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ORIGINAL ARTICLE

Topical treatment of diabetic macular edema using dexamethasone ophthalmic suspension: A randomized, double-masked, vehicle-controlled study

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Abstract

Purpose: To evaluate topical dexamethasone ophthalmic suspension OCS-01 (Oculis SA, Lausanne, Switzerland) in diabetic macular edema (DME).

Methods: This was a multicenter, double-masked, parallel-group, randomized, Phase 2 study. Patients aged 18–85 years with DME of <3 years duration, ETDRS central subfield thickness ≥ 310 µm by SD-OCT, and ETDRS letter score ≤ 73 and ≥ 24 in the study eye were randomized 2:1 to OCS-01 or matching vehicle, 1 drop 3 times/day for 12 weeks. Efficacy was evaluated as change from baseline to Week 12 of ETDRS letter score and central macular thickness (CMT). The primary analysis used a linear model with baseline ETDRS letters as a covariate, and missing data imputed using multiple imputation pattern mixture model techniques. Active treatment was considered superior to vehicle if the one-sided *p*-value was <0.15 and the difference in mean change from baseline in ETDRS letters was >0.

Results: Mean CMT showed a greater decrease from baseline with OCS-01 ($N = 99$) than vehicle ($N = 45$) at Week 12 (−53.6 vs −16.8 µm, $p = 0.0115$), with significant differences favouring OCS-01 from Weeks 2 to 12. OCS-01 was well-tolerated, and increased intraocular pressure was the most common adverse event. Mean change in ETDRS letter score from baseline to Week 12 met the p was +2.6 letters with topical OCS-01 and 1 letter with vehicle ($p = 0.125$). In a post-hoc analysis, there was a greater difference in patients with baseline BCVA ≤65 letters, the OCS-01 group improved 3.8 letters compared with 0.9 letters with vehicle.

Conclusion: Topical OCS-01 was significantly more effective than vehicle in improving central macular thickness in patients with DME. Visual improvement was better in eyes with lower baseline vision.

KEYWORDS
clinical trials, cyclodextrin, dexamethasone, diabetic macular edema, formulation technology, topical treatment

[†]DX-211 study group members are presented in Supporting Information.

1 | INTRODUCTION

Currently, intravitreally administered inhibitors of vascular endothelial growth factor (VEGF) or corticosteroid implants are the main treatments for diabetic macular edema (DME; Browning et al., 2018). These therapies are highly effective in both increasing visual acuity and reducing central macular thickness (CMT). Not all DME patients have access to intravitreal therapies, however, for financial and geographic reasons, among others. Intravitreal administration can be uncomfortable and involve risk of inflammation, infection and surgical mishaps, and not all patients respond to anti-VEGF treatment (Browning et al., 2018; Pham et al., 2019; Ramu et al., 2015).

Effective topical therapies for DME would improve patient comfort and safety, accessibility, cost and allow individualized dosing (Sharma & Bandello, 2015). However, despite some initial reports of successful treatment (Campochiaro et al., 2010; Nakano et al., 2010), current topical therapies are not considered effective, and no topical treatments are currently approved for DME. Using topical administration to achieve therapeutic drug concentrations in the posterior segment of the eye has generally been regarded as extremely difficult, due to the anatomic barriers to drug penetration and the distance from the surface of the eye (del Amo et al., 2017).

OCS-01 (ophthalmic suspension, previously referred to as solubilizing nanoparticle aggregate dexamethasone eye drops, Oculis SA, Lausanne, Switzerland) is a novel formulation of dexamethasone at high concentration, designed to enhance drug penetration into both the anterior and posterior segments of the eye with long duration following topical application into the conjunctival sac. As demonstrated using earlier formulations, the use of nanoparticle aggregates based on γ-cyclodextrin allows lipophilic drugs to be solubilized at high concentrations in aqueous media, achieving sustained high drug concentrations in the tear film after topical application. Lipophilic drugs are readily released from the nanoparticles and can penetrate the membrane barriers of the conjunctiva and cornea efficiently (Loftsson & Stefánsson, 2017). Studies in rabbits demonstrated therapeutic concentrations of dexamethasone in the retina following application of cyclodextrin-based eye drops (Johannsdottir et al., 2018a,b; Loftsson et al., 2007).

Small pilot studies and case series with earlier dexamethasone nanoparticle aggregate formulations of eye drops in patients with DME (Ohira et al., 2015; Tanito et al., 2011) and uveitic cystoid macular edema (Krag & Hessellund, 2014; Shulman et al., 2015) demonstrated decreases in central macular thickness (CMT) and/or improvements in visual acuity. In these studies, the main safety finding was increased intraocular pressure (IOP), as would be expected with corticosteroid treatment and which diminished upon cessation of the eye drops.

Here, we report a vehicle-controlled Phase 2 study designed to evaluate the efficacy (in terms of improvements in visual acuity and CMT) and safety of OCS-01 eye drops in patients with DME.

2 | METHODS

2.1 | Study design

This was a multi-center, randomized, double-masked, parallel-group, vehicle-controlled study. The study was conducted at 27 centers in 6 countries in the European Union (Denmark, Estonia, Finland, Hungary, Latvia, and Sweden). The study is registered in EudraCT (number 2017–001172-36).

Patients were eligible for study entry if they were 18–85 years of age at baseline; had DME of less than 3 years duration, with intraretinal and/or subretinal fluid in the study eye, involving the central macula, in the opinion of the investigator and on spectral domain optical coherence tomography (SD-OCT), Early Treatment Diabetic Retinopathy Study (ETDRS) central subfield thickness of ≥310 μm, with ETDRS best corrected visual acuity (BCVA) letter score ≤73 (Snellen 20/40) and ≥24 (Snellen 20/320) in the study eye. A documented diagnosis of type 1 or type 2 diabetes mellitus and a glycated haemoglobin (HbA1c) of ≤12.0% at the screening visit were also required.

