Clinical Trial Protocol: DX211

Protocol Title:	Efficacy and safety of dexamethasone nanoparticles eye drops in diabetic macular edema.
Protocol Number:	DX211
Study Phase:	Phase IIb
Investigational Product Name:	DexNP 15mg/mL
EudraCT Number:	2017-001172-36
Indication:	Diabetic Macular Edema
Duration of treatment:	12 weeks active treatment
Principal Investigator:	Dr. Michael Larsen, Copenhagen
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SYNOPSIS

Protocol Title:	Efficacy and safety of dexamethasone nanoparticles eye drops in diabetic macular edema.
Protocol Number: **EudraCT Number** **Principal Investigator**	DX211 2017-001172-36 Dr. Michael Larsen
Investigational Product:	Eye drops, DexNP 15 mg/mL, suspension Eye drops, Vehicle, suspension
Study Phase:	Phase IIb
Primary Objective(s):	The objective of this study is to evaluate the efficacy and safety of DexNP in the improvement of visual acuity in subjects with DME.
Secondary Objective(s):	Safety Morphologic changes Quality of Life
Endpoints:	Primary endpoint of the study is mean change in ETDRS BCVA letters at Week 12 compared to baseline. Secondary endpoints of the study are number of patients with BCVA improvements of ≥ 10 or 15 letters versus baseline, patients reaching 20/20 vision, central macular thickness on OCT, intraocular pressure, patient satisfaction.
Overall Study Design:	
Structure:	Multi-center, double-masked, randomized, vehicle controlled, prospective, parallel CT
Duration:	Maximum of 4 weeks of screening period, 12 weeks treatment until primary endpoint. Follow up without treatment for 4 weeks, total active study duration: 16 weeks.
Controls:	Vehicle.
Dosage/Dose Regimen/ Instillation/Application/Use:	Self-administrations. 1 drop into the study eye three times a day (8 hourly) for 12 weeks. Randomization is 2:1 (DexNP eye drops vs. Vehicle eye drops)
Summary of Visit Schedule:	Study visit schedule • Screening Visit (Day -1 to -28) • Baseline (Day 1) • Week 2 • Week 4 • Week 8 • Week 12 - Endpoint assessment

	• Week 16 - final visit Visit window is ± 3 days
Measures Taken to Reduce Bias:	Randomization will be used to avoid bias in the assignment of subjects to treatment, to increase the likelihood that known and unknown subject attributes (e.g., demographics and baseline characteristics) are evenly balanced across treatment groups, and to enhance the validity of statistical comparisons across treatment groups. Double-masked treatment will be used to reduce potential of bias during data collection and evaluation of clinical endpoints
Study Population Characteristics:	
Number of Subjects:	96
Estimated number of sites	About 13 clinical study sites are planned
Condition/Disease:	Diabetic macular edema of less than 3 years duration since diagnosis with VA 73-24 ETDRS letters, i.e. 20/40 to 20/320.
Inclusion Criteria:	Subjects must: a) Have DME of less than 3 years duration since diagnosis with presence of intraretinal and/or subretinal fluid in the study eye, with central macular thickness, CMT, of ≥ 310μm by SD-OCT at baseline (Visit 2) (as measured by the Investigator) b) Have definite retinal thickening in the study eye due to DME involving the central macula based on the Investigator's clinical evaluation and by SD-OCT; Note: If the DME consists of circumscribed, focal leakage that the evaluating Investigator believes should be treated with laser and no other treatments, the eye is not eligible to be a study eye. c) Have an ETDRS BCVA letter score ≤ 73 (Snellen 20/40) and ≥ 24 (Snellen 20/320) in the study eye at baseline (Visit 2) d) Have a documented diagnosis of type 1 or type 2 diabetes mellitus and a glycosylated hemoglobin A1c (HbA1c) of ≤ 12.0% (≤108mmol/mol) at Visit 1 e) Have a negative urine pregnancy test at Visit 1, if female of childbearing potential those who have experienced menarche and who are not surgically sterilized [bilateral tubal ligation, hysterectomy or bilateral oophorectomy] or post-menopausal [12 months after last menses]) and must use adequate birth control throughout the study period.

	Adequate birth control is defined as hormonal – oral, implantable, injectable, or transdermal contraceptives; mechanical – spermicide in conjunction with a barrier such as condom or diaphragm; intrauterine device (IUD); or surgical sterilization of partner. For non-sexually active females, abstinence may be regarded as an adequate method of birth control; f) Agree to not participate in another interventional study after providing informed consent and until the study is completed g) Provide written informed consent prior to any study procedure being performed and subject is as per the discretion of the Investigator, considered to be able to comply with the requirements of the protocol h) Be 18-85 years of age at baseline (Visit 2), of either sex and any race or ethnicity
Exclusion Criteria:	<u>Subjects must not:</u> a) Have macular edema considered to be due to a cause other than DME; Note: an eye should not be considered eligible if: (1) the macular edema is considered to be related to ocular surgery such as cataract extraction;(2) clinical exam and/or OCT suggest that vitreoretinal interface abnormalities disease (e.g., a taut posterior hyaloid or epiretinal membrane) is the primary cause of the macular edema, or (3) the macular edema is considered to be related to another condition such as age-related macular degeneration, uveitis, retinal vein occlusion, or drug toxicity b) Have a decrease in BCVA due to causes other than DME (e.g., foveal atrophy, pigment abnormalities, dense subfoveal hard exudates, previous vitreoretinal surgery, central serous retinopathy, non-retinal condition, substantial cataract, macular ischemia) that is likely to be decreasing BCVA by three lines or more (i.e., cataract would be reducing acuity to 20/40 or worse if eye was otherwise normal) c) Have significant macular ischemia, as assessed by the investigator, which in the opinion of the investigator would prevent gain in visual acuity. d) Have any other ocular disease that may cause substantial reduction in BCVA, including, retinal detachment,

	epiretinal membrane, vitreous hemorrhage or fibrosis involving the macula in the study eye, ocular inflammation (uveitis), other retinal inflammatory or infectious diseases e) Have active peri-ocular or ocular infection (e.g., blepharitis, keratitis, scleritis, or conjunctivitis) f) Have a history of non-infectious uveitis g) Have high myopia in study eye (-8 diopter or more correction) h) Must NOT wear contact lenses during the 12-week active treatment study period i) Have a history of any ocular surgery within 3 months prior to Visit 1 in the study eye; j) Have a history of YAG laser capsulotomy within 3 months prior to Visit 1 in the study eye;; k) Have a history of panretinal scatter photocoagulation (PRP) or focal laser within 3 months prior to Visit 1 or an anticipated need for PRP during the course of the study in the study eye; l) Have a history of prior IVT, subtenon, or periocular, non-sustained release, steroid therapy within 3 months prior to Visit 1 (e.g., triamcinolone) in the study eye; m) Have a history of intravitreal sustained release dexamethasone therapy within six months prior to Visit 1 in the study eye; n) Have a history of intravitreal sustained release fluocinolone within three years prior to Visit 1 in the study eye; o) Have a history of prior treatment of intravitreal (IVT) aflibercept within 8 weeks and ranibizumab/bevacizumab within 6 weeks of Visit 1 in the study eye; p) Have a history of prior treatment for DME with any other (than previously listed) approved treatment which is not labeled for DME within one year prior to Visit 1 in the study eye; q) Have high-risk proliferative diabetic retinopathy (PDR), defined in the ETDRS study as at least one of the following: • New vessels within one disc diameter of the optic disc (NVD) $\geq$ 1/3 disc area; • Any NVD with vitreous or pre-retinal hemorrhage;

	• New vessels elsewhere in the retina (NVE) ≥ ½ disc area and pre-retinal or vitreous hemorrhage; r) Have uncontrolled ocular hypertension or glaucoma in either eye, defined as intraocular pressure (IOP) ≥ 22 mmHg on more than 1 IOP lowering medications at Visit 1 s) Have poor media clarity, pupillary constriction (i.e., senile miosis), or lack cooperation that, in the opinion of the evaluating Investigator, would interfere with any study procedures, evaluations, or interpretation of data t) Have any ocular condition that, in the opinion of the Investigator, may require intervention, interfere with evaluations of efficacy or safety or interpretation of data collected in the study u) Have an estimated Glomerular Filtration Rate (eGFR) of < 15mL/min/1.73m2 as per CKD-EPI equation at Visit 1 v) Have a systolic blood pressure < 90 or > 160 mmHg and / or a diastolic blood pressure > 100 mmHg at Visit 1 and 2 w) Have a known or suspected hypersensitivity to any components of the test agent x) Be a female subject who is pregnant or lactating or has a positive pregnancy test at Visit 1 or has been pregnant within 6 months before Visit 1 or breast-feeding within 3 months before Visit 1, or planning to become pregnant within 9 months from Visit 1 y) Have participated in any interventional clinical study or been treated with any investigational drugs within 30 days or 5 half-lives of the investigational drug, whichever is longer, prior to the initiation of Visit 1 z) Have any other condition, which in the opinion of the evaluating Investigator, precludes the subject's participation in the trial
Study Formulations and Formulation Numbers:	DexNP and DexNP Vehicle
Evaluation Criteria:	A complete eye examination will be performed. • Visual acuity will be measured on ETDRS chart at 4m with best corrective lenses. • Intraocular pressure (IOP) will be measured with Goldmann tonometry or I-CARE tonometry (standardized in each center and the same device to be used for a given patient

	throughout the study) and the eye examined by slitlamp. • Fundus is examined through dilated pupils (i.e. using Tropicamide hydrochloride 1% and phenylephrine 2.5%), fundus photographs obtained (optional) and ocular coherence tomography (SD OCT preferably using Heidelberg Spectralis) performed to measure retinal thickness in the central macula. • In phakic eyes cataract formation will be graded using the LOCS III system.
Safety Measures:	Irritation will also be evaluated by slit lamp biomicroscopy, fluorescein staining when deemed necessary.
Other:	Quality of life as assessed by NEI VFQ-25 at baseline and 12 weeks.

