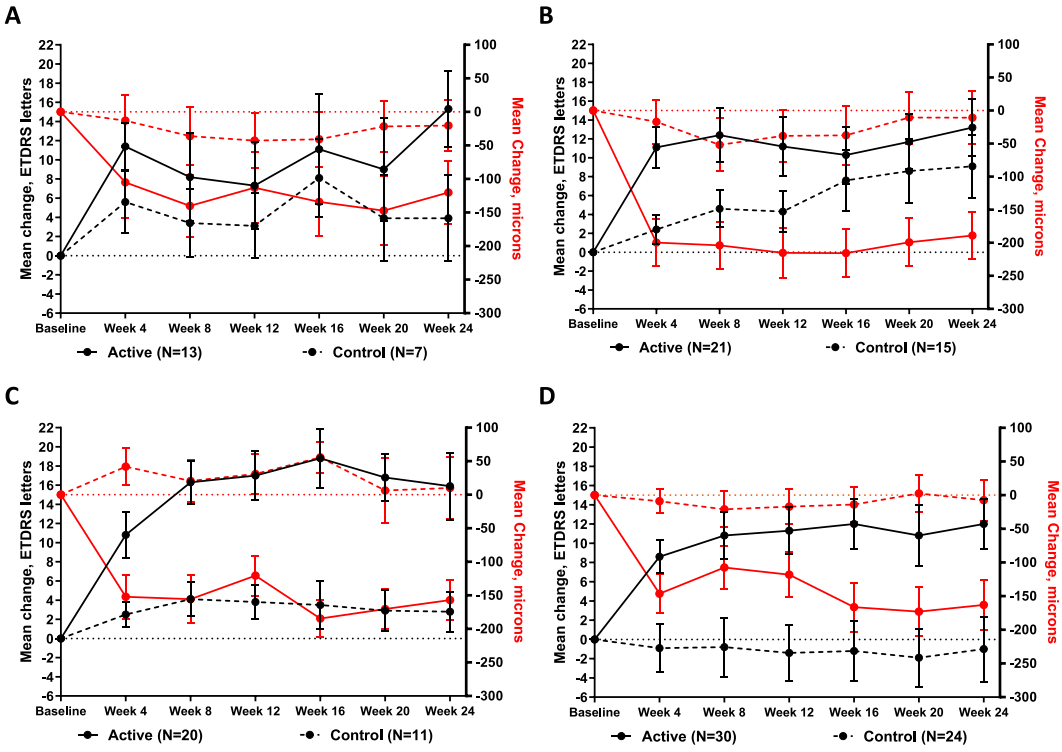

Figure 2. Mean (± standard error) change from baseline in best corrected visual acuity letter score (Black Lines) and mean change from baseline in central subfield thickness (Red Lines) by anatomic subtype. A, Patients diagnosed with anterior uveitis. B, Patients diagnosed with intermediate uveitis. C, Patients diagnosed with posterior uveitis. D, Patients diagnosed with panuveitis. Analyses are based on the intent-to-treat population, defined as all randomized patients. Values for missing data and data post-rescue imputed using the method of last observation carried forward.

Table 2. Ocular adverse events in the study eye.