Key ocular exclusion criteria were macular edema or decreased visual acuity due to a cause other than DME, macular ischemia that would prevent visual gain in the opinion of the investigator, ETDRS high-risk proliferative diabetic retinopathy in the study eye, other ocular disease that could potentially cause substantial reduction in BCVA during the study, active peri-ocular or ocular infection, history of non-infective uveitis, myopia −8 diopters or worse in the study eye, uncontrolled intraocular hypertension or glaucoma in either eye, need to use contact lenses during the treatment period, prior ocular surgery, prior YAG laser capsulotomy, prior panretinal scatter photocoagulation, or prior focal laser treatment in the study eye within 3 months of study entry. Patients were also excluded if they had a history of intravitreal, subtenon, or periocular corticosteroid treatment in the study eye as follows: non-sustained release preparations used within 3 months, sustained release dexamethasone used within 6 months, or sustained release fluocinolone used within 3 years prior to study entry. Additional exclusion criteria were administration of intravitreal aflibercept within 8 weeks and ranibizumab/bevacizumab within 6 weeks of study entry, as was use of any unapproved treatment for DME within the previous 1 year.

At baseline, eligible patients were randomized in a 2:1 ratio to OCS-01 suspension eye drops or vehicle eye drops. Randomization was performed on behalf of the sponsor by a CRO (Parexel International, Dublin, Republic of Ireland). Randomization numbers were printed onto sealed opaque envelopes containing the treatment assignment. Patients were randomized in blocks of six. Treatment was masked to patients, investigators and other study site personnel, and sponsor staff. OCS-01 and vehicle eye drops were dispensed in single dose containers, prepared in identical packaging to maintain masking. Treatments were administered as 1 drop 3 times a day (every 8 h) for 12 weeks. OCS-01 eye drops are a 1.5% w/v dexamethasone suspension. A single drop from an eye drop bottle is approximately

30 µl and, therefore, contains approximately 0.45 mg of dexamethasone. Three times a day dosing would contain 1.35 mg of dexamethasone a day. Vehicle eye drops were identical to the active treatment but without dexamethasone. Rescue with standard-of-care medication was allowed based upon criteria for BCVA and CMT changes from baseline associated with the progression of DME (10 letters or more decrease in BCVA or CMT increase of 20% or more at 2 consecutive visits, assessed by the treating physician to be due to DME).

2.2 | Assessments

Study visits were at baseline (Day 1), then at Weeks 2, 4, 8, 12 and 16 post-baseline. At each visit, an ophthalmic examination was undertaken, assessing visual acuity (using ETDRS chart at 4 m with best corrective lenses) and IOP (Goldmann or I-CARE tonometry, standardized at each center, with the same device used for each patient throughout the study), followed by biomicroscopic examination of the anterior segment and the fundus, SD-OCT for assessment of macular thickness (images graded at the Bern Photographic Reading Center, Bern University Hospital, Inselgruppe AG, Switzerland). Lens opacity was graded using the LOCS III system at baseline and at Week 12 in phakic eyes.

2.3 | Study end points

The primary efficacy endpoint was the change from baseline in BCVA in ETDRS letters at Week 12. Secondary efficacy endpoints were mean change from baseline in BCVA at each visit, mean BCVA at each visit, proportions of patients who gained ≥10 or ≥15 ETDRS letters at Week 12 compared to baseline, proportion of patients reaching 20/20 vision at Week 12, proportion of patients who lost ≥15 ETDRS letters at Week 12 compared to baseline, mean change from baseline in CMT and mean CMT at each visit.

Safety was assessed in terms of ocular and non-ocular adverse events (AEs) coded using MedDRA version 21.0, clinical laboratory assessments (biochemistry and haematology), IOP measurements, and results of anterior segment and fundus biomicroscopy.

2.4 | Statistical analyses

The planned sample size was based on an expected difference between OCS-01 and vehicle in the mean BCVA change from baseline to Week 12 of 3.5 letters, a common standard deviation in the change from baseline ETDRS letters to Week 12 of 8 letters within each treatment group, and the overall 1-sided alpha = 0.15 selected for this exploratory study. Assuming a 2:1 randomization, 86 OCS-01 and 43 Vehicle patients, with one study eye per patient were required in order to have a 90% power to reject the null hypothesis. Allowing for a 10% discontinuation rate, a total of 144 subjects were to be randomized.

Primary and secondary efficacy analyses were based on the intent-to-treat (ITT) population, defined as all randomized patients, analysed under the treatment to which they were randomized. The primary analysis of the primary endpoint employed a linear model with change from baseline in ETDRS letters as the response, baseline ETDRS letters as a covariate, and treatment as a main effect factor, with multiple imputation pattern mixture model techniques used to impute missing data. The active treatment was considered superior to vehicle if the one-sided p-value was less than 0.15 and the difference in mean change from baseline in ETDRS letters was greater than 0. The primary efficacy endpoint was summarized by treatment group using descriptive statistics, including 70%, 90% and 95% confidence intervals (CIs). The least squared mean, standard error, and 70%, 90% and 95% CIs for each treatment group, and the difference between treatment groups were presented as well as a 1-sided p-value testing the difference versus the null hypothesis value of 0. Analysis of covariance (ANCOVA) provided a method for comparing response means among two treatment groups adjusted for baseline values as a covariate only. Analyses were also performed using a two-sample t-test.

Secondary efficacy endpoints mean and mean change from baseline in ETDRS letters at Weeks 2, 4, 8, and 16, and mean and mean change from baseline in CMT at Weeks 2, 4, 8, 12 and 16 were analysed using similar methods to the primary endpoint, but using observed data only with no imputation of missing values. The proportions of patients who gained ≥10 or ≥15 ETDRS letters at Week 12 compared to baseline, and who lost ≥15 ETDRS letters at Week 12 compared to baseline were summarized using descriptive summary statistics. Pearson's chi-squared statistics, with Fisher's exact statistic used for any comparison with an expected cell frequency of 5 or less, were used for treatment comparisons. Confidence intervals (70%, 90%, and 95%) were presented for each treatment group and the difference between treatment groups, using asymptotic or exact methodology as consistent with the employed testing procedure.

2.5 | Study oversight

At each participating site, an institutional review board or independent ethics committee reviewed and approved the clinical study protocol, informed consent form, and all other appropriate study-related documents. The study was designed and performed in accordance with the International Conference on Harmonization Harmonized Tripartite Guidelines for Good Clinical Practice and with the ethical principles of the Declaration of Helsinki. Patients were required to understand and sign the informed consent form.