General Statistical Methods and Types of Analyses

Hypothesis

The statistical hypotheses for the primary endpoint of mean change from baseline BCVA ETDRS letters in the study eye at Week 12 are as follows:

H0: The difference between study eyes treated with DexNP and study eyes treated with Vehicle (DexNP – Vehicle) in the mean change from baseline ETDRS BCVA letters to Week 12 (Week 12 – Baseline) ≤ 0.

H_1: The difference between study eyes treated with DexNP and study eyes treated with Vehicle (DexNP – Vehicle) in the mean change from baseline ETDRS BCVA letters to Week 12 (Week 12 – Baseline) > 0.

The study will be considered a success if H_0 is rejected in favor of H_1 and superiority of DexNP to Vehicle is claimed.

Methods of Analysis

Summaries for continuous variables will include the sample size, mean, standard deviation, median, minimum, and maximum. Summaries for discrete variables will include frequencies and percentages. Differences between treatment groups will be calculated as DexNP – Vehicle and change from baseline will be calculated as follow-up visit – baseline. The baseline visit will be defined as the last non-missing measure prior to initiation of investigational treatment. All efficacy analyses will use a one-sided alpha = 0.15 test unless otherwise stated.

All summaries will be presented by treatment group and where appropriate by visit.

Interim analysis

An interim analysis will be conducted by an independent biostatistician when approximately 50% of the subjects (44 subjects) complete Week 12.

Summary of Known and Potential Risks and Benefits to Human Subjects

Possible risks for the patient are side effects of dexamethasone, which is a registered and widely used drug. Possible side effects from dexamethasone are cataract formation, increased IOP and infection.

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List of Abbreviations

AE	adverse event
API	active pharmaceutical ingredient
BCVA	best-corrected visual acuity
CAC	conjunctival allergen challenge
CFR	Code of Federal Regulations
CI	confidence interval
CMT	Central Macular Thickness
CRA	clinical research associate
CRF	case report form
CRO	contract research organization
D	Diopter
DME	Diabetic Macular Edema
ERB	Ethical Review Board
ETDRS	Early Treatment of Diabetic Retinopathy Study
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IOP	intraocular pressure
IRB	institutional/independent review board
ITT	intent to treat
LOCF	last observation carried forward
logMAR	logarithm of the minimum angle of resolution
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Milligram
mL	Milliliter
µm	micrometer
mmHg	millimeters of mercury
N.A.	Not Applicable
NEI	National Eye Institute
OD	right eye
OS	left eye
PP	per protocol
SAE	serious adverse event
SD	standard deviation
SD-OCT	Spectral Domain Optical Coherence Tomography
SOP	standard operating procedures

TID	three times daily
USP	United States Pharmacopeia
VA	visual acuity
w/v	weight per unit volume

1 INTRODUCTION

Anti-inflammatory or anti-angiogenic drugs play an ever increasing role in the treatment of diabetic macular edema (DME). In order to reach the retina, corticosteroids (Schwartz et al. 2016) and/or vascular endothelial growth factor antibodies (Lally et al. 2016) must be injected into the vitreous cavity or slow release drug capsules surgically implanted into the eye (Nguyen et al. 2010; Rensch et al. 2010; Steijns et al. 2010; Bandello et al. 2011; Boyer et al. 2011). Intravitreal injections and intravitreal implantation are a surgical approach in drug delivery, and therefore run the risk of surgical complications, including infection, hemorrhages and cataract and place a huge demand on eye care resources. In addition, anti VEGF intravitreal injections significantly increase the risk of cardiovascular events and death (Avery & Gordon 2016). A non-invasive drug delivery platform with steroid eye drops, reaching the back of the eye to treat DME and other retinal diseases would circumvent most of these problems.

We have developed a drug delivery platform for ocular therapy. It is based on cyclodextrin nanoparticles that dissolve in the tear fluid to form water-soluble drug/cyclodextrin complex nanoparticles. Nanoparticulate 1.5% (w/v) dexamethasone/γ-cyclodextrin eye drops have been shown to effectively deliver the drug to the retina and vitreous humor in rabbits (Loftsson et al. 2007; Sigurdsson et al. 2007; Loftsson et al. 2008; Jansook et al. 2010). Other cyclodextrin based dexamethasone eye drop solutions have previously been tested in human patients and shown excellent penetrance into the anterior segment of the eye (Kristinsson et al. 1996; Saari et al. 2006).

Our earlier pharmacology studies in rabbits and humans demonstrated that the cyclodextrin nanoparticle dexamethasone eye drops reach the retina in human patients and thus should be therapeutically effective for retinal disease such as diabetic macular edema. We therefore embarked on the clinical trials of dexamethasone eye drops for topical treatment of diabetic macular edema, which demonstrated that our DexNP eye drops successfully treat DME.

In all, 60 patients have received DexNP eye drops in past clinical trials for up to 12 weeks and 101 patients have received earlier cyclodextrin eye drops containing dexamethasone. The DexNP eye drops were well tolerated and reached clinical efficacy comparable to intravitreal injections (in indirect comparisons).

Clinical trial #1 DME (Tanito et al. 2011): 19 patients treated with DexNP

Consecutive 19 eyes of 19 patients with DME received dexamethasone cyclodextrin eye drops 3 or 6 times a day for 4 weeks and then followed for 4 weeks without treatment. Visual acuity, intraocular pressure, and spectral domain optical coherent tomography-measured central macular thickness recordings were assessed at weeks 0 (baseline), 4, and 8. These parameters were compared using Bonferroni-corrected paired t-tests (Tanito et al. 2011).

At weeks 0, 4, and 8, LogMAR visual acuity (mean+/-SD) was 0.52+/-0.41, 0.37+/-0.40 (p=0.0025 vs baseline), and 0.45+/-0.41, respectively; central macular thickness (μm) was 512+/-164, 399+/-154 (p=0.0016 vs baseline), and 488+/-172 (p=0.0116 vs week 4), respectively; and intraocular pressure (IOP, mmHg) was 15.2+/-3.1 at baseline and 17.4+/-4.2 at 4 weeks (p=0.0015 vs baseline), and 15.8+/-4.0 at 8 weeks, respectively. At week 4, in 12 of 19 eyes (63%) central macular thickness had decreased more than 10 %, and the mean change was - 20% (-65% to +10%). In 14 of 19 eyes (74%) visual acuity (LogMAR) had improved more than 0.1 at week 4.

No subjects showed severe adverse effects related to the eye drops. Only modest increase in IOP was observed.

Clinical trial #2: DME (Ohira et al. 2015): 12 patients treated with DexNP

This clinical trial (Ohira et al. 2015) was a randomized, controlled trial topical 1.5% dexamethasone γ-cyclodextrin nanoparticle eye drops (DexNP) vs. posterior subtenon injection of triamcinolone acetonide in diabetic macular oedema (DME). This trial ran for 16 weeks with DexNP applied for 12 weeks.

In this prospective, randomized, controlled trial, 22 eyes of 22 consecutive patients with DME were randomized to (i) topical treatment with DexNP ×3/day (weeks 1-4), ×2/day (weeks 5-8) and ×1/day (weeks 9-12) and no eye drops weeks 13-16 or (ii) one posterior subtenon injection of 20 mg triamcinolone acetonide. Study visits were at baseline and 4, 8, 12 and 16 weeks.

The logMAR (Snellen) visual acuity (mean ± SD) improved significantly with DexNP from 0.41 ± 0.3 (Snellen 0.39) to 0.32 ± 0.25 (0.48) and 0.30 ± 0.26 (0.50) at 4 and 8 weeks, respectively. One-third of the DexNP group improved more than 0.3 logMAR units. For triamcinolone, logMAR changed significantly from 0.42 ± 0.28 (0.38) at baseline to 0.32 ± 0.29 (0.48) at 4w and 0.33 ± 0.37 (0.47) at 12w. The central macular thickness (CMT) decreased significantly with DexNP from 483 ± 141 μm to 384 ± 142 μm at 4w and 342 ± 114 μm at 8w (Figure 1). For triamcinolone, CMT decreased significantly at all time-points: 494 ± 94 μm, 388 ± 120, 388 ± 145, 390 ± 136 and 411 ± 104 μm at 0, 4, 8, 12 and 16 weeks, respectively.