	Anterior Uveitis		Intermediate Uveitis		Posterior Uveitis		Panuveitis	
Study Eye, n (%)	Active n (%)	Control n (%)	Active n (%)	Control n (%)	Active n (%)	Control n (%)	Active n (%)	Control n (%)
No. of Patients	13	7	21	15	20	11	30	24
Total number of ocular adverse events	10	4	30	15	23	12	55	15
Number of patients with ≥1 ocular AE	7 (53.8)	4 (57.1)	13 (61.9)	10 (66.7)	8 (40.0)	6 (54.5)	18 (60.0)	12 (50.0)
Treatment-related ocular AEs	2 (15.4)	0	7 (33.3)	2 (13.3)	4 (20.0)	2 (18.2)	13 (43.3)	3 (12.5)
Serious ocular AEs	0	0	1 (4.8)	0	0	0	0	0
Treatment-related serious AEs	0	0	0	0	0	0	0	0
TEAEs leading to study drug discontinuation	1 (7.7)	1 (14.3)	3 (14.3)	1 (6.7)	0	1 (9.1)	1 (3.3)	0
Number of patients with ≥1 eye disorder	4 (30.8)	4 (57.1)	13 (61.9)	10 (66.7)	8 (40.0)	5 (45.5)	18 60.0)	12 (50.0)
Adverse events								
Cataract[a]	0	0	4 (19.0)	1 (6.7)	2 (10.0)	1 (9.1)	1 (3.3)	2 (8.3)
Cystoid macular edema	0 (0.0)	2 (28.6)	0 (0.0)	4 (26.7)	0 (0.0)	2 (18.2)	0 (0.0)	1 (4.2)
Eye pain[b]: time of procedure	1 (7.7)	0	2 (9.5)	1 (6.7)	0	0	8 (26.7)	1 (4.2)
Eye pain: any time post procedure	0	0	3 (14.3)	0	1 (5.0)	0	2 (6.7)	0
Elevated IOP[c]: time of procedure	1 (7.7)	0	0	0	1 (5.0)	0	6 (20.0)	0
Elevated IOP[c]: pertaining to corticosteroid[d]	1 (7.7)	1 (14.3)	3 (14.3)	1 (6.7)	3 (15.0)	2 (18.2)	3 (10.0)	3 (12.5)
Uveitis	0 (0.0)	1 (14.3)	1 (4.8)	3 (20.0)	1 (5.0)	1 (9.1)	0 (0.0)	1 (4.2)
Vitreous detachment	1 (7.7)	0 (0.0)	1 (4.8)	0 (0.0)	2 (10.0)	0 (0.0)	1 (3.3)	0 (0.0)

[a]Cataract includes the preferred terms (a) cataract, (b) cataract subcapsular, and (c) cataract nuclear.
[b]"Eye pain" includes the preferred terms (a) eye pain, (b) injection site pain, and (c) injection site discomfort.
[c]"Elevated IOP" includes the preferred terms (a) IOP increased, and (b) ocular hypertension, and (c) open angle glaucoma.
[d]Includes all events of elevated IOP that did not occur on the day of the procedure.

Control patients (Figure 3). Excluding short-term, volume-related IOP elevations following the injection procedures (Figure 4), the percentage of patients experiencing an IOP rise from baseline of 10 mmHg or more was higher in the Active arm compared to the Control among patients diagnosed with posterior uveitis (20.0%, Active; 9.1%, Control) and panuveitis (20.0%, Active; 12.5%, Control), were no different among patients with intermediate uveitis (14.3%, Active; 13.3%, Control), and was lower than the Control among patients diagnosed with anterior uveitis (7.7%, Active; 28.6%, Control). A higher percentage of patients in the Active arm diagnosed with intermediate uveitis had an IOP ≥30 mmHg at any time during the study compared to the Control arm (9.5%, Active; 0%, Control); however, more Control patients with anterior uveitis had a similar rise (0%, Active, 14.3%, Control), and no meaningful difference was noted in patients diagnosed with posterior uveitis (5.0%, Active; 9.1%, Control) or panuveitis (6.7%, Active; 8.3%, Control). The use of IOP-