2.6 | Patient disposition and baseline characteristics

Patient disposition is summarized in Figure 1. The study was conducted between September 2017 and March 2019.

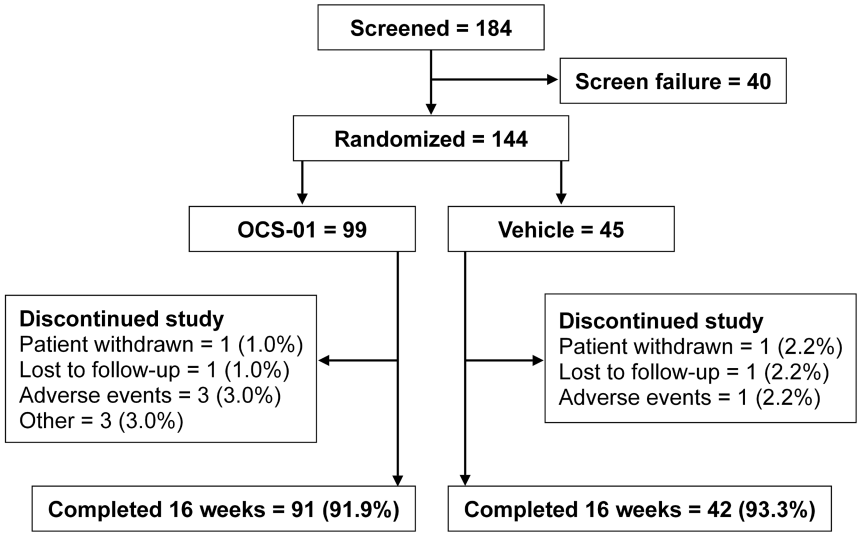

FIGURE 1 Patient disposition.

Of 184 patients screened, 144 were randomized, 99 to OCS-01 and 45 to vehicle. More than 90% of patients in both treatment groups completed the study.

Table 1 shows baseline characteristics for the ITT population. Treatment groups were well-matched for demographic characteristics, other than age, where the vehicle group was slightly older, with a higher proportion of patients aged ≥70 years.

3 | RESULTS

3.1 | Efficacy outcomes

OCS-01 was compared to vehicle in the primary efficacy analysis, in that the least square estimates of mean change from baseline of ETDRS BCVA letters from ANCOVA with control based multiple imputation showed an effect of treatment meeting the pre-specified criteria for superiority to vehicle (between-group difference 1.58 letters, 70% CI 0.15–3.01, $p = 0.13$, at an alpha of 0.15, Table 2, Figure 2). The secondary analysis performed using two sample *t*-test also showed a mean difference from baseline between the two treatment arms (mean difference 1.75 letters, 70% CI 0.34, 3.16, $p = 0.09$), without adjusting for baseline ETDRS BCVA.

Higher proportions of patients in the OCS-01 group gained ≥10 ETDRS letters (14/99, 14%) or ≥15 ETDRS letters (5/99, 5%) than in the vehicle group (4/45, 9% and zero, respectively), but the between-group differences were not statistically significant. There was no statistically significant difference between groups in the proportion of patients losing ≥15 ETDRS letters (zero in the active treatment group and 1/45, 2% in the vehicle group).

Mean CMT showed a statistically significantly greater decrease from baseline in the OCS-01 group than the vehicle arm at Week 12 (Table 3), and at all post-baseline time points up to Week 12 (Figure 3). The difference was statistically significant when analysed using either ANCOVA or *t*-test. Mean CMT also showed statistically significant differences between groups at all visits from Week 2 to Week 12, although the differences were not significant in the secondary analysis using the t-test. Individual patient changes from baseline to Week 12 in CMT are presented in Figure 4.

Representative imaging pre- and post-treatment from patients treated with OCS-01 are presented in Figure 5.

In an exploratory post-hoc analysis, changes from baseline in both BCVA and CMT were summarized according to baseline visual acuity, using the BCVA criteria ≤65 letters or >65 letters (corresponding to ≤20/50 or >20/50 Snellen), as used in the analysis of the Diabetic Retinopathy Clinical Research Network (DRCR.net) Protocol T data (Wells et al., 2016). Both BCVA and CMT showed greater improvements from baseline in patients with baseline BCVA ≤65 letters. CMT showed greater reduction with OCS-01 than vehicle in both baseline BCVA subgroups. Using criteria of baseline BCVA ≤60 letters and >60 letters, a similar pattern was observed (Figure 6). It should be noted that the sample sizes in the ≤60 letters subgroup were small (27 patients for OCS-01 and seven patients for vehicle), so these results should be interpreted with caution.

3.2 | Safety outcomes

At baseline, IOP was <30 mmHg in all patients in both treatment groups (median baseline values were 16 mmHg in the OCS-01 group, 15 mmHg in the vehicle group). Changes from baseline in IOP at each visit up to Week 12 were greater in the OCS-01 group (median changes from baseline in the study eye of zero at all time points in the vehicle group, ranging from 1 to 3 mmHg at different time points in the OCS-01 group). Mean changes from baseline in the OCS-01 group ranged from 1.17 mmHg at Week 2 to 4.53 mmHg at Week 12. At Week 12, 14/99 (14.1%) patients in the OCS-01 group had increases of ≥10 mmHg from baseline. No such increases were observed in the vehicle group at any visit. At Week 16, 4 weeks after the end of treatment, IOP had normalized in the OCS-01 group: median changes from baseline were zero in both treatment groups, and only a single patient (1%) in the OCS-01 group showed a ≥10 mmHg increase

TABLE 1 Baseline demographic and clinical characteristics (ITT population)

