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Suprachoroidal CLS-TA for non-infectious uveitis: an open-label, safety trial (AZALEA)

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ABSTRACT

Purpose To evaluate local and systemic safety of suprachoroidal (SC) triamcinolone acetonide injectable suspension (CLS-TA) injections in subjects with non-infectious uveitis (NIU).

Design Open-label, prospective multicentre safety study.

Participants Thirty-eight subjects with NIU, with and without macular oedema (MO).

Methods Treatment consisted of two suprachoroidal injections of CLS-TA 4 mg, 12 weeks apart. Best-corrected visual acuity (BCVA), adverse event (AE) assessment, ophthalmic examinations and optical coherence tomography (OCT) were conducted every 4 weeks for 24 weeks. Blood samples were analysed for plasma triamcinolone acetonide (TA) concentrations.

Main outcome measures The main outcome measure was frequency of AEs. Other endpoints included plasma TA concentrations, change in signs of inflammation, BCVA and retinal central subfield thickness (CST).

Results Based on a CST of >300 µm, 20 out of 38 subjects had MO at baseline. Mean intraocular pressure (IOP) was 13.3 mm Hg at baseline and 15.2 mm Hg at week 24 in the study eye. A total of six (15.8%) subjects had an IOP rise >10 mm Hg compared with baseline, in the study eye, and two (5.3%) subjects had IOP >30 mm Hg (maximum 34 mm Hg at week 8 and 38 mm Hg at week 20). Cataract formation AEs were reported in four study eyes; one of which was deemed treatment-related. No serious ocular AEs in the study eye occurred in the study. Quantifiable post-injection TA plasma concentration was <1 ng/mL. Efficacy parameters showed improvement over the 24-week study period.

Conclusions Suprachoroidally administered CLS-TA was safe and well tolerated over the 24-week, open-label study in NIU subjects with and without MO.

have remained a mainstay of treatment for NIU but are associated with significant limitations. Topical steroid drops have limited intraocular penetration and are used most frequently in anterior uveitis. Periocular or intravitreal steroids, including intravitreal corticosteroid implants, are often used for non-infectious intermediate, posterior and panuveitis, but are associated with relatively high rates of cataract and intraocular pressure (IOP) elevations. Systemic corticosteroids, used long term, have well-established systemic side effects, including weight gain, hypertension, hyperglycaemia, osteoporosis and psychiatric disturbances. For these reasons, guidelines and recommendations by expert panels have advised using steroid-sparing immunomodulatory therapy for chronic or severe NIU when long-term treatment with systemic corticosteroids would otherwise be necessary. These immunosuppressive agents carry their own set of systemic risks, such as haematotoxicity, liver/kidney injury and an increased incidence of certain malignancies.

Suprachoroidal (SC) administration of an investigational corticosteroid formulation (triamcinolone acetonide injectable suspension (CLS-TA)) via a microinjector is a minimally invasive, alternative therapeutic approach to macular oedema (MO) associated with NIU.³ In preclinical studies, SC CLS-TA demonstrated improved bioavailability to the posterior segment and reduced exposure of anterior segment structures. Proof of concept of the efficacy and safety of SC triamcinolone acetonide (TA) treatment for posterior uveitis was established in a porcine animal model.⁴ Human clinical trials validated the utility of this approach, culminating in the successful phase III PEACHTREE trial using SC CLS-TA to treat MO associated with NIU. MO is the leading cause of uveitic vision loss for which there is no specific approved treatment.³ PEACHTREE demonstrated clinically meaningful ≥ 15 ETDRS letter gain for nearly half of the subjects treated, marked reduction of central subfield thickness (CST), and clinically and statistically significant resolution of anterior and posterior segment inflammation in approximately 70% of subjects. Furthermore, CLS-TA had a favourable adverse event (AE) profile, inclusive of events related to IOP increase and cataracts.