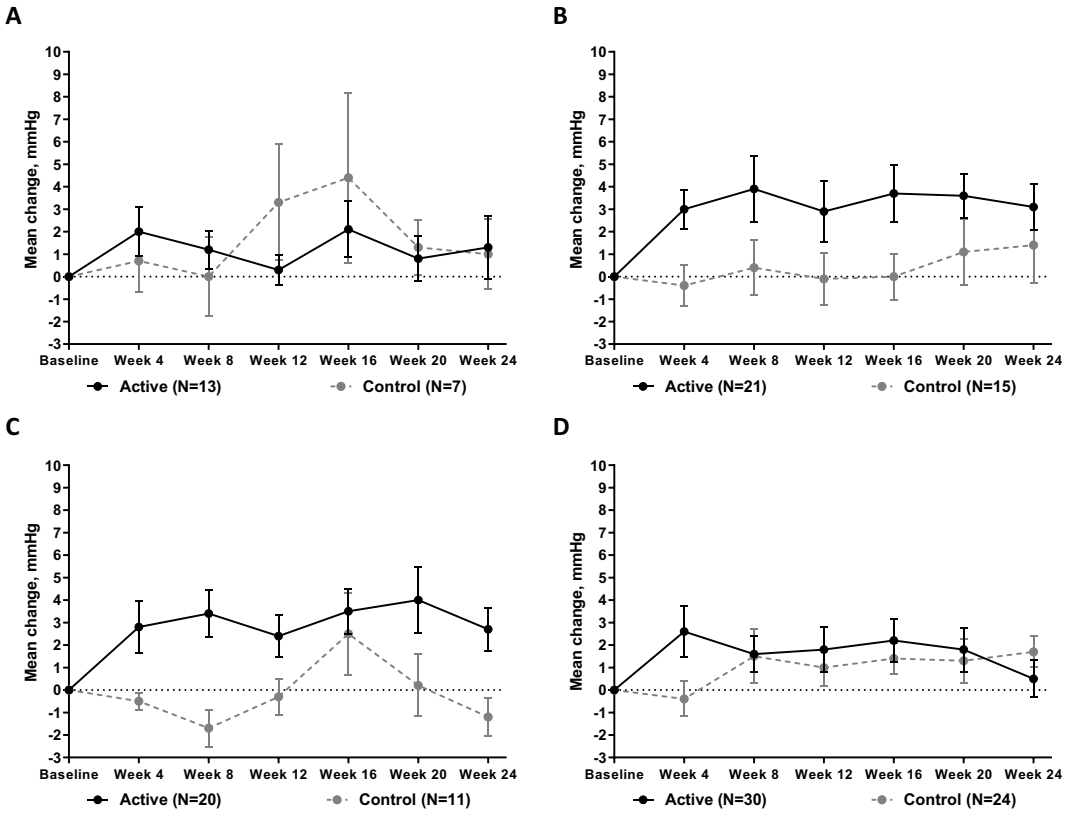

Figure 3. Mean (± standard error) change from baseline in intraocular pressure by anatomic subtype. A, Patients diagnosed with anterior uveitis. B, Patients diagnosed with intermediate uveitis. C, Patients diagnosed with posterior uveitis. D, Patients diagnosed with panuveitis. Analyses are based on the safety population, defined as all patients receiving study drug.

lowering medications mirrored the incidence of patients having an IOP ≥30 mmHg, except in patients diagnosed with anterior uveitis (7.7%, Active; 28.6%, Control).

Discussion

The phase 3 PEACHTREE trial assessed the safety and efficacy of CLS-TA, a proprietary suspension of triamcinolone acetonide, administered by suprachoroidal route in patients with ME associated with NIU.[3] While PEACHTREE demonstrated the efficacy of CLS-TA in NIU patients with ME pooled across anterior, intermediate, posterior, or panuveitis, there has been limited information on outcomes stratified by anatomic NIU subtype. Consequently, this post-hoc analysis of the PEACHTREE trial assessed outcomes based on a discrete anatomic subtype. In this post hoc analysis, patients noted to have both anterior and posterior uveitis were categorized as having panuveitis. Across these anatomic locations, patients in the Active arm consistently showed increases in BCVA at week 24 ranging from 12.1 to 15.9 letters, along with reductions in CST ranging from 120.1 µm to 189.0 µm when compared to baseline. Adverse events were noted to be generally similar between the Active and Control arms, regardless of anatomic subtype.

Although this study is limited by its post hoc nature, small sample size, and some baseline imbalances, these post-hoc analyses corroborate the published results for PEACHTREE. Results demonstrate that there is a clinical benefit regardless of uveitic anatomic subtype, with clinically meaningful improvements in BCVA, CST, and inflammation from baseline in patients treated with CLS-TA.

Interestingly, the benefit, with respect to signs of inflammation, noted in cases of anterior uveitis may initially seem counterintuitive, given that preclinical studies of SC CLS-TA demonstrated low corticosteroid exposure anteriorly relative to the posterior segment. Nevertheless, after SC injection, CLS-TA likely extends anteriorly to the scleral spur, which may be sufficiently anterior to exert sufficient and potent enough of an anti-inflammatory effect among this uveitis subtype. This distribution may also account for the inability to completely limit the risks of ocular hypertension and cataract.