	OCS-01 (*N* = 99)	Vehicle (*N* = 45)	Overall (*N* = 144)
Age (years)			
n	99	45	144
Mean (SD)	63.6 (9.50)	66.1 (9.92)	64.4 (9.67)
Median (Min, Max)	64.0 (33, 85)	69.0 (36, 80)	65.0 (33, 85)
Age category (years), *n* (%)			
<50	9 (9.1)	4 (8.9)	13 (9.0)
50–70	60 (60.6)	21 (46.7)	81 (56.3)
≥70	30 (30.3)	20 (44.4)	50 (34.7)
Gender, *n* (%)			
Male	64 (64.6)	28 (62.2)	92 (63.9)
Female	35 (35.4)	17 (37.8)	52 (36.1)
Race, *n* (%)			
Asian	1 (1.0)	0	1 (0.7)
Caucasian	98 (99.0)	45 (100)	143 (99.3)
ETDRS BCVA letter score			
n	99	45	144
Mean (SD)	63.0 (9.78)	65.8 (8.25)	63.9 (9.39)
Median (Min, Max)	66.0 (30, 77)	68.0 (35, 76)	67.0 (30, 77)
Central macular thickness			
n	99	45	144
Mean (SD)	471.8 (140.18)	448.5 (117.80)	464.5 (133.61)
Median (Min, Max)	424.0 (234, 896)	413.0 (241, 712)	422.5 (234, 896)
Intraocular pressure			
n	99	45	144
Mean (SD)	15.3 (3.02)	14.7 (3.66)	15.1 (3.23)
Median (Min, Max)	16.0 (8, 24)	15.0 (7, 22)	15.5 (7, 24)
Diabetes mellitus type, *n* (%)			
Type 1	11 (11.1)	1 (2.2)	12 (8.3)
Type 2	86 (86.9)	44 (97.8)	130 (90.3)
Not Stated	2 (2.0)	0	2 (1.4)
Years of diabetes mellitus			
n	48	23	71
Mean (SD)	15.78 (11.645)	15.17 (7.920)	15.58 (10.529)
Median (Min, Max)	15.19 (0.9, 48.9)	15.91 (0.9, 27.6)	15.87 (0.9, 48.9)
Years of diabetic macular edema			
n	99	45	144
Mean (SD)	1.20 (1.168)	1.60 (2.506)	1.33 (1.704)
Median (Min, Max)	0.88 (0.016, 7.135)	1.01 (0.025, 16.723)	0.95 (0.016, 16.723)

from baseline. Seven patients in the OCS-01 group received topical ocular medication due to increased IOP, and all responded to treatment.

The results of slit lamp biomicroscopy and dilated indirect ophthalmoscopy did not show major differences between treatment groups.

Treatment emergent adverse events (AEs) were reported in a higher proportion of patients in the OCS-01 group (70/99, 70.0%) than the vehicle group (24/45, 53.3%). The most frequent AE in the active treatment group was IOP increase (common ocular AEs are summarized in Table 4). This was the only AE that was much more frequent in the OCS-01 group than in the vehicle group. No cases of IOP increase were considered to be severe, but two patients discontinued due to these AEs, which were the only ocular AEs leading to discontinuation. All cases of IOP increase were considered to be treatment-related. The only ocular AE reported as severe was diabetic macular edema (i.e. worsening of DME), reported in 1/99 (1.0%) patient in the OCS-01 group. Other common AEs, which occurred in both treatment groups at similar rates, were influenza, nasopharyngitis, and diabetic retinal edema. No other AEs were reported in more than 5% of patients in either treatment group.

Serious adverse events (SAEs) were reported in 11/99 (11.1%) patients in the OCS-01 group and 1/45 patients (2.2%) of the vehicle group. Only one patient experienced an ocular SAE: this was retinal detachment, in a patient

TABLE 2 Statistical analysis of change from baseline to week 12 in study eye ETDRS BCVA letters using multiple imputation (ITT population)

	OCS-01 (*N* = 99)	Vehicle (*N* = 45)	*p*-value
Number of patients included in model	99	45	
Effects			
Treatment			0.1258
ETDRS BCVA letters at Baseline			0.1721
LS Mean			
Estimate (SE)	2.62 (0.7582)	1.04 (1.1113)	
Two-sided (70% CI)	(1.831, 3.403)	(−0.115, 2.189)	
Two-sided (90% CI)	(1.369, 3.865)	(−0.792, 2.865)	
Two-sided (95% CI)	(1.129, 4.104)	(−1.142, 3.216)	
Difference in LS Means			
DexNP – Vehicle	1.58		0.1258
Two-sided (70% CI)	(0.151, 3.009)		
Two-sided (90% CI)	(−0.688, 3.849)		
Two-sided (95% CI)	(−1.124, 4.284)		
Student's two-sample T-test			
Mean difference	1.75		0.0993
Two-sided (70% CI)	(0.340, 3.168)		
Two-sided (90% CI)	(−0.491, 3.999)		
Two-sided (95% CI)	(−0.922, 4.430)		

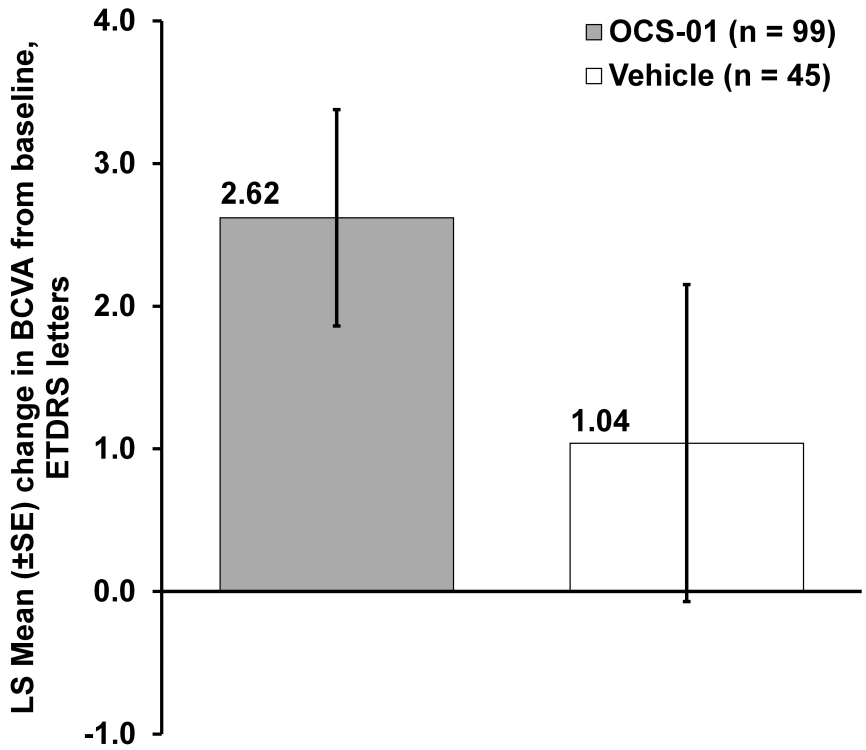

FIGURE 2 Least squares mean change from baseline to week 12 in ETDRS BCVA letter score. Between-group difference 1.58 letters (70% CI, 0.15–3.01), $p = 0.1258$. Superiority of OCS-01 over vehicle is claimed when the one-sided p-value is <0.15 and the difference in mean change from baseline in BCVA is greater than zero. ITT population, multiple imputations for missing data.