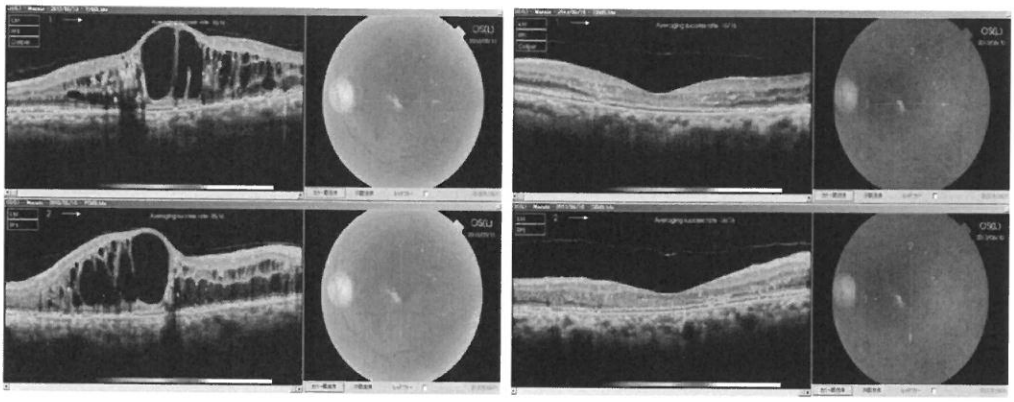

Figure 1: OCT images at baseline and after 4 weeks of DexNP TID in an eye with DME (Ohira et al. 2016)

There was a modest increase in intraocular pressure (IOP) at all time-points with DexNP while no increase was seen with triamcinolone. IOP was 14 ± 4 mmHg at baseline and rose an average of 5 ± 6 mmHg at 4 weeks, 6 ± 7mmHg at 8 weeks and 7 ± 7mmHg at 12 weeks. IOP returned to normal and was 1 ± 6mmHg higher than baseline at 16 weeks, i.e. 4 weeks after DexNP treatment was stopped.

Serum cortisol was mildly affected by both treatments. With DexNP Cortisol was 9.7 ± 3.7 at baseline and fell by 5.5 ± 5.1 at 4 weeks, 5.0 ± 4.2 at 8 weeks, 2.5 ± 4.5 at 12 weeks and 0.4 ± 2.5 at 16 weeks. Cortisol changed also in the triamcinolone injected group and the change was sustained longer. Here is was 14.2 ± 4.5 at baseline and fell by 3.1 ± 2.2 at 4 weeks,3.8 ± 4.8 at 8 weeks, 2.8 ± 3.3at 12 weeks and 3.5 ± 5.3 at 16 weeks.

HbA1c was unaffected. It was 7.05 ± 1.08 % at baseline and rose by 0.19 ± 0.80% at 12 weeks. The triamcinolone group was similar.

Topical DexNP significantly improve visual acuity and decrease macular thickness in patients with DME (Figure 2). The effect is similar to that of subtenon triamcinolone and that of ranibizumab (using indirect comparison with published data). A modest increase in IOP was seen with the nanoparticle eye drops, but IOP normalized after the discontinuation of treatment.

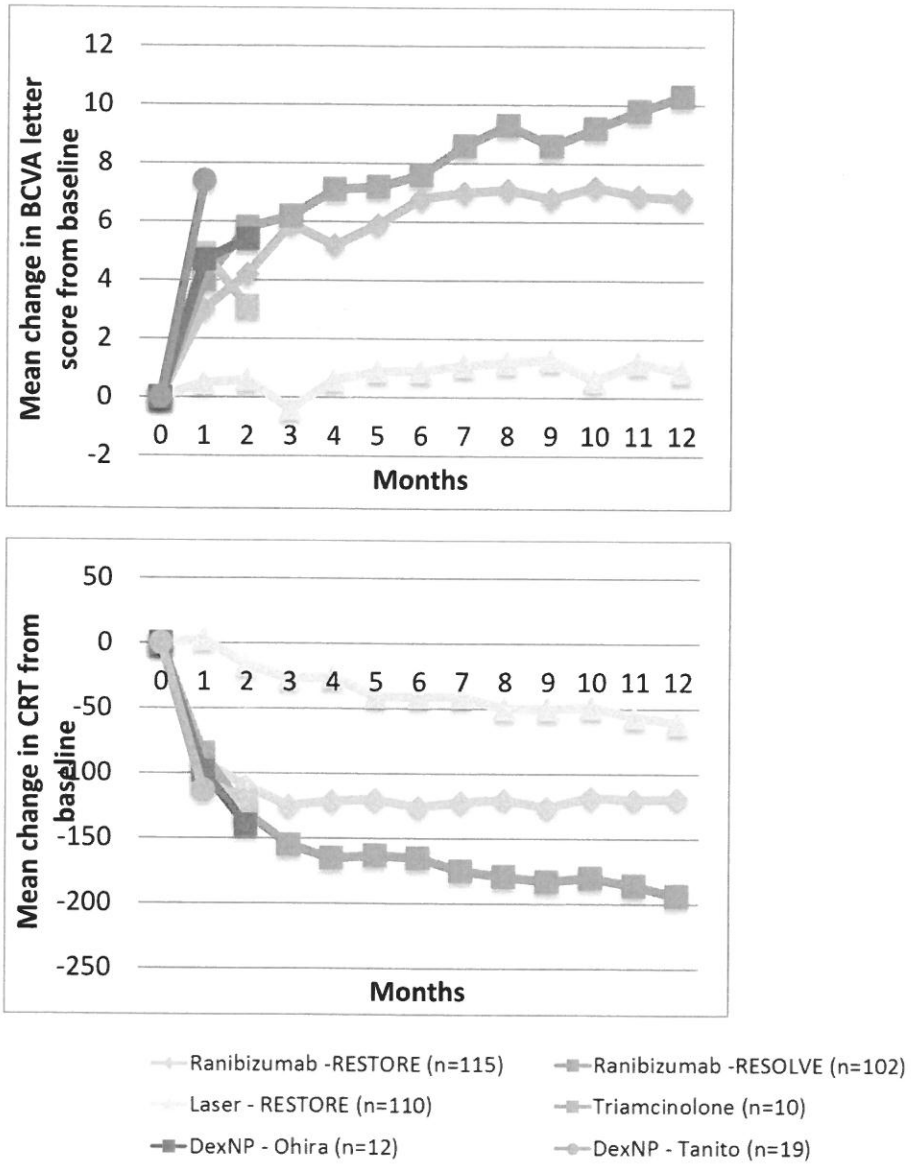

Figure 2: The data on visual acuity (above) and central retinal thickness (below) is compared between two DexNP studies (in colour; see colour code above)) and ranibizumab clinical trials (gray). Ohira et al. 2015; Tanito et al. 2011; Massin et al. 2010 (RESOLVE); Mitchell et al. 2011 (RESTORE)

Diabetic macular edema may be treated with topical eye drops. The dexamethasone-cyclodextrin nanoparticle eye drops significantly reduce retinal thickness and improve visual acuity in diabetic macular edema.

Other studies on eye drops for macular edema:

Earlier studies have suggested that macular edema may be treated with topical eye drops with other drug molecules. Campochiaro et al. showed that administration of topical mecamylamine, a nonspecific nicotinic acetylcholine receptor blocker, has positive effects in patients with diabetic macular edema. (Campochiaro et al. 2010) Genead and Fishman reported that topical therapy with dorzolamide hydrochloride 2%, improved visual acuity and macular edema in patients with retinitis pigmentosa and Usher syndrome.

(Genead & Fishman 2010) Nakano et al. showed that treatment of refractory diabetic macular edema with difluprednate ophthalmic emulsion 0.05% is effective in vitrectomized eyes. (Nakano et al. 2010) In our study we found more effect in (albeit few) vitrectomized eyes, probably due to the easier drug transport through the eye after removal of the viscous vitreous gel. (Gisladottir et al. 2009) These studies all agree that topical eye drops influence macular edema. However, Friedman (Friedman et al. 2015) did not find meaningful effect of topical napofenac eye drops on DME. Kaur (Kaur et al. 2016) evaluated the efficacy and safety of treatment of diabetic macular edema (persistent type) with difluprednate ophthalmic emulsion 0.05 % . 20 patients with persistent diabetic macular edema were treated with difluprednate ophthalmic emulsion 0.05 % three times daily for 3 months. There was no control group. At the end of 3 months the visual acuity had increased by two lines to a mean value of 0.61 ± 0.18 on logMAR from a baseline value of 0.885 ± 0.20 and the central retinal thickness had decreased from 423 ± 72.04 microns to 345 ± 68.7 microns. Hence, there was a total of 18.4 % decrease in retinal thickness on difluprednate. Major side effects included raised intraocular pressure in 20 %.

Based on those compelling data, the old dogma that drugs in eye drops cannot reach the retina and are therefore ineffective in treatment of retinal disease is wrong. Eye drops can play a role in drug delivery to the retina and treatment of retinal disease, including diabetic macular edema.

Clinical studies 3 & 4. Uveitis: DexNP: (Krag & Hessellund 2014; Shulman et al. 2015). 8 patients treated with DexNP

Two clinical studies with DexNP have been performed in patients with intermediate/posterior uveitis and cystoid macular edema (Krag et al. 2014; Shulman et al. 2015).

Shulman et al. evaluated the safety and efficacy of 1.5% dexamethasone nanoparticle (DexNP) drops in eyes with non-infectious uveitic macular oedema and vitritis. In a prospective pilot study, DexNP drops were administered four times a day for 4 weeks followed by drops tapering over a period of another 4 weeks. Follow-up time was 12 weeks. Five eyes with macular oedema and three eyes with vitritis were included in the study. Best corrected visual acuity (BCVA) significantly improved from a median of 0.2 logMAR to a median of 0.15 logMAR at 4 weeks' time ($p < 0.05$). Median BCVA was 0.175 logMAR and 0.2 logMAR, at week 8 and 12, respectively ($p > 0.05$). Macular oedema significantly improved at all time-points as compared to baseline ($p < 0.05$) and resolved in all eyes during follow-up (Figure 3). One eye had macular oedema relapse at week 12. Vitritis improved in all eyes and resolved completely in two eyes. One eye had intraocular pressure (IOP) elevation which was well controlled with topical antihypertensive treatment, and one eye had cataract progression.