Herein, we report results of a companion study (AZALEA) designed to assess the safety of 4 mg of CLS-TA administered via SC injection for the treatment of subjects with NIU, both with and without the presence of MO. This study provides

Uveitis is a group of inflammatory ocular diseases that is responsible for 5%–20% of cases of legal blindness in the USA and Europe and up to 25% of cases of blindness in the developing world. Uveitis frequently occurs between the ages of 20 and 60, affecting patients during their most productive earning years.^{1,2} While some uveitis cases are infectious in origin, non-infectious uveitis (NIU) comprises up to 90% of cases, affecting nearly 300 000 adults and 22 000 children in the USA.²

The primary goals of NIU treatment are to control inflammation, preserve vision and minimise risk of treatment-related sequelae. Corticosteroids



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Table 1 Subject and disease characteristics (safety population)

Subject characteristic	Safety population (N=38)	
Age at screening (years)		
Mean (SD)	52.4 (15.80)	
Min, Max	22, 77	
Sex, n (%)		
Male	13 (34.2%)	
Female	25 (65.8%)	
Race/Ethnicity, n (%)		
White—not Hispanic or Latino	26 (68.4%)	
Black/African American—not Hispanic or Latino	7 (18.4%)	
White—Hispanic or Latino	5 (13.2%)	
Disease characteristic (N=38)	Study eye*	Fellow eye†
Uveitis type, n (%)		
Anterior uveitis	12 (31.6%)	10 (26.3%)
Intermediate uveitis	15 (39.5%)	12 (31.6%)
Posterior uveitis	10 (26.3%)	8 (21.1%)
Panuveitis	10 (26.3%)	7 (18.4%)
Uveitis onset, n (%)		
Sudden	16 (42.1%)	4 (10.5%)
Insidious	20 (52.6%)	10 (26.5%)
Uveitis duration, n (%)		
Limited (≤ 3 months duration)	5 (13.2%)	3 (7.9%)
Persistent (> 3 months duration)	31 (81.6%)	11 (28.9%)
Uveitis course, n (%)		
Acute	1 (2.6%)	1 (2.6%)
Recurrent	11 (28.9%)	1 (2.6%)
Chronic	24 (63.2%)	12 (31.6%)
Aetiology of uveitis, n (%)		
Idiopathic or not specified	21 (55.3%)	15 (39.5%)
Sarcoidosis	8 (21.1%)	8 (21.1%)
HLA-B27 related	3 (7.9%)	2 (5.3%)
Reactive arthritis	2 (5.3%)	2 (5.3%)
Vogt-Koyanagi-Harada syndrome	1 (2.6%)	1 (2.6%)
Birdshot retinochoroidopathy	3 (7.9%)	3 (7.9%)

*Two study eyes were not assessed for disease characteristics.

†Thirty-one out of 38 fellow eyes were diagnosed with uveitis.

new information regarding the use of CLS-TA in NIU subjects without MO, while corroborating PEACHTREE results in NIU subjects with MO, and also reporting systemic pharmacokinetic (PK) outcomes for the first time.

METHODS

Study participants

Institutional Review Board approval was obtained for this study (ClinicalTrials.gov identifier NCT03097315), which adhered to the tenets of the Declaration of Helsinki. Subjects ≥ 18 years of age were eligible if they had a diagnosis of active or inactive NIU of any aetiology in any anatomic location and an ETDRS best-corrected visual acuity (BCVA) score of ≥ 5 letters in the study eye. Subjects were excluded if they had any active ocular disease other than uveitis or infection in the study eye; IOP > 22 mmHg; severe or uncontrolled glaucoma; or recent use of topical, intraocular or periocular steroids. Systemic corticosteroids at doses of ≤ 20 mg/day for oral prednisone (or equivalent for other corticosteroids) as well as non-steroidal anti-inflammatory drugs and/or systemic immunomodulatory therapies at stable doses for the previous two or more weeks were permissible. In subjects with IOP ≤ 22 mmHg, use of up to two IOP-lowering medications was allowed. All subjects provided informed consent for the study and separately for PK sampling.