in the OCS-01 group. Most of the SAEs affected the cardiovascular system: in the OCS-01 group, two patients had cardiac failure, two had atrial fibrillation, and one had peripheral arterial occlusive disease. One patient in the vehicle group had a myocardial infarction. Other SAEs were diabetes mellitus (referring to worsening of diabetes), diabetic ulcer, influenza, urinary tract infection, and respiratory distress (one patient each in the active treatment group). No SAEs were considered by the investigators to be related to study treatment. Two patients, both in the OCS-01 group, died during the study. These were a 71-year-old Caucasian male patient, with a

TABLE 3 Statistical analysis of change from baseline in study eye central macular thickness using multiple imputation (ITT population)

	OCS-01 (*N* = 99)	Vehicle (*N* = 45)	*p*-value
Number of patients included in model	99	45	
Effects			
Treatment			0.0115
Central Macular Thickness at Baseline			<0.001
LS mean			
Estimate (SE)	−53.68 (8.9723)	−16.87 (13.4459)	
Two-sided (70% CI)	(−62.980, −44.380)	(−30.812, −2.935)	
Two-sided (90% CI)	(−68.441, −38.920)	(−38.997, 5.250)	
Two-sided (95% CI)	(−71.269, −36.091)	(−43.238, 9.491)	
Difference in LS means			
OCS-01 – Vehicle	−36.81		0.0115
Two-sided (70% CI)	(−53.576, −20.038)		
Two-sided (90% CI)	(−63.422, −10.191)		
Two-sided (95% CI)	(−68.524, −5.090)		
Student's two-sample T-test			
Mean difference	−43.29		0.0064
Two-sided (70% CI)	(−61.321, −25.250)		
Two-sided (90% CI)	(−71.910, −14.660)		
Two-sided (95% CI)	(−77.396, −9.174)		

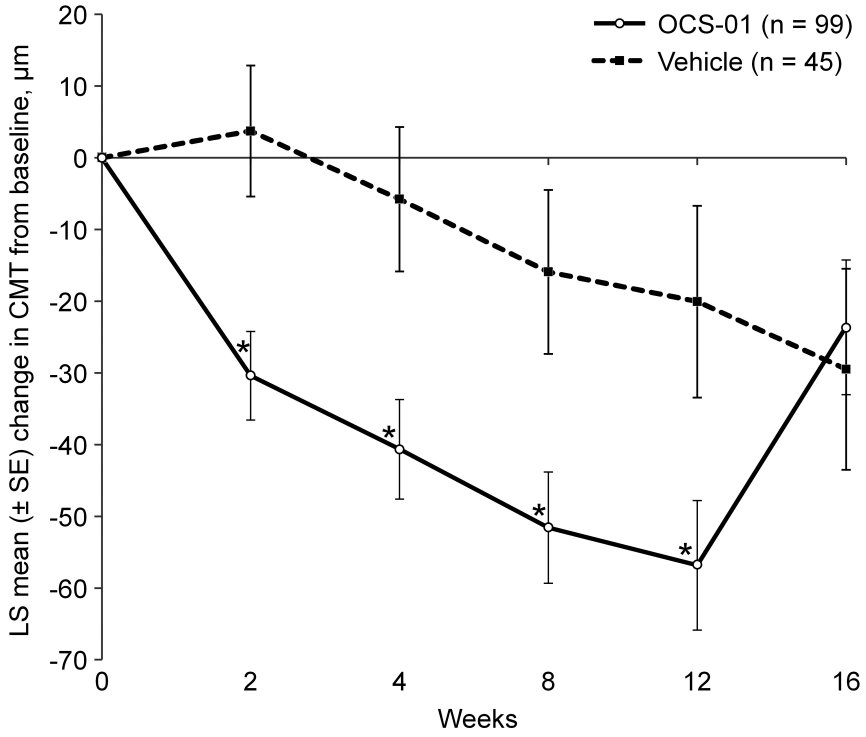

FIGURE 3 LS mean change from baseline in CMT, ITT population, observed data. *$p<0.05$, **$p<0.01$, ***$p<0.005$ vs vehicle, ANCOVA using baseline CMT as a covariate. Week 12 = end of treatment. LS mean (SE) baseline CMT: OCS-01, 471.8 (140.2) µm; vehicle, 448.5 (117.8) µm. ITT population, observed data only.

history of hypertension, who died on Day 5 due to sudden cardiac death and heart failure, and a 61-year-old Caucasian male patient, a type 1 diabetic with a history of hypertension, hypercholesterolemia, macroangiopathy, and nephropathy who died on Day 57, with the event reported as "death". Neither of the two deaths were suspected to be related to study treatment.

4 | DISCUSSION

Current therapy for diabetic macular edema depends primarily on the use of intravitreally administered therapies. These include inhibitors of VEGF (Browning et al., 2018), which have been demonstrated to be highly effective in both increasing visual acuity and reducing