(Krag & Hessellund 2014) treated 3 patients with DexNP eye drops 4 times a day for one month. Clinical effect was good and similar to Shulman et al. and no adverse effects were reported.

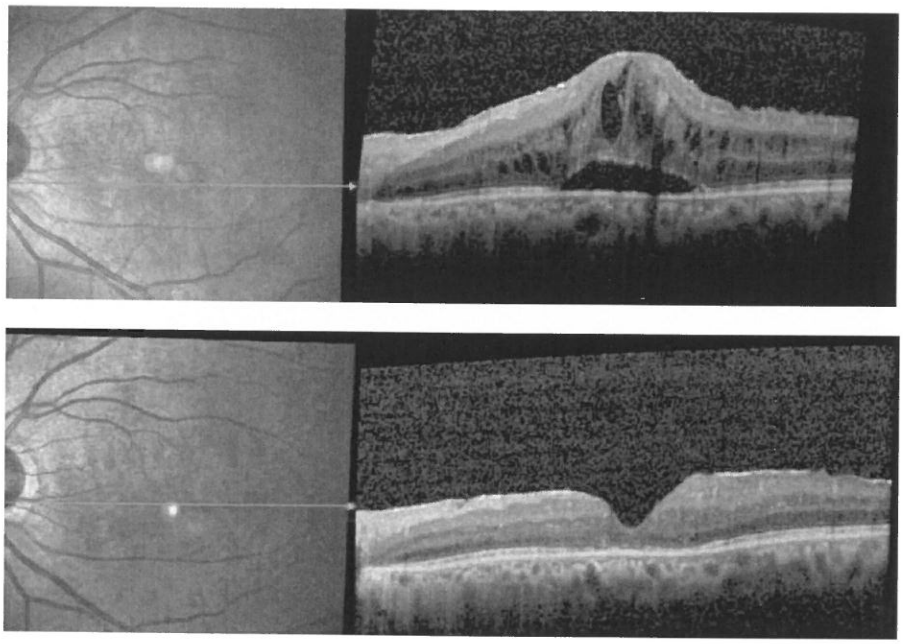

Figure 3: OCT images showing cystoid macular edema in intermediate uveitis. Baseline above. Below is after 8 weeks of treatment with DexNP eye drops, QID with taper (Shulman et al. 2015).

Clinical study #5 . Post op-trabeculectomy. DexNP (Gottfredsdottir et al. 2016). 15 patients treated with DexNP

In a study of DexNP for trabeculectomy (Gottfredsdottir et al., 2016, manuscript in preparation) 15 patients received DexNP 6 times a day for 4 weeks followed by 4 times a day for 2 weeks and 2 times a day for 2 weeks, 8 weeks in all. No serious adverse effects were noted. The group that was treated for 8 weeks with DexNP a day had similar IOP and visual acuity as the 10 patient control group treated with mitomycin C and Maxidex(R) 4 times a day for 8 weeks. No infections, corneal damage or other adverse effects were seen in this study.

Clinical study #6 Post op-trabeculectomy. DexNP (Jóhannesson et al. 2014). 6 patients treated with DexNP

Six subjects received one DexNP eye drop in one eye. The peak concentration (μg/mL ± standard deviation) of dexamethasone for DexNP eye drops (636.6 ± 399.1) was up to 19-fold higher than with Maxidex® (39.3 ± 18.9) ($p < 0.001$). At 4 hrs, DexNP was still 10 times higher than Maxidex®. In addition, DexNP resulted in about 30-fold higher concentration of dissolved dexamethasone in the tear fluid of extended time period allowing more drug to partition into the eye tissue. No adverse effects were noted.

Clinical study #7 PK with cataract surgery. Dexamethasone cyclodextrin eye drops (Kristinsson et al. 1996) ; 91 patients treated with dexamethasone cyclodextrin eye drops

Using an earlier preparation for 0.3 and 0.7% dexamethasone hydroxypropyl-β-cyclodextrin eye drop preparation, (Kristinsson et al. 1996) applied one eye drop to 91 patients before cataract surgery and measured dexamethasone concentration in aqueous humor. No adverse effects were reported.

Clinical study #8 Post op-cataract. Dexamethasone cyclodextrin eye drops (Saari et al. 2006); 10 patients treated with dexamethasone cyclodextrin eye drops

Saari applied a 0.7% dexamethasone, 2-hydroxypropyl-β-cyclodextrin eye drop once a day for 3 weeks to patients following cataract surgery. All patients fared well and no adverse effects were reported.

Safety profile

The side effects of corticosteroids in the eye are well known and include cataract formation, increased intraocular pressure and increased risk of infections. During the relatively short duration of treatment in our trials, 4-12 weeks, we did not identify noticeable cataract formation on slitlamp examination and no visual impairment due to cataract.

The intraocular pressure rose modestly during the Tanito study (Tanito et al. 2011) and only one patient had an increase as high as 8 mmHg. This regressed following cessation of treatment and no patient needed treatment for increased intraocular pressure. The Ohira study (Ohira et al. 2015) that went on for 16 weeks (DexNP treatment for 12 weeks) also showed only modest IOP rise. Again, in a longer term study increased intraocular pressure may be more prevalent, but cessation of the DexNP eye drops has been shown to lead to a reduction in IOP to baseline values. We saw no infections in this clinical trial or other adverse events. Side effects of cyclodextrin in this formulation have not been seen and are unlikely.

Cyclodextrins can be found in several marketed eye drops as well as parenteral solutions. (Loftsson & Brewster 2010) γ-Cyclodextrin, the cyclodextrin used in this study, has GRAS (generally regarded as safe) status (http://www.accessdata.fda.gov/scripts/fcn/fcnDetailNavigation.cfm?rpt=grasListing&id=46) and can also be found in FDA's list of inactive pharmaceutical ingredients

(http://www.accessdata.fda.gov/scripts/cder/iig/, search word "cyclodextrin").

γ-Cyclodextrin, unlike α- and β-cyclodextrin, is rapidly digested by salivary and pancreatic α-amylase (Munro et al. 2004) and indeed the degradation is started by α-amylase in the tear fluid. Our group has tested several cyclodextrin containing eye drops

in human subjects without any significant adverse effects. (Kristinsson et al. 1996; Gudmundsdóttir et al. 2000; Saari et al. 2006) The possibility of treating diabetic macular edema with noninvasive topical eye drops is a good option for patients and doctors alike. The effectiveness of the drug delivery platform in diabetic macular edema also suggests that it may be useful for other retinal and intraocular diseases, also with other drug molecules.

Summary of human use:

To summarize the human use of DexNP eye drops, they have been used in 19 patients for 4 weeks 3 to 6 times a day (Tanito et al. 2011); 12 patients for 12 weeks 3, 2 and 1 times a day (Ohira et al. 2015), 8 eyes in 5 patients for 8 weeks, 4 times a day with taper (Shulman et al. 2015), 3 patients for one month 4 times a day (Krag & Hessellund 2014), 15 patients 6 to 2 times a day for 8 weeks (Gottfredsdottir et al. 2016). Jóhannesson (Jóhannesson et al. 2014) gave DexNP to 6 patients. This is 60 patients treated for up to 12 weeks with up to 6 times a day frequency. No serious adverse effects have been noted.

In addition 101 patients received an earlier dexamethasone cyclodextrin eye drops either once or once a day for 3 weeks with no adverse effects.

The effectiveness by the dexamethasone cyclodextrin nanoparticle eye drops in clinical trials is promising. The dexamethasone cyclodextrin nanoparticle eye drops may have a role as monotherapy, and also in combination with intravitreal injections, implants and laser treatment.

Additional information regarding the study treatment is available in the Investigators Brochure.

2 STUDY OBJECTIVES

1. Compare the effects of DexNP eye drops and eye drops containing vehicle on visual acuity and central macular thickness in patients with DME over 12 weeks.
2. Monitor safety of the DexNP eye drop suspension treatment over 12 weeks.

3 CLINICAL HYPOTHESES

1. Proprietary DexNP eye drops improve visual acuity and decrease central macular thickness significantly more than vehicle in patients with DME.
2. Proprietary DexNP eye drop formulation is safe and well tolerated.

4 OVERALL STUDY DESIGN

Multi-center
Double-masked
Parallel group
Randomized (2: 1; active: vehicle)
Vehicle controlled
Prospective
12 weeks active treatment, 4 weeks safety follow-up without treatment
1 drop three times a day

5 STUDY POPULATION

5.1 Number of Subjects (approximate)

Based on 80% power, it was estimated that 96 randomized patients are needed, 64 in the DexNP arm and 32 in the vehicle arm.

Approximately 13 sites will be included, expected number of patients recruited per site per months is 2-5. Sites can enroll more patients if feasible, the recruitment will be competitive, i.e. the enrolment will be stopped once all planned 96 patients are recruited.

5.2 Study Population Characteristics

Diabetic macular edema of less than 3 years duration since diagnosis with VA 73-24 ETDRS letters, i.e. 20/40 to 20/320.

Patients who are diagnosed with DME will be approached by ophthalmologists in their clinics. They will be informed about the study and if willing to participate, they will be asked to read and sign an informed consent form.

Participants will undergo a complete eye examination and fill out a questionnaire on medical and eye health, drug use and allergies.