Table 2 Ocular adverse events

Study eye, n (%)	CLS-TA 4.0 mg (N=38)
Total number of ocular adverse events	41
Number of patients with ≥ 1 ocular AE	19 (50.0)
Treatment-related ocular AEs	7 (18.4)
Serious ocular AEs	0
Treatment-related serious AEs	0
TEAs leading to study drug discontinuation	0
Adverse events	
Cataract*	4 (10.5)
Cystoid macular oedema	0
Endophthalmitis	0
Eye pain†: time of procedure	3 (7.9)
Eye pain†: any time post procedure	1 (2.6)
Elevated IOP‡: time of procedure	1 (2.6)
Elevated IOP‡: pertaining to corticosteroid§	5 (13.2)
Retinal detachment	0
Suprachoroidal haemorrhage	0
Worsening of uveitis	1 (2.6)
Vitreous detachment	1 (2.6)

*Cataract includes the medDRA preferred terms (a) cataract, (b) cataract subcapsular and (c) cataract nuclear.

†'Eye pain' includes the preferred terms (a) eye pain and (b) injection site pain.

‡'Elevated IOP' includes the preferred terms (a) IOP increased and (b) ocular hypertension.

§Includes all events of elevated IOP that did not occur on the day of the procedure.

AE, adverse event; CLS-TA, investigational triamcinolone acetonide injectable suspension; IOP, intraocular pressure.

Study design

This open-label, prospective multicentre safety study was conducted at 11 sites in the USA from April 2017 to January 2018. Subject eligibility was established up to 30 days prior to baseline (day 0). If both eyes met the study criteria, the right eye was designated the study eye.

Eligible subjects returned to the clinic for treatment at day 0; screening and treatment could occur on the same day. Qualified subjects received a single unilateral SC injection of CLS-TA, 4 mg (0.1 mL of 40 mg/mL), at day 0 and at week 12. SC injection was administered via a proprietary microinjector (Clearside Biomedical, Alpharetta, Georgia, USA) with a 900 or 1100 μ m needle length, approximately 4 mm posterior from the limbus, in the temporal hemisphere.

Follow-up visits, consisting of AE assessment, BCVA, slit lamp examination, IOP measurement, indirect ophthalmoscopy and spectral-domain optical coherence tomography (SD-OCT), were conducted every 4 weeks up to 24 weeks for a total of 8 visits. Subjects providing consent for PK analysis had blood samples collected at day 0, week 4, week 12 and week 24. On day 0 and week 12, the blood samples were obtained prior to CLS-TA injection administration.

Beginning at week 4, a rescue treatment could be introduced if any of the following criteria were met in the study eye: (1) decrease of 10 or more ETDRS BCVA letters read from baseline; (2) increase in CST of ≥ 100 μ m or 20%, whichever was lower, from baseline; (3) a ≥ 1.5 step increase from baseline in the level of inflammation (eg, anterior chamber (AC) cells, AC flare or vitreous haze) or an increase from 3+ to 4+; (4) decrease of 10 or more ETDRS BCVA letters read compared with the best ETDRS BCVA data observed during the study, along with an increase in other signs or complications associated with uveitis; or (5) the uveitic complications in the study eye had not improved and the condition needed to be addressed according to the investigator's medical judgement.

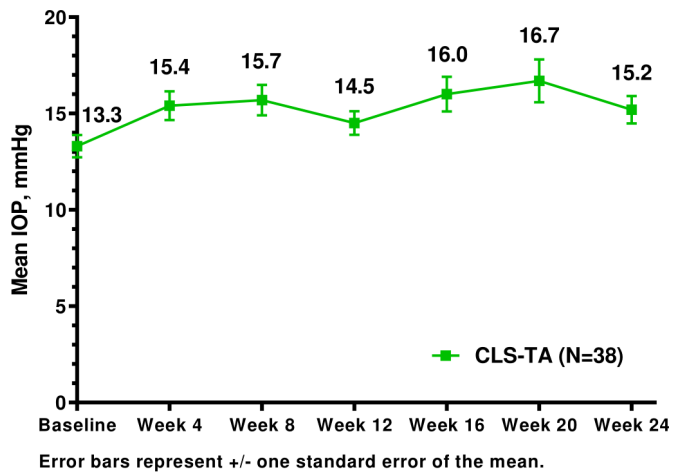


Figure 1 Mean (SEM) intraocular pressure. CLS-TA, investigational triamcinolone acetonide injectable suspension; IOP, intraocular pressure.