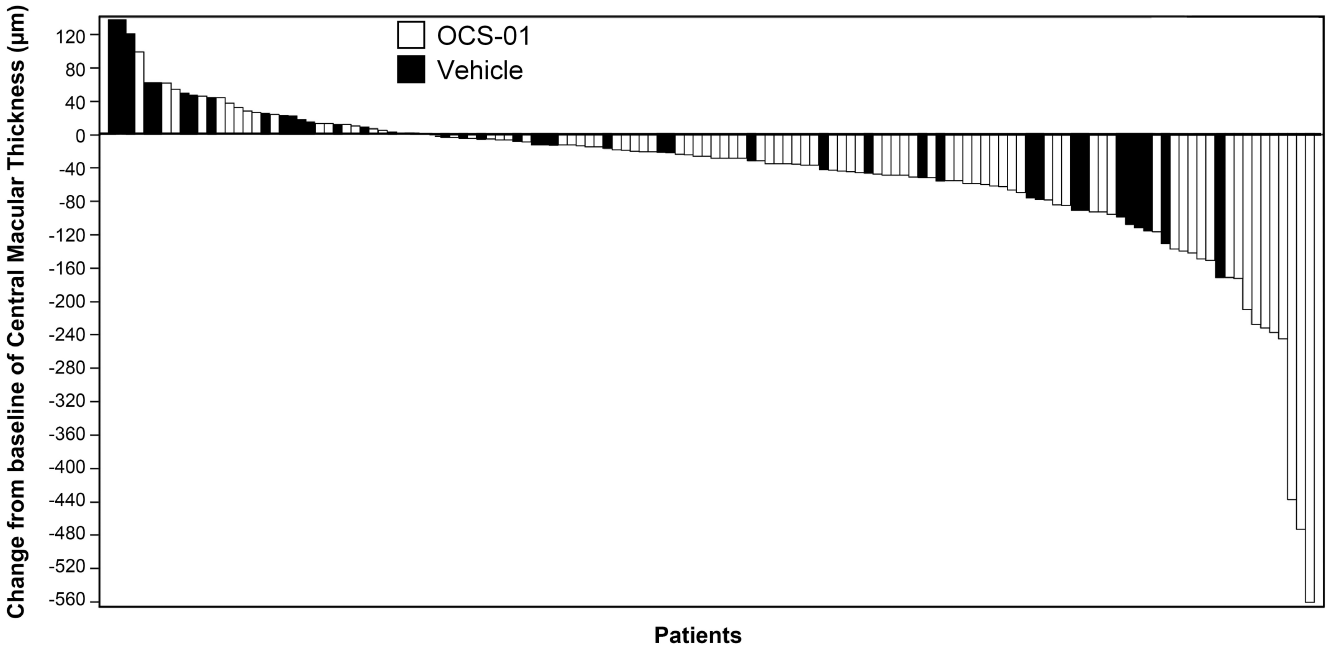

FIGURE 4 Individual patient changes from baseline in CMT (µm) from baseline to week 12, ITT population.

CMT (Cai & Bressler, 2017) although not all patients respond to treatment (Browning et al., 2018; Pham et al., 2019; Ramu et al., 2015). Some meta-analyses (Avery & Gordon, 2016; Ueta et al., 2014) have suggested there may be an increased risk of arterial thromboembolic events following intravitreal use of VEGF inhibitors, particularly over long periods, although others have not identified increased risks of major cardiovascular events (Ntjam et al., 2021).

Intravitreal corticosteroids, most commonly implants containing dexamethasone (Ozurdex®; Allergan, Irvine, CA, USA) or fluocinolone acetonide (Iluvien®; Alimera, Alpharetta, GA, USA) are used in patients who do not respond to anti-VEGF therapies (Urbančič & Gardašević, 2019). These implants release drug over a period of up to 6 months or up to 3 years, respectively, following implantation (Fusi-Rubiano et al., 2018). In common with other forms of corticosteroid therapy for ophthalmologic conditions, intravitreal corticosteroid implants are associated with IOP increases, potentially leading to glaucoma, and cataract formation (Boyer et al., 2014; Fusi-Rubiano et al., 2018; Phulke et al., 2017; Tripathi et al., 1999; Urbančič & Gardašević, 2019).

Intravitreal treatment carries the risk of complications including infections, retinal detachments, haemorrhages and cataracts, and places considerable demands on patients, caregivers, and health care providers. There is a requirement for both highly skilled personnel and specialized facilities to perform the procedure. Burdens associated with intravitreal therapies include expense (and in some countries difficulties with reimbursement), anxiety, discomfort and the time (including travelling time) required for appointments (Spooner et al., 2019). These factors may lead patients and clinicians to extend intervals between injections, which reduces the effectiveness of therapy as compared to that in clinical trials (Ciulla et al., 2021; Holekamp et al., 2018). For some patients, access to intravitreal therapies may be limited by geography if they live in rural areas where facilities for intravitreal treatment are not available without long journeys. Effective topical therapy for DME could provide a more convenient, easily accessible, less expensive, safer, less burdensome, and more flexible alternative to intravitreal treatment.

Here, we describe the first vehicle-controlled study with topical OCS-01 dexamethasone ophthalmic suspension in DME. CMT showed a statistically significantly greater decrease from baseline to Week 12 in eyes receiving OCS-01 than vehicle-treated eyes, and mean CMT was statistically significantly lower in the active treatment group at all post-baseline visits up to Week 12. After discontinuation of OCS-01, CMT values began to return towards baseline over the 4 week follow-up period, demonstrating an on–off treatment pattern that further supports a therapeutic effect after topical dosing. In the primary efficacy analysis, the difference between OCS-01 and vehicle in change from baseline in ETDRS BCVA letters at Week 12 showed a trend for improved BCVA. Higher proportions of patients gained ≥10 or ≥15 ETDRS BCVA letters in the OCS-01 group than the vehicle group.

It should be noted that no formal studies to identify the optimum dose or duration of OCS-01 treatment have yet been undertaken, and while the efficacy observed in the current proof of concept study indicates that therapeutic concentrations of dexamethasone were achieved in the posterior segment with the dosing regimen used in this study, the optimal dose for the treatment of DME might be higher.