Once a study subject has signed informed consent, he/she will be randomized to active treatment or vehicle.

5.3 Inclusion Criteria

Each subject <u>must</u>:

a) Have DME of less than 3 years duration since diagnosis with presence of intraretinal and/or subretinal fluid in the study eye, with central

macular thickness, CMT, of ≥ 310μm by SD-OCT at baseline (Visit 2) (as measured by the Investigator).

b) Have definite retinal thickening in the study eye due to DME involving the central macula based on the Investigator's clinical evaluation and by SD-OCT; Note: If the DME consists of circumscribed, focal leakage that the evaluating Investigator believes should be treated with laser and no other treatments, the eye is not eligible to be a study eye.

c) Have an ETDRS BCVA letter score ≤ 73 (Snellen 20/40) and ≥ 24 (Snellen 20/320) in the study eye at baseline (Visit 2)

d) Have a documented diagnosis of type 1 or type 2 diabetes mellitus and a glycosylated hemoglobin A1c (HbA1c) of ≤ 12.0% at Visit 1

e) Have a negative urine pregnancy test at Visit 1, if female of childbearing potential those who have experienced menarche and who are not surgically sterilized [bilateral tubal ligation, hysterectomy or bilateral oophorectomy] or post-menopausal [12 months after last menses]) and must use adequate birth control throughout the study period. Adequate birth control is defined as hormonal – oral, implantable, injectable, or transdermal contraceptives; mechanical – spermicide in conjunction with a barrier such as condom or diaphragm; intrauterine device (IUD); or surgical sterilization of partner. For non- sexually active females, abstinence may be regarded as an adequate method of birth control;

f) Agree to not participate in another interventional study after providing informed consent and until the study is completed

g) Provide written informed consent prior to any study procedure being performed and be able and willing to follow all instructions and attend all study visits

h) Be 18-85 years of age at baseline (Visit 2), of either sex and any race or ethnicity

5.4 Exclusion Criteria

Each subject <u>must not</u>:

i) Have macular edema considered to be due to a cause other than DME; Note: an eye should not be considered eligible if: (1) the macular edema is considered to be related to ocular surgery such as cataract extraction;(2) clinical exam and/or OCT suggest that vitreoretinal interface abnormalities disease (e.g., a taut posterior hyaloid or epiretinal membrane) is the primary cause of the macular edema, or (3) the macular edema is considered to be related to another condition

such as age-related macular degeneration, uveitis, retinal vein occlusion, or drug toxicity

j) Have a decrease in BCVA due to causes other than DME (e.g., foveal atrophy, pigment abnormalities, dense subfoveal hard exudates, previous vitreoretinal surgery, central serous retinopathy, non-retinal condition, substantial cataract, macular ischemia) that is likely to be decreasing BCVA by three lines or more (i.e., cataract would be reducing acuity to 20/40 or worse if eye was otherwise normal)

k) Have significant macular ischemia, as assessed by the investigator, which in the opinion of the investigator would prevent gain in visual acuity.

l) Have any other ocular disease that may cause substantial reduction in BCVA, including, retinal detachment, epiretinal membrane, vitreous hemorrhage or fibrosis involving the macula in the study eye, ocular inflammation (uveitis), other retinal inflammatory or infectious diseases

m) Have active peri-ocular or ocular infection (e.g., blepharitis, keratitis, scleritis, or conjunctivitis)

n) Have a history of non-infectious uveitis

o) Have high myopia (-8 diopter or more correction) in study eye

p) Wear contact lenses during the 12 week active treatment study period

q) Have a history of any ocular surgery within 3 months prior to Visit 1 in the study eye;

r) Have a history of Yttrium-Aluminum-Granate (YAG) laser capsulotomy within 3 months prior to Visit 1 in the study eye;

s) Have a history of panretinal scatter photocoagulation (PRP) or focal laser within 3 months prior to Visit 1 or an anticipated need for PRP during the course of the study in the study eye;

t) Use other ophthalmic formulations during the study. However, IOP lowering eye drops are allowed if they become necessary due to increased IOP.

u) Have a history of prior IVT, subtenon, or periocular, non-sustained release, steroid therapy within 3 months prior to Visit 1 in the study eye (e.g., triamcinolone)

v) Have a history of intravitreal sustained release dexamethasone therapy within six months prior to Visit 1 in the study eye;

w) Have a history of intravitreal sustained release fluocinolone within three years prior to Visit 1 in the study eye;

x) Have a history of prior treatment of intravitreal (IVT) aflibercept within 8 weeks and ranibizumab/bevacizumab within 6 weeks of Visit 1 in the study eye;

y) Have a history of prior treatment for DME with any other (than previously listed) approved treatment which is not labeled for DME within one year prior to Visit 1 in the study eye;

z) Have high-risk proliferative diabetic retinopathy (PDR), defined in the ETDRS study as at least one of the following:
   - New vessels within one disc diameter of the optic disc (NVD) ≥ 1/3 disc area;
   - Any NVD with vitreous or pre-retinal hemorrhage;
   - New vessels elsewhere in the retina (NVE) ≥ ½ disc area and pre-retinal or vitreous hemorrhage;

aa) Have uncontrolled ocular hypertension or glaucoma in either eye, defined as intraocular pressure (IOP) ≥ 22 mmHg on more than 1 IOP lowering medications at Visit 1

bb) Have poor media clarity, pupillary constriction (i.e., senile miosis), or lack cooperation that, in the opinion of the evaluating Investigator, would interfere with any study procedures, evaluations, or interpretation of data

cc) Have any ocular condition that, in the opinion of the Investigator, may require intervention, interfere with evaluations of efficacy or safety or interpretation of data collected in the study

dd) Have an estimated Glomerular Filtration Rate (eGFR) of < 15mL/min/1.73m2 as per CKD-EPI equation at Visit 1

ee) Have a systolic blood pressure < 90 or > 160 mmHg and / or a diastolic blood pressure > 100 mmHg at Visit 1 and 2

ff) Have a known or suspected hypersensitivity to any components of the test agent

gg) Be a female subject who is pregnant or lactating or has a positive pregnancy test at Visit 1 or has been pregnant within 6 months before Visit 1 or breast-feeding within 3 months before Visit 1, or planning to become pregnant within 9 months from Visit 1

hh) Have participated in any interventional clinical study or been treated with any investigational drugs within 30 days or 5 half-lives of the investigational drug, whichever is longer, prior to the initiation of Visit 1

ii) Have any other condition, which in the opinion of the evaluating Investigator, precludes the subject's participation in the trial

5.5 Withdrawal Criteria (if applicable)

Should a subject wish to stop treatment in the trial or if an investigating physician decides to withdraw a subject from the trial due to side effects, incompliance or for other reasons, he/she needs to inform the CRO as soon as possible.

Withdrawn subjects will not be replaced.

6 STUDY PARAMETERS

6.1 Efficacy Measures

6.1.1 Primary Efficacy Variable(s)

Mean change in ETDRS BCVA at Week 12 compared to baseline.

6.1.2 Secondary Efficacy Variable(s)

Mean change in ETDRS BCVA letters at Weeks 2, 4, 8, and 16 compared to baseline;

Mean ETDRS BCVA letters at Weeks 2, 4, 8, 12, and 16:

Percent of patients who gain ≥10 or ≥15 ETDRS letters at week 12 compared to baseline;

Percent of patients who lose ≥15 ETDRS letters or more at week 12 compared to baseline;

Mean change in central macular thickness (CMT) as assessed by SD-OCT at Weeks 2, 4, 8, 12, and 16 compared to baseline;

Mean CMT as assessed by SD-OCT at Weeks 2, 4, 8, 12, and 16;

Quality of life as assessed by NEI VFQ-25 at baseline and week 12

6.2 Safety Measures

Subjects will be monitored for safety on all study visits.
Adverse Events
Safety Laboratory Tests: Biochemistry and Hematology
Slit Lamp Examination Parameters indicating ocular toxicity to the investigational drug
Intraocular Pressure
Dilated Indirect Ophthalmoscopy

6.3 Other Measures

At baseline and week 12 blood samples will be drawn for measurements of HbA1c, haematology and chemistry.

Hematology:
Complete blood count
Hemoglobin
Hematocrit
Red blood cell count
Mean corpuscular volume
Mean cell hemoglobin
Mean cell hemoglobin concentration
Red cell distribution width
White blood count with differential:
- Neutrophils
- immature granulocytes
- lymphocytes
- monocytes
- eosinophils
- basophils

Platelets
Hemoglobin A1c

Chemistry:
Sodium
Potassium
Bicarbonate
Calcium
Chloride
Glucose
Phosphate
Creatinine
Blood urea nitrogen
Creatine phosphokinase
Uric acid
Albumin
Alkaline phosphatase (ALP)
Alanine amino transferase (ALT)
Aspartate amino transferase (AST)
Gamma glutamyl transferase (GammaGT)
Lactate dehydrogenase (LDH)
Total protein
Total bilirubin

Total cholesterol
Triglycerides

7 STUDY MATERIALS

7.1 Study Treatment(s)

7.1.1 Study Treatment(s)/ Formulation(s)/ Medical Device Composition or Design

The eye drop suspensions, DexNP 1.5% w/v, consist of the following ingredients:

Dexamethasone, γ-cyclodextrin, disodium edetate, poloxamer, sodium chloride and purified water. All ingredients comply with their Ph. Eur. or USP monographs or both. The formula is patent protected.