As noted above, the current work is limited by its post hoc methodology and small sample size. Patient randomization into the trial did not take into account the uveitic subtype at onset, and respective stratification was not performed, creating the potential for these results to be confounded by other patient characteristics. Additionally, the concurrent use of low-dose, stable oral corticosteroids and/or immunosuppressants at baseline entry was higher in patients diagnosed with panuveitis compared to the other uveitic subgroups. Despite these limitations, the efficacy and safety results of the current post hoc study appear consistent with the findings of PEACHTREE, and are of interest to clinicians who treat patients with uveitic ME. In particular, uveitic ME may develop as a result of inflammation in any of the uveal components, and this post hoc study demonstrates a clinically meaningful benefit of CLS-TA with respect to improvement in BCVA, CST thickness, ME reduction, and a reduction in inflammatory markers, regardless of the anatomic subtype of involvement.

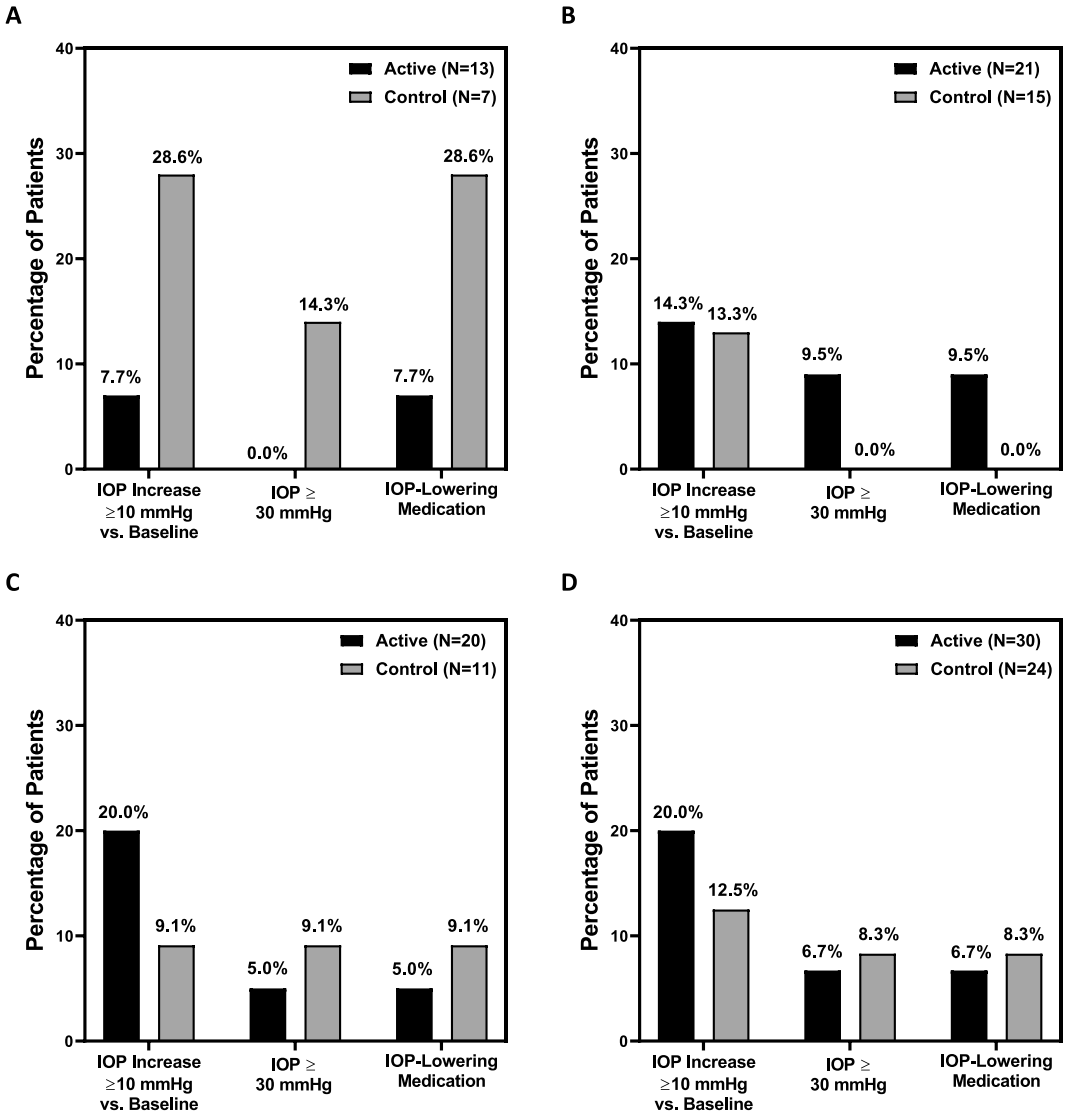

Figure 4. Percentage of patients experiencing intraocular pressure related events by anatomic subtype. A, patients diagnosed with anterior uveitis. B, patients diagnosed with intermediate uveitis. C, patients diagnosed with posterior uveitis. D, patients diagnosed with panuveitis. Analyses are based on the safety population, defined as all patients receiving study drug.

Acknowledgment

Acknowledgement to all Peachtree Study Investigators and respective study teams.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

Dr Wykoff and Dr Barakat report recent consultancy funding from Clearside Biomedical. Dr Wykoff, Dr Barakat, Dr Shah, and Dr Khurana report research grant funding from Clearside Biomedical. Mr Kapik and Dr Ciulla report employment and personal financial interest in Clearside Biomedical.

ORCID

Thomas A. Ciulla, MD, MBA http://orcid.org/0000-0001-5557-6777