Although the observed improvement in BCVA in this study met the prospectively specified criteria for superiority to vehicle, it was not as large as that reported in studies with intravitreal VEGF inhibitors (Korobelnik et al., 2014; Nguyen et al., 2012) or corticosteroid implants (Boyer et al., 2014; Ramu et al., 2015). In those studies, however, baseline BCVA was lower, and in some cases baseline duration of DME was longer, than in the current study. Greater therapeutic effect in

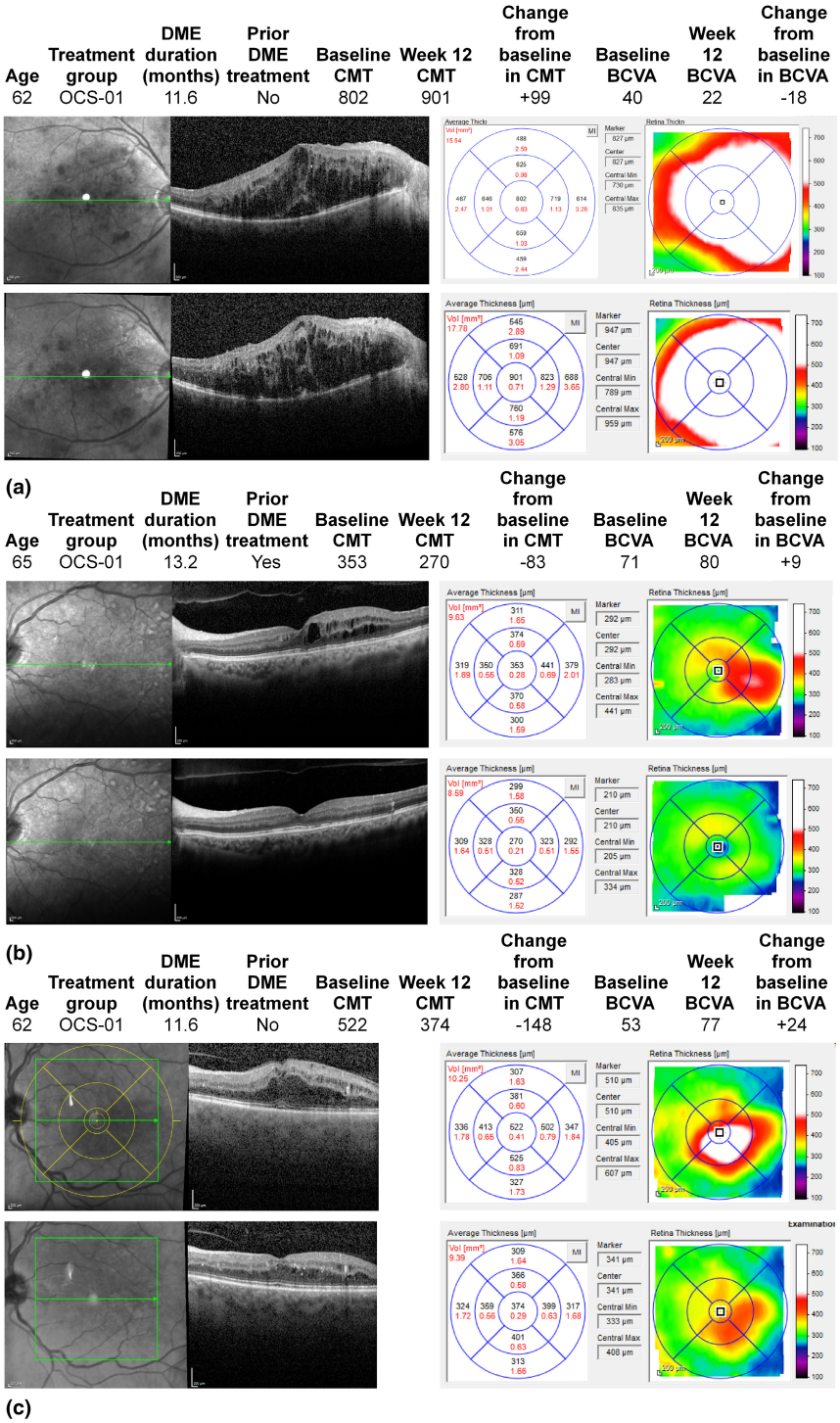

FIGURE 5 Representative OCT imaging and BCVA for patients treated with OCS-01. Patient (a) showed an increase in CMT (of 99 μm) from baseline to week 12, accompanied by a decrease of 18 letters in BCVA; no improvement is apparent on imaging. In patients (b) and (c) clear improvement is visible on imaging, with a decrease in CMT accompanied by improvements in BCVA.

patients with lower baseline visual acuity has been observed previously (Dugel et al., 2016; Wells et al., 2016), and it has been suggested that a plateau effect, in which the possible BCVA gain has an upper limit, may be observed with some VEGF inhibitors (Dugel et al., 2016). In post-hoc analyses in the current study, both CMT and BCVA showed greater improvements and greater differences between OCS-01 and vehicle in patients with lower baseline visual acuity (≤65 or ≤60 letters BCVA). In these subgroups, changes from baseline in BCVA and CMT were similar to those observed in a Phase III study with Ozurdex corticosteroid implants (Boyer et al., 2014). It is likely, therefore, that if entry criteria had included lower baseline BCVA, as in some studies with intravitreal therapies (Boyer et al., 2014; Urbančič & Gardašević, 2019), a larger improvement in baseline BCVA would have been seen across the study population.

DME is a disease with a large range of response to treatment, and as this was a Phase 2 study with a relatively small patient population, CMT rather than visual acuity can be considered a more objective way to evaluate the potential effectiveness of OCS-01 in achieving therapeutic concentrations in the retina. Data from