The eye drop suspensions, DexNP 15 mg/ml, consist of the following ingredients:

γ-cyclodextrin, disodium edetate, poloxamer, sodium chloride and purified water. All ingredients comply with their Ph. Eur. or USP monographs or both.

The dexamethasone cyclodextrin NP suspension eye drops and the Vehicle eye drops will be dispensed in single dose containers. An appropriate number of unit dose containers are dispensed for each patient in order to have enough medication until the next visit.

Vehicle eye drops will be prepared in identical packaging. The DexNP eye drops and vehicle will be packaged in a primary one dose vial. Secondary package will be in the foil envelopes and foil envelopes will be packaged in a box.

The dexamethasone cyclodextrin suspension eye drops and the comparator drug will be kept under controlled conditions at study sites or affiliated pharmacies where dispensing records will be kept.

7.1.2 Instructions for Use and Administration

- The eye drops are milky white and in single dose units.

Study group.

The study eye will receive 1 DexNP eye drop 3 times a day (every 8 hrs) for 12 weeks.

Control group.

The study eye will receive 1 vehicle eye drop 3 times a day (every 8 hrs) for 12 weeks.

- The eye drops should be stored in their container at room temperature protected from direct sunlight.

- Directions for the use of DexNP 15mg/mL eye drops and DexNP Vehicle.

1. Wash your hands thoroughly with soap and water.
2. Twist off the top of the container. Check the container tip to make sure that it is not chipped or cracked.
3. Avoid touching the container tip against your eye or anything else – eye drops and containers must be kept clean.
4. While tilting your head back, pull down the lower lid of your eye with your index finger to form a pocket.
5. Hold the container (tip down) with the other hand, as close to the eye as possible without touching it.
6. Brace the remaining fingers of that hand against your face.
7. While looking up, gently squeeze the dropper so that a single drop falls into the pocket made by the lower eyelid. Slowly remove your index finger from the lower eyelid.
8. Close your eye for 2 to 3 minutes and tip your head down as though looking at the floor. Try not to blink or squeeze your eyelids.
9. Place a finger on the tear duct and apply gentle pressure.
10. Wipe any excess liquid from your face with a tissue.
11. Keep the used container after use and return to your study site at next scheduled visit.
12. Wash your hands to remove any medication.

8 STUDY METHODS AND PROCEDURES

8.1 Subject Entry Procedures

8.1.1 Overview

Subjects as defined by the criteria in section 5.2, 5.3, and 5.4 will be included in this study.

8.1.2 Informed Consent

Prior to a subject's participation in the trial (i.e., changes in a subject's medical treatment and/or study related procedures), the study will be discussed with each subject, and subjects wishing to participate must give written informed consent using an informed consent form. The informed consent form must be the most recent version that has received approval/favorable review by a properly constituted Ethics Committee.

8.1.3 Washout Intervals

As per exclusion criteria, section 5.4.

IVT, subtenon, or periocular, non-sustained release, steroid therapy: 3 months prior to Visit 1 (e.g., triamcinolone)

IVT sustained release dexamethasone therapy: 6 months prior to Visit 1.

IVT sustained release fluocinolone: 3 years prior to Visit 1.

IVT aflibercept: within 8 weeks and ranibizumab/bevacizumab: 6 weeks of Visit 1.

History of prior treatment for DME with any other (than previously listed) approved treatment which is not labeled for DME: 1 year prior to Visit 1.

8.1.4 Procedures for Final Study Entry

Patients who have current DME and overall DME of less than 3 years duration since diagnosis will be approached by the personnel (including but not limited to nurses, optometrists, ophthalmologists) in their clinics. They will be informed about the study by qualified and trained personnel and if willing to participate, they will be asked to read and sign an informed consent form.

Participants will undergo a complete eye examination and fill out a questionnaire on medical and eye health, drug use and allergies.

Patients need to fulfill all inclusion criteria including vision as assessed by ETDRS charts and retinal thickness as assessed by SD-OCT. They must not meet any of the exclusion criteria.

8.1.5 Methods for Assignment to Treatment Groups:

At visit 2, the subject will be randomized in a 2:1 ratio to active drug or the vehicle group.

8.2 Concurrent Therapies

The use of any concurrent medication, prescription or over-the-counter, is to be recorded on the subject's source document and corresponding case report form (CRF) along with the reason the medication was taken.

Concurrent use of other eye drops is not allowed. Should concurrent treatment with IOP lowering eye drops (prefer prostaglandin) become necessary due to increased IOP, those eye drops should be administered in the evening 15 minutes before DexNP/Vehicle eye drops.

Other treatments for DME are not allowed in the study eye while the patients are included in the study except if they meet the rescue criteria as described in 8.2.2 below.

If the fellow eye needs any treatment for DME or any other conditions, standard of care (i.e. anti-VEGF for DME) can be applied except steroids. So i.e. Ozurdex or topical dexamethasone will not be allowed for the treatment of the fellow eye during the course of the study.

The use of contact lenses is NOT allowed during the active study treatment phase of 12 weeks.

Concurrent enrollment in another investigational drug or medical device study is not permitted.

8.2.1 Prohibited Medications/Treatments

Other ophthalmic formulations e.g. eye ointment, eye drops.

Other DME treatment (incl. triamcinolone, dexamethasone, fluocinolone, aflibercept, ranibizumab and bevacizumab) in the study eye

See exclusion criteria.

8.2.2 Escape Medications

If IOP rises above 25 mmHg a topical prostaglandin analog will be considered. If IOP rises above 32 mmHg, the study drug will be discontinued, (DexNP or vehicle eye drops) and the IOP treated with glaucoma drugs or other treatment at the discretion of the study ophthalmologists.

If BCVA drops by 10 letters or more or CMT increases by 20% or more at 2 consequent visits and the changes are judged by the treating physician to be due to DME the patient should be stopped to receive the DexNP or vehicle experimental eye drops and may be treated at the discretion of the investigator with standard of care, i.e. anti VEGF injections or steroid implant. The patient should be asked to return for all scheduled control visits, even if the study drug has been discontinued

If BCVA drops by 10 letters at 2 consequent visits and the decrease in vision is felt by the treating physician to be due to cataract formation the patient shall be offered cataract surgery and IOL implantation. The patient stays in the study and continues with eye drops as indicated by the protocol.

8.3 Examination Procedures

8.3.1 Procedures to be performed at Each Study Visit with Regard to Study Objective(s)

A complete eye examination will be performed. (Detailed descriptions may be found in an optional study manual if deemed necessary by the sponsor)

- Visual acuity will be measured at every visit using ETDRS chart at 4m with best corrective lenses.
- Intraocular pressure (IOP) will be measured at every visit with Goldmann tonometry or I-CARE tonometry (standardized in each center and the same device to be used for a given patient throughout the study)
- Eye examined at every visit by slitlamp.
- Fundus is examined at every visit through dilated pupils (i.e. using Tropicamide hydrochloride 1% and phenylephrine 2.5%),
- Fundus photographs obtained (optional)
- Optical coherence tomography (SD OCT preferably using Heidelberg Spectralis) performed at each visit to measure central macular thickness (CMT).
- In phakic eyes cataract formation will be graded using the LOCS III system.
- Irritation will be evaluated at every visit by slit lamp biomicroscopy, fluorescein staining when deemed necessary

- Blood pressure should be measured on the patient sitting for at least 2 minutes, on the right arm.
- Quality of life as assessed by NEI VFQ-25 at baseline and 12 weeks.

The full eye examination will be performed before start of the study at screening and then at each visit (Day 1, weeks 2, 4, 8, 12 and 16) until end of the study period.

Optional imaging

At the discretion of the investigator, additional imaging of the eye / macula can be performed for diagnostic purposes to evaluate the safety and efficacy of the experimental DexNP eye drops or vehicle while the study is ongoing, including fundus photographs, fluorescein angiography (FA) additional OCT's or angio-OCTs. All those diagnostic procedures are standard of care and used for the standard daily clinical routine diagnostic.

Adverse events will be monitored throughout the study. All adverse events will be promptly reviewed by the investigator for accuracy and completeness. All adverse events will be documented on the appropriate case report form.

If a female has a positive pregnancy test during the study, then the investigator will notify IRW Consulting immediately. The investigator shall request from the subject and/or the subject's physician copies of all related medical reports during the pregnancy and shall document the outcome of the pregnancy. The investigator will retain these reports together with the subject's source documents and will provide a copy of all documentation to IRW Consulting.

Investigating physicians will fill out a CRF where all measurements are recorded. The ophthalmologist performing the complete eye examination will be masked to which drug the patients are receiving. The patients will receive either DexNP eye drops or vehicle at the same frequency (double blind).

Participants will be asked to fill out the NEI-VFQ 25 questionnaire at baseline and week 12. This will be filled out during a study visit. Participants will be encouraged to report any adverse effects.

All participants will be offered to contact the investigating physician should they notice any signs or symptoms related to the investigation.

8.4 Schedule of Visits, Measurements and Dosing

8.4.1 Scheduled Visits

Refer to Appendix 1 for a schedule of visits and measurements.

8.4.2 Unscheduled Visits

Unscheduled visits are possible at every time and will be documented in the respective CRF.

8.5 Compliance with Protocol

Investigators agree to follow the protocol for the study. The study monitor will verify compliance.

8.6 Subject Disposition

8.6.1 Completed Subjects

A completed subject is one who has not been discontinued from the study.