Safety endpoints

The main safety outcome assessed was the incidence of treatment-emergent AEs (TEAEs) and serious AEs (SAEs) in the safety population. Additional safety outcomes included frequency of vision loss in the study eye, elevated IOP, frequency and severity of cataract formation, and plasma TA concentrations post-treatment.

Visual and anatomical outcomes

Efficacy measures included change in grade from baseline of AC cells, AC flare and vitreous haze as measured by Standardization of Uveitis Nomenclature (SUN) working group criteria⁵ at each visit; mean change from baseline in ETDRS BCVA; mean change from baseline in CST assessed by spectral-domain optical coherence tomography; the percentage of subjects with a decrease in systemic concomitant uveitis medications; and the percentage of subjects in whom any additional therapy was initiated to manage uveitis.

Statistical analysis

Statistical analyses were descriptive in nature. Continuous variables were summarised by descriptive statistics, and categorical variables were summarised by counts and percentages. The safety population included all subjects who entered this study and were administered at least 1 dose of CLS-TA. All safety analyses were performed for the safety population. The intent-to-treat (ITT) population included all subjects eligible to be treated with CLS-TA who did not fail screening. Values for missing data were imputed using the method of last observation carried forward. Subjects given additional treatment for uveitis had all data following the administration of additional treatment set to missing and imputed using the Last Observation Carried Forward (LOCF) method. The ITT population was used for efficacy assessments. The PK population included all subjects who were administered at least 1 dose of CLS-TA and provided a blood sample for the measurement of TA concentrations. Analyses were conducted on all samples collected during the study. A sample size of 35 subjects would provide approximately 80% probability of detecting at least one subject with an IOP >30 mmHg over the 24-week follow-up period if the true incidence is 5% based on a binomial distribution.

RESULTS

Forty-three subjects consented to screening, and 38 enrolled in the study, comprising the ITT population. The same 38 subjects received at least 1 dose of CLS-TA and were therefore included in the safety population. Thus, the safety population and ITT population were identical. Six subjects had significant protocol deviations, leaving 32 subjects in the per-protocol population. Four were related to the injection procedure, and two were schedule-related deviations per the protocol; 37 subjects completed the study. Subjects were predominantly female and white (table 1). Uveitis was bilateral in 81.6% of cases. The most common anatomical classification was intermediate uveitis, followed by anterior uveitis, and then posterior and panuveitis (table 1), and 20 out of 38 subjects had MO based on a CST of >300 µm.

A total of six subjects were receiving one or more systemic corticosteroids or immunosuppressants at baseline, and six subjects were receiving inhaled or nasal corticosteroids. Systemic medications included adalimumab (n=3), methotrexate (n=2), mycophenolate mofetil (n=1), prednisone (n=4), rituximab (n=1), secukinumab (n=1) and vedolizumab (n=1). Each of these patients remained on at least one systemic medication for the duration of the study. A total of seven subjects were receiving IOP-lowering medication(s) in their study eye at baseline. Topical IOP-lowering medications included brimonidine (n=3), dorzolamide (n=2), timolol (n=1), combination brimonidine/timolol (n=1), combination brinzolamide/brimonidine (n=1) and combination dorzolamide/timolol (n=2). All patients remained on at least one medication for the duration of the study. No patients were on systemic IOP-lowering medications.

Safety

Treatment with CLS-TA was well tolerated over 24 weeks. Eye pain at the time of the injection procedure was reported in three (7.9%) subjects. Study eye TEAEs from AZALEA are summarised in table 2.