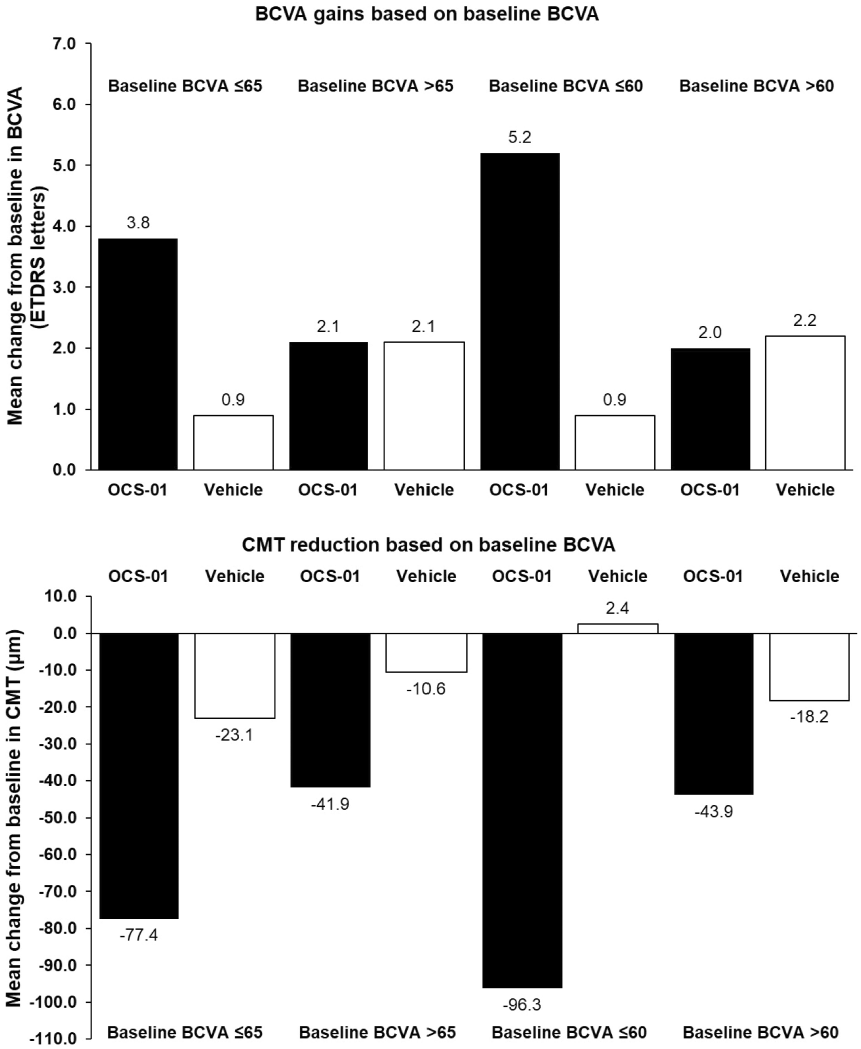

FIGURE 6 Changes from baseline to week 12 in CMT and ETDRS BCVA by baseline BCVA. Post-hoc analysis of changes from baseline to week 12 in BCVA (ETDRS letters) and CMT (µm), by baseline BCVA subgroups (≤65 ETDRS letters and >65 ETDRS letters, ≤60 ETDRS letters and >60 ETDRS letters).

TABLE 4 Most frequent ocular treatment emergent adverse events (those occurring in at least 2% of patients in the OCS-01 group) by system organ class and preferred term (safety population)

	OCS-01 (*N* = 99)		Vehicle (*N* = 45)	
System organ class preferred term	Number (%) of patients	Number of events	Number (%) of patients	Number of events
At least one TEAE	47 (47.5)	69	16 (35.6)	28
Eye disorders	33 (33.3)	41	15 (33.3)	24
Diabetic retinal edema	6 (6.1)	6	3 (6.7)	3
Eye irritation	3 (3.0)	3	0	0
Ocular hypertension	3 (3.0)	3	1 (2.2)	1
Visual acuity reduced	3 (3.0)	3	2 (4.4)	2
Cataract	2 (2.0)	2	1 (2.2)	1
Diabetic retinopathy	2 (2.0)	3	0	0
Visual acuity reduced transiently	2 (2.0)	2	0	0
Vitreous haemorrhage	2 (2.0)	2	0	0
Investigations	24 (24.2)	26	1 (2.2)	1
Intraocular pressure increased	24 (24.2)	26	0	0

the Protocol T study suggest at best a moderate correlation between changes in macular thickness and improvements in visual acuity (Bressler et al., 2019). Consistent with those observations, in this study, the decrease in CMT was more striking than the observed improvement in visual acuity, although both showed

statistically significant differences between OCS-01 and vehicle.

Assessment of the benefit–risk balance for a topical therapy is clearly different from that for an invasive intravitreal treatment. Increased IOP was the most frequent adverse event observed in the OCS-01 group. As noted above, increased IOP is a well-known side-effect of corticosteroid treatment, whether administered by topical ocular, periocular, intravitreal, or systemic routes. IOP decreased quickly after the end of treatment, suggesting that any IOP increase observed during OCS-01 treatment for DME should rapidly resolve after discontinuation of treatment. The ability to stop topical treatment quickly if IOP increases is in contrast to intravitreal corticosteroid implants, which are designed for long-term release of drug and cannot easily be removed. Other adverse events reported were not unexpected in the diabetic population studied, many of whom were elderly.

Diabetic macular edema is a chronic disease where patients present with a range of symptoms, needs and circumstances over time. An effective, well-tolerated topical therapy would provide an additional and differentiated intervention for the management of DME. Topical therapy differs from existing therapies in that it is non-invasive, readily tailored to patient needs in terms of dose and frequency, and its administration does not impose an office visit burden on patients or healthcare systems. These differences create useful potential synergies in DME management between the use of topical therapies and injectables or implants. Topical therapies can be used in situations where intravitreal treatment is not accessible, feasible or desired.

For example, after diagnosis of DME it may take weeks before patients can access intravitreal treatment, waiting until there is availability at properly equipped retina centers. For corticosteroids, implant and topical formulations have different modalities and time duration that can complement each other. Eye drops can be used before implants and to continue therapy as the effects of implants wane. Topical treatment would also help to meet eye care professionals' need for more flexibility in customizing their DME therapy according to patients' specific circumstances, including access to treatment, and the individual balance of benefits and risks.

In summary, the current study demonstrated that topical ocular administration of OCS-01 was more effective than vehicle in the treatment of DME, particularly with respect to CMT reduction and also with a trend towards improvement in visual acuity and. Patients with lower baseline BCVA benefited more from treatment, as with other effective treatments. Apart from the expected increase in IOP, treatment was well-tolerated. Topical administration of this ophthalmic suspension containing solubilizing nanoparticle aggregates clearly resulted in therapeutic effects. A Phase 2/3 study is ongoing to confirm these findings in a larger patient population. This study demonstrated that topical therapies based on the cyclodextrin nanoparticle aggregate formulation technology can deliver therapeutic drug concentrations to the retina. Although the precise mechanism by which topically applied drugs reach the retina is unclear (and could be the basis of future studies), the use of this formulation clearly improves drug penetration relative to other topical preparations. The use of this platform, potentially carrying other drugs, may also lead to the development of additional topical alternatives for the treatment of other retinal diseases (Loftsson & Stefánsson, 2022).

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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