8.6.2 Discontinued Subjects

Subjects may be discontinued prior to their completion of the study – either discontinue study medication or completely leave the study (i.e. due to loss of follow-up). Patients who discontinue study medication generally should be followed through to the final visit.

Reasons for discontinuation may be:

- adverse events
- protocol violations
- lack of efficacy
- administrative reasons (eg, inability to continue, lost to follow up)
- sponsor termination of study
- other

Note: In addition, any subject may be discontinued for any sound medical reason and the study subjects are free to discontinue the study participation on their discretion.

Notification of a subject discontinuation and the reason for discontinuation will be made to IRW and/or study sponsor and will be clearly documented on the CRF.

8.7 Study Termination

The study may be stopped at any time by the sponsor with appropriate notification.

8.8 Study Duration

16 weeks study duration, preceded by a maximum 4 week screening period.

8.9 Monitoring and Quality Assurance

During the course of the study an IRW Consulting monitor, or designee, will make routine site visits to review protocol compliance, assess study drug accountability, and ensure the study is being conducted according to the pertinent regulatory requirements. The review of the subjects' medical records will be performed in a manner that adequately maintains subject confidentiality. Further details of the study monitoring will be outlined in a monitoring plan.

Regulatory authorities of domestic and foreign agencies, quality assurance and or its designees may carry out on-site inspections and/or audits which may include source data checks. Therefore direct access to the original source data will be required for inspections and/or audits. All inspections and audits will be carried out giving consideration to data protection as well as subject confidentiality to the extent that local, state, and federal laws apply.

8.10 Potential risks and benefits

The aim is to test the hypotheses that DexNP eye drops improve VA in patients with DME, and are safe and well tolerated. If the hypothesis proves right, DexNP may potentially be developed further into an approved product of a new formulation of dexamethasone eye drops that can be given topically to replace intravitreal injections.

Possible risks for the patient are side effects of dexamethasone, which is a registered and widely used drug. Possible side effects from dexamethasone are cataract formation, increased IOP and infection.

In previous clinical trials conducted with DexNP eye drops, participants received the new eye drops 1 - 6 times a day for up to 12 weeks with no reported serious adverse effects. In these studies there was no noticeable cataract formation (except one case with modest progression), moderate reversible increase in IOP (reversed after discontinuation of DexNP) and no infections.

The DexNP formulation contains γ-cyclodextrin. Cyclodextrins are already being used in registered eye drop products. Gamma cyclodextrin has GRAS status with FDA.

Participants will have to have SD-OCT imaging, visual acuity and IOP measured regularly during the study which can cause them inconvenience i.e. need to visit the ophthalmic unit on regular basis for these evaluation and monitoring for side effects.

A significant benefit for the participating patients receiving active drug can be expected. Previous clinical data and clinical data using dexamethasone (approved and off-label) in different formulations for the treatment of ophthalmic indications showed significant clinical benefit. In

addition, participating patients will benefit from a very close and elaborated monthly monitoring of their ophthalmic conditions and their general health status. This intensive care for the health of the patients usually provides a significant benefit for the patients' overall conditions.

DexNP promises to replace in part intravitreal injections of anti VEGF drugs, which involve surgical risks such as infection, hemorrhage and injury as well as increased risk of cardiovascular events and death (Avery et al. 2016).

9 ADVERSE EVENTS

9.1 Adverse Event

An adverse event is defined as any untoward medical occurrence in a participating patient associated with the use of an investigational medicinal product (IMP) which does not necessarily have a causal relationship with IMP. An adverse event can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product and judged by the Investigator as clinically significant.

All AEs are reported by the subject and/or in response to an open question from study personnel or revealed by observation, physical examination or other diagnostic procedures will be recorded in the source document and on the AE pages eCRF. Any clinically relevant deterioration in clinical finding is considered an AE and must be recorded. When possible, signs and symptoms indicating a common underlying pathology should be noted as one comprehensive event.

Documentation and evaluation regarding the adverse event should be made as of:

- type of event
- seriousness
- degree of severity
- duration (start - end)
- action taken
- causality with IMP
- outcome of the adverse event

For AE reporting purposes, no distinction should be made between the IMP and any reference/comparator/placebo product.

9.1.1 Severity

Severity of an adverse event is defined as a qualitative assessment of the degree of intensity of an adverse event as determined by the investigator or reported to him/her by the patient/subject. The assessment of severity is made

irrespective of relationship to investigational product or seriousness of the event and should be evaluated according to the following scale:

- *Mild*: Event is noticeable to the subject, but is easily tolerated and does not interfere with the subject's daily activities.
- *Moderate*: Event is bothersome, possibly requiring additional therapy, and may interfere with the subject's daily activities.
- *Severe*: Event is intolerable, necessitates additional therapy or alteration of therapy, and interferes with the subject's daily activities.

9.1.2 Relationship to Investigational Product

The relationship of each adverse event to the investigational product should be determined by the investigator using these explanations:

- *Related*: A reasonable possibility exists that the investigational product caused the adverse event.
- *Not Related*: A reasonable possibility does not exist that the investigational product caused the adverse event.

9.2 Serious Adverse Events

An adverse event is considered to be serious if, in the view of the investigator it results in any of the following outcomes at any dose of IMP:

- Death;
- A life-threatening or places the participant at immediate risk of death from the event as it occurred;
- Inpatient hospitalization or prolongation of existing hospitalization;
    - Note: The term "inpatient hospitalization" refers to any hospital admission (even if less than 24 hours). Planned hospitalization for pre-existing condition without a serious deterioration in health, is not considered to be a serious adverse event.
    - Note: The term "prolongation of existing hospitalization" refers to any extension of an inpatient hospitalization beyond the stay anticipated or required for the reason for the initial admission as determined by the investigator or treating physician.
- A persistent or significant disability, incapacity or substantial disruption of the ability to conduct normal life functions;

- Note: A serious adverse event specifically related to visual threat would be interpreted as any potential impairment or damage to the subject's eyes (e.g., hemorrhage, retinal detachment, central corneal ulcer or damage to the optic nerve).

- A congenital anomaly/birth defect.

Important medical events that may not result in death, are life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

9.3 Procedures for Reporting Adverse Events

All adverse events and their outcomes must be reported to IRW.

9.3.1 Reporting a Serious Adverse Event (SAE)

All SAEs must be reported by the Investigator using phone or email or fax within 24 hours of knowledge of the event to the Monitor or other members of the staff at IRW, regardless of the time that may have elapsed from the time the event occurred to when the Investigator first learns of it. The Initial Report should contain as much information as possible, but a minimum the following information:

* subject identification
* treatment specification (blinded information, if code not broken)
* adverse event diagnosis
* time specification for the medical event
* name of the original reporter

A Serious Adverse Event Report Form must also be completed, signed by the Investigator and submitted to IRW no later than 24 hours after the initial information was received. Apart from the information above, this Follow-up Report should also contain the following information:

* assessment of severity
* assessment of causality

No distinction should be made between the investigational product or reference/placebo product regarding reporting of SAEs as long as the code is not broken.

SAEs should be reported to IRW even after the clinical trial has been finished, if, in the judgment of the Investigator, there might be an association between the event and the previous use of the IMP or as a result of the trial procedures.

The contact details of the safety team and reporting procedure are described in the separate Safety Manuals (Site and Sponsor/CRO obligations).

9.3.2 Reporting a Suspected Unexpected Adverse Reaction (SUSAR)

Only SAEs that are both unexpected and related to the investigational product, Suspected Unexpected Serious Adverse Reactions (SUSARs), are subject to expedited reporting to the respective CA and IEC.

IRW is responsible for informing all Investigators concerned of relevant information about SUSARs that could adversely affect the safety of subjects. The appropriate IEC and CA as per local requirements, should be informed by IRW about SAEs associated with the use of the product (SUSARs).

9.4 Procedures for Unmasking (if applicable)

Investigators will be provided with emergency code-break envelopes for all subjects and a complete set of emergency code-break envelopes will be retained by IRW.

Breaking the code must only be done in medical emergency situations and should only be used when knowledge of the treatment is necessary for the proper management of the subject. If the treatment code envelopes are broken, the reason and the date should be recorded on the envelopes and signed by the Investigator. Decoding of the blinded treatment must be reported to IRW and Oculis as soon as possible.

9.5 Type and Duration of the Follow-up of Subjects after Adverse Events

If a trial Subject is withdrawn due to an AE, or if an AE persists at the end of the trial treatment period, this should be followed up until the condition has ceased or until the subject is under professional medical care and a potential causality between the investigational product and the AE has been penetrated. An outcome assessment should be performed when an AE persists.

9.6 Periodic Safety Reporting

During the course of the trial, annual safety reports (DSUR) should be sent to the Competent Authority and IEC, as applicable. The reporting time frame for annual reports starts with the date of the first authorization by a Competent Authority.