There were no TEAEs leading to study discontinuation or death, and no SAEs involving the study eye. Seven subjects (18.4%) experienced a TEAE that was considered by the investigator to be related to the study drug. One subject (2.6%) had a TEAE immediately following the injection procedure at baseline and five (13.2%) subjects had a TEAE associated with the corticosteroid. At the conclusion of the study, all causally related events were resolved, except one event of increased IOP, two events of ocular hypertension and one event of posterior subcapsular cataract. MedDRA preferred terms 'IOP increased' and 'ocular hypertension' were grouped together under 'Elevated IOP' in table 2.

With respect to IOP, mean values were 13.3 mmHg at baseline to 15.2 mmHg at week 24 in the study eye (figure 1). A total of six (15.8%) subjects had an IOP rise >10mmHg compared with baseline, in the study eye, and two (5.3%) subjects had an IOP >30mmHg (maximum 34 mmHg at week 8 and 38 mmHg at week 20). Four subjects were treated with one additional IOP-lowering medication and three subjects were treated with two additional IOP-lowering medications. Of the seven subjects receiving IOP-lowering medications at baseline, three subjects experienced a sponsor-defined IOP event (eg, an increase from baseline >10mmHg), and two of the three were treated with additional topical IOP-lowering medications. No subjects discontinued the study because of elevated IOP or required surgery related to elevated IOP.

The formation or worsening of cataracts occurred in four (10.5%) subjects, one of which was considered to be treatment-related. No cases of cataract were related to the injection procedure itself; furthermore, penetration of the sclera to the lens would not be possible based on the length of the microneedle. Investigator descriptions of