References

1. Thorne JE, Suhler E, Skup M, et al. Prevalence of noninfectious uveitis in the United States: a claims-based analysis. *JAMA Ophthalmol*. 2016;134(11):1237–1245. doi:10.1001/jamaophthalmol.2016.3229.
2. Rothova A, Suttorp-van Schulten MSA, Treffers WF, Kijlstra A. Causes and frequency of blindness in patients with intraocular inflammatory disease. *Br J Ophthalmol*. 1996;80(4):332–336. doi:10.1136/bjo.80.4.332.
3. Yeh S, Khurana RN, Shah M, et al. Efficacy and safety of suprachoroidal CLS-TA for macular edema secondary to noninfectious uveitis: phase 3 randomized trial. *Ophthalmology*. 2020;127(7):948–955. doi:10.1016/j.ophtha.2020.01.006.
4. Wan C-R, Muya L, Kansara V, Ciulla TA. Suprachoroidal delivery of small molecules, nanoparticles, gene and cell therapies for ocular diseases. *Pharmaceutics*. 2021;13(2):288. doi:10.3390/pharmaceutics13020288.
5. Hancock SE, Wan C-R, Fisher NE, Andino RV, Ciulla TA. Biomechanics of suprachoroidal drug delivery: from benchtop to clinical investigation in ocular therapies. *Expert Opin Drug Deliv*. 2021;18(6):777–788. doi:10.1080/17425247.2021.1867532.
6. Thorne JE, Sugar EA, Holbrook JT, et al. Periocular triamcinolone vs. Intravitreal triamcinolone vs. Intravitreal dexamethasone

implant for the treatment of uveitic macular edema: the PeriOcular vs. INTravitreal corticosteroids for uveitic macular edema (POINT) trial. *Ophthalmology*. 2019;126(2):283–295. doi:10.1016/j.ophtha.2018.08.021.

7. Jabs DA, Nussenblatt RB, Rosenbaum JT, 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;140:509–516.
8. Nussenblatt RB, Palestine AG, Chan CC, Roberge F. Standardization of vitreal inflammatory activity in intermediate and posterior uveitis. *Ophthalmology*. 1985;92(4):467–471. doi:10.1016/S0161-6420(85)34001-0.
9. Lowder C, Belfort R Jr., Lightman S, et al. Dexamethasone intravitreal implant for noninfectious intermediate or posterior uveitis. *Arch Ophthalmol*. 2011;129(5):545–553. doi:10.1001/archophthalmol.2010.339.