10 STATISTICAL HYPOTHESES AND METHODS OF ANALYSES

10.1 Study Endpoints

10.1.1 Primary Efficacy Endpoints

- Mean change in ETDRS BCVA letters at Week 12 compared to baseline

10.1.2 Secondary Efficacy Endpoints

- Mean change in ETDRS BCVA letters at Weeks 2, 4, 8, and 16 compared to baseline
- Mean ETDRS BCVA letters at Weeks 2, 4, 8, 12, and 16
- Proportion of subjects with ≥10 and ≥15 ETDRS BCVA letter improvements from baseline.
- Proportion of subjects reaching 20/20 vision at week 12
- Proportion of subjects with ≥15 ETDRS BCVA letter loss from baseline.
- Mean change in central macular thickness (CMT) as assessed by SD-OCT at Weeks 2, 4, 8, 12, and 16 compared to baseline
- Mean CMT as assessed by SD-OCT at Weeks 2, 4, 8, 12, and 16
- Quality of life as assessed at week 12 by NEI VFQ-25

10.1.3 Safety Endpoints

- Adverse Events
- Safety laboratory tests: biochemistry and hematology
- Intraocular pressure
- Slit lamp biomicroscopy
- Dilated Indirect Ophthalmoscopy

10.2 Hypotheses

The statistical hypotheses for the primary endpoint of mean change from baseline BCVA ETDRS letters in the study eye at Week 12 are as follows:

H_0: The difference between study eyes treated with DexNP and study eyes treated with Vehicle (DexNP – Vehicle) in the mean change from baseline ETDRS BCVA letters to Week 12 (Week 12 – Baseline) ≤ 0.

H_1: The difference between study eyes treated with DexNP and study eyes treated with Vehicle (DexNP – Vehicle) in the mean change from baseline ETDRS BCVA letters to Week 12 (Week 12 – Baseline) > 0.

The study will be considered a success if H_0 is rejected in favor of H_1 and superiority of DexNP to Vehicle is claimed.

10.3 Sample Size

Assuming a difference in the mean change from baseline ETDRS BCVA to Week 12 of 3.5 letters between DexNP and vehicle, a common standard deviation in the change from baseline ETDRS BCVA letters to Week 12 of 8 letters within each treatment group, an overall 1-sided alpha = 0.15, a 2:1 randomization, and an interim analysis when 50% of the subjects complete Week 12 using and O'Brien-Fleming alpha spending function, 58 DexNP and 29 Vehicle subjects (study eyes) are required to have 80% power to reject the null hypothesis. Assuming 10% discontinuation rate, a total of 96 subjects will be randomized.

10.4 Interim Analysis

An interim analysis will be conducted by an independent biostatistician (to avoid introducing an operational bias) when approximately 50% of the subjects (44 subjects) complete Week 12. Statistical inference at the interim will be made at a 1-sided alpha = 0.04177. Statistical inference at the final analysis will be made at a 1-sided alpha = 0.13793. While there is no plan to stop early for a claim of superiority the O'Brien-Fleming boundary will serve to mitigate any concerns about that possibility and impacts overall power only minimally. If the interim is completed when precisely 50% of the subjects complete the trial through Week 12, the hypotheses will be tested using an efficacy boundary of 1.73051, corresponding to a one-sided alpha of 0.04177 at the interim analysis and using an efficacy boundary of 1.08968, corresponding to a one-sided alpha of 0.13793 at the final analysis. Note the actual boundaries will be calculated based on the percent of information used in the interim analyses.

No other study personnel other than the designated unmasked statistician and SAS programmers will be unmasked to the individual subject treatment assignments at the interim analysis. Additionally, a person appointed by the sponsor will be unmasked to treatment group summaries.

10.5 Study Populations

ITT Population: The intent-to-treat (ITT) population will consist of all randomized subjects, analyzing subjects under the treatment to which they were randomized.

PP Population: The per-protocol (PP) population is a subset of the ITT population and includes subjects who do not deviate from the protocol in any way likely to seriously affect the primary outcome of the study, analyzing subjects under the treatment actually received. Important protocol deviations related to study inclusion or exclusion criteria,

conduct of the trial, subject management, or subject assessment will be identified prior to unmasking treatment.

Safety Population: The safety population includes all randomized subjects who receive at least one dose of study medication. The safety population will be analyzed as treated and will be used for the safety analyses. No data will be excluded for any reason.

10.6 Statistical Analysis

10.6.1 Methods of Analysis

Summaries for continuous variables will include the sample size, mean, standard deviation, median, minimum, and maximum. Summaries for discrete variables will include frequencies and percentages. Differences between treatment groups will be calculated as DexNP – Vehicle and change from baseline will be calculated as follow-up visit – baseline. The baseline visit will be defined as the last non-missing measure prior to initiation of investigational treatment. All efficacy analyses will use a one-sided alpha = 0.15 test unless otherwise stated.

All summaries will be presented by treatment group and where appropriate by visit.

10.6.2 Subject Demographics and Baseline Characteristics

Continuous summary statistics will be presented for the quantitative variable age (years), by treatment group and for all subjects. Discrete summary statistics will be generated for qualitative demographic variables: age category, gender, ethnicity, race, and iris color for the study eye, tabulated by treatment group and for all subjects.

Medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA®). Medical history will be summarized using discrete summary statistics for each MedDRA® system organ class (SOC) and preferred term (PT) by treatment group and for all subjects. Medical history will be presented separately for ocular and non-ocular histories. Subjects with multiple medical histories in the same SOC or PT will be counted only once for that respective SOC or PT.

10.6.3 Primary Efficacy Analysis

The primary efficacy variable (change from baseline in ETDRS BCVA letters to Week 12) will be summarized using continuous summary statistics, including 70%, 90% and 95% confidence intervals (CIs) for each treatment group. The primary analysis of the primary variable will employ a linear model with change from baseline ETDRS BCVA letters as the response, baseline ETDRS BCVA letters as a covariate, and treatment as a main effect factor, using the ITT population and with multiple imputation pattern mixture model techniques used to impute missing data. Subjects who receive rescue medication prior to Week 12 will have their Week 12 measure replaced with

their last observation prior to receiving rescue medication. The least squared mean, standard error, and CI for each treatment group, and the difference between treatment groups, will be presented as well as a 1-sided p-value testing the difference versus the null hypothesis value of 0. The study will be considered a success and DexNP superior to Vehicle if the one-sided p-value is less than 0.15 and the difference in mean change from baseline ETDRS BCVA letters is greater than 0. Analyses will secondarily be completed using a two-sample t-test.

The primary efficacy analyses will secondarily be performed on the ITT population using observed data only (ODO), last observation carried forward (LOCF), and baseline observation carried forward (BOCF) to assess the robustness of the results from the primary model. The primary efficacy analyses using multiple imputation and ODO will also secondarily be completed on the PP population. In all of these analyses, subjects who receive rescue medication prior to Week 12 will have their Week 12 measure replaced with their last observation prior to receiving rescue medication.

10.6.4 Secondary Efficacy Analyses

Change from baseline in ETDRS BCVA letters to Weeks 2, 4, 8, and 16and ETDRS BCVA letters at Weeks 2, 4, 8, 12, and 16 will be analyzed similarly to the primary efficacy analyses using ODO on the ITT population.

Mean and mean change in central retinal subfield thickness will be analyzed similarly to ETDRS BCVA.

The proportion of study eyes a) gaining at least 10 or 15 letters BCVA and b) losing at least 15 letters will be summarized using discrete summary statistics. Treatment comparisons will be completed using Pearson's chi-squared statistic, with Fisher's exact statistic used for any comparison with an expected cell frequency of 5 or less. Confidence intervals (70%, 90%, and 95%) will also be presented for each treatment group and the difference between treatment groups, using asymptotic or exact methodology as consistent with the employed testing procedure. The analyses will be completed primarily on the ITT population and secondarily on the PP populations using ODO.

In all of these analyses, data from subject visits after receipt of rescue medication will be imputed using last observation prior to receiving rescue medication for continuous endpoints and will be imputed as failures for success/failure variables.

The VFQ-25 measurements will be summarized using continuous summary statistics for the total score, subscale scores, and each individual question score using observed data only. Imputation of missing individual question scores in calculating subscale and total scores will be detailed in the formal statistical analysis plan and will follow methodology used in developing the instrument.

One-sample t-tests will be used to primarily analyze the mean change from baseline within a treatment group; additionally, the non-parametric Wilcoxon signed-rank test will be used secondarily to analyze the change from baseline. Two-sample t-tests will be used to primarily analyze the difference in the mean scores between treatments at each visit and change from baseline; additionally, the non-parametric Wilcoxon rank-sum test will be used secondarily to analyze the differences in scores between treatments.

10.6.5 Safety Analyses

All safety analyses will be performed on the safety population.

The primary safety analysis will summarize ocular and non-ocular treatment-emergent AEs (TEAEs) using discrete summaries at the subject level by system organ class and preferred term for each treatment group. Ocular TEAEs will be summarized separately for all study and fellow eyes. A TEAE will be defined as occurring after the first dose of study medication. Serious adverse events and treatment-related ocular and non-ocular TEAEs will be summarized similarly. Ocular and non-ocular TEAEs will also be summarized by severity.

Slit lamp biomicroscopy and dilated indirect ophthalmoscopy measures will be summarized at each visit using discrete summary statistics.

Intraocular pressure will be summarized at each visit, using continuous and discrete summary statistics, including change from baseline and the proportion of study eyes with an increase from baseline in IOP of 10 mmHg or more and the proportion of study eyes with IOP of 30 mmHg or more.

Safety laboratory data will be summarized at each visit, using continuous summary statistics, including change from baseline.

11 COMPLIANCE WITH GOOD CLINICAL PRACTICES, ETHICAL CONSIDERATIONS, AND ADMINISTRATIVE ISSUES

The trial will be performed in accordance with ICH Guidelines for Good Clinical Practice (CPMP/ICH/135/95) July 1996 and The Declaration of Helsinki adopted by the 18th World Medical Assembly, in Helsinki, Finland, with later revisions.

Randomization codes will be kept at secure locations accessible by the Investigators and delegated study staff only until the study has finished (last patient has finished treatment and