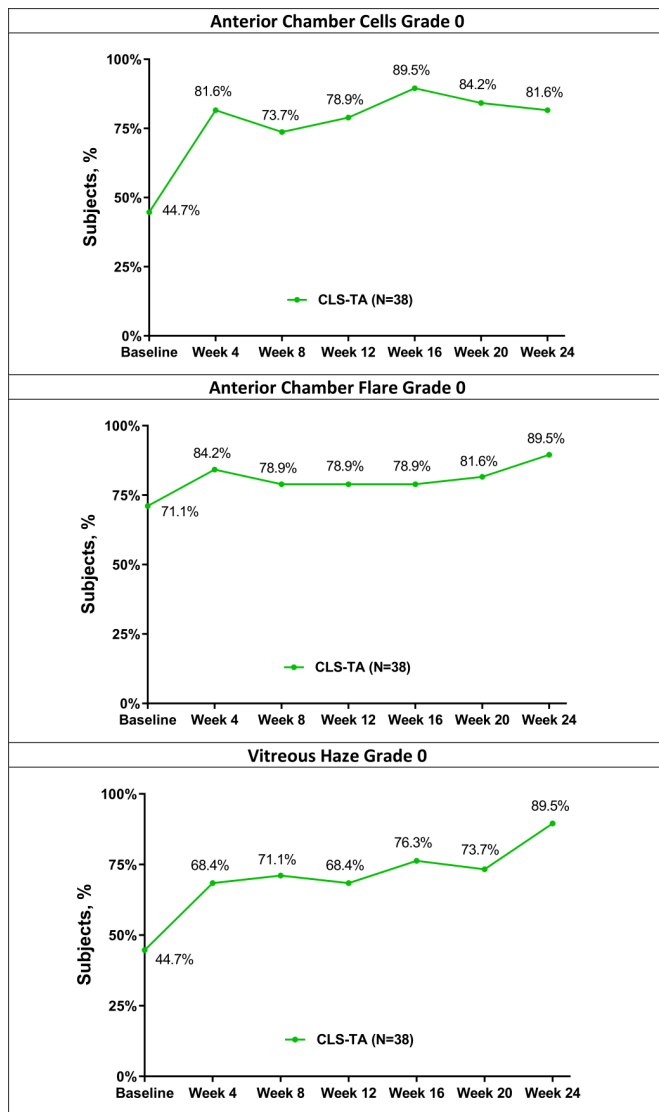


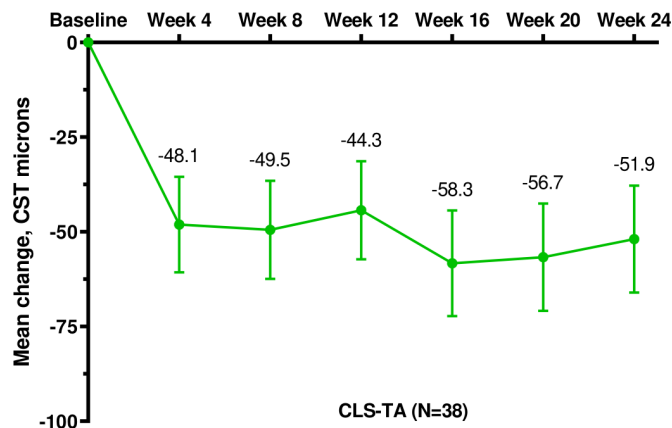
Figure 2 Percentage of subjects with resolution of anterior chamber cells, anterior chamber flare and vitreous haze (safety population). CLS-TA, investigational triamcinolone acetonide injectable suspension

cataract progression included worsening of posterior subcapsular cataract, worsening of nuclear sclerosis, trace nuclear sclerosis and worsening of cataract. No patients required cataract surgery. Of note, two of these subjects developed cataracts, in the fellow eye, either concurrently or subsequently, during the trial. No patients experienced endophthalmitis or suprachoroidal haemorrhage.

Thirty-seven of 38 subjects contributed at least 1 PK sample for analysis and were included in the PK population. Analyses were conducted on all 91 samples collected during the study. Thirty-eight of 91 samples had no quantifiable TA levels, or <10.00 pg/mL (below the limit of quantitation (BLQ)) TA plasma concentration values. The quantifiable TA plasma concentration values for post-injection samples were all lower than 1 ng/mL and were no higher than those observed with intravitreal injected TA as reported in the product label.

Vision and anatomical outcomes

Figure 2 summarises the effect of CLS-TA on the grading of AC cells, AC flare and vitreous haze in study eyes of the ITT population. The number of subjects with AC cell grade of 0 improved from 17 (44.7%) at baseline to 31 (81.6%) at week 24. Over



Intention-to-treat population; LOCF imputation. Error bars represent +/- one standard error of the mean (SEM). Mean (SEM) CST at baseline was 335.9 (13.79) microns.

Figure 3 Mean (SEM) change from central subfield retinal thickness (intent-to-treat population).

the same timeframe, the number of subjects with AC flare grade of 0 improved from 27 (71.1%) at baseline to 34 (89.5%) at week 24. The number of subjects with a vitreous haze grade of 0 improved from 17 (44.7%) at baseline to 34 (89.5%) at week 24. Per predefined criteria, four subjects received rescue therapy including nepafenac, triamcinolone acetonide, aflibercept, prednisolone or prednisolone acetate. No subjects had a decrease in systemic concomitant uveitis medications during the study.

At baseline, the mean BCVA in the study eye was 68.9 (SD 19.07) for the ITT population. The mean BCVA improved at all post-baseline visits, measuring 75.0 (SD 16.93) at week 8 and 75.9 (SD 15.82) at week 24. In subjects with a baseline BCVA of ≤ 80 letters (27 subjects), 17 subjects (63.0%) had a gain of at least 5 letters at visit 8 (week 24).

MO was not required for inclusion in this trial. At baseline, the mean CST in the study eye was 335.9 μm (SD 85.00) in the ITT population. At all post-baseline visits, mean CST improved, and at week 24, mean CST was 284.0 μm (SD 76.44), a decrease of 15%. Excess retinal thickness, an estimate of the amount of edematous tissue in the retina, was defined as the observed thickness minus a 'normal' subfield thickness of 300 μm . At baseline, 20 subjects in the ITT population had excess retinal thickness >300 μm in the study eye. Over time, between 70% and 85% of subjects with MO at baseline experienced a decrease in excess retinal thickness of 20% or more compared with baseline. CST results are summarised in **figure 3**.

DISCUSSION

The goal of suprachoroidal delivery of corticosteroid is to provide a targeted therapy compartmentalised for safety and with the potential for prolonged PK for durability. AZALEA corroborates and augments the successful phase III PEACHTREE trial using SC CLS-TA for MO associated with NIU, assessing CLS-TA in NIU subjects both with and without MO, as well as reporting systemic PK outcomes for the first time. In preclinical studies involving a rabbit model, TA concentrations in plasma peaked 1 day after bilateral CLS-TA injection (4 mg/0.1 mL), with mean maximal serum concentrations of 12 ng/mL. Plasma TA concentrations were still quantifiable at very low levels in individual animals 60 days after each injection, and were undetectable in most animals 90 days after each injection. In this open-label trial, after treatment with 4 mg CLS-TA, quantifiable TA plasma

concentration was <1ng/mL in all samples and therapy was well tolerated over 24 weeks. There were no TEAEs leading to study discontinuation or death, and no ocular SAEs. Of note, this novel delivery method showed AEs related to pain which was similar to the previous PEACHTREE study³ and compared favourably with intravitreal injection of other corticosteroids.⁶

Although the primary objective of this study was to assess safety of SC CLS-TA in NIU, visual and anatomical outcomes were also explored. Overall, all efficacy parameters showed improvement over the 24-week AZALEA study, with the majority of subjects demonstrating improvement in the signs of inflammation (AC cells, flare and vitreous haze). The majority of patients did not require rescue therapy, similar to the PEACHTREE trial.

BCVA and CST showed modest improvement in this trial. Unlike the PEACHTREE trial, AZALEA had broader inclusion criteria and allowed subjects with active and inactive NIU to participate regardless of the presence of MO. The lack of MO among AZALEA subjects is consistent with better baseline mean BCVA and CST than in PEACHTREE subjects, potentially creating a relative ceiling effect for improvement in AZALEA compared with PEACHTREE.

The AZALEA study has several limitations, including the small number of subjects, the open-label study design and the lack of a control group. Nevertheless, CLS-TA shows meaningful promise, noted from preclinical testing through clinical studies, including AZALEA. In preclinical studies, suprachoroidal injection of TA demonstrated favourable ocular distribution with greater concentrations in the chorioretinal tissues than anterior tissues, along with prolonged therapeutic tissue levels. Also, preclinical uveitis models demonstrated the potential benefits of targeted delivery to affected tissue, as suprachoroidal injection of TA was as effective as intravitreal injection of TA at 1/10th the dose. This prolonged targeted compartmentalisation and preclinical efficacy correlated to results from AZALEA and its companion study, PEACHTREE, demonstrating clinically meaningful efficacy and safety manifested by both low IOP and cataract adverse events. In the future, CLS-TA may represent an additional promising local corticosteroid option for NIU.

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Correction notice This article has been corrected since it was published online. An error was introduced during the production process in the results section of the abstract. In the Abstract results, first sentence: 'Based on a CST of ≥ 300 μm , 20 out of 38 subjects had MO at baseline.' has been changed to: 'Based on a CST of >300 μm , 20 out of 38 subjects had MO at baseline.' Further, in the Abstract results, fourth sentence: 'Cataract formation AEs were reported in four study eyes; two of which were deemed treatment-related.' should be: 'Cataract formation AEs were reported in four study eyes; one of which was deemed treatment-related.'

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Competing interests CRH reports receiving consulting fees from Clearside Biomedical and Bausch & Lomb. MS reports receiving grant support from Clearside Biomedical. MRB reports receiving consulting fees from Allegro, Allergan, Alimera, Bausch & Lomb, Genentech, Novartis and Regenxbio. RNK reports receiving consulting fees from Allergan, Clearside Biomedical, Genentech and Regeneron. He also reports receiving grant support from Allergan, Chengdu Kanghong, Clearside Biomedical, Roche and Santen. LR reports receiving consulting fees from Bausch & Lomb. SY reports receiving consulting fees from Clearside Biomedical and Santen. He also reports receiving grant funding from Clearside Biomedical. CH and TC are employees of Clearside Biomedical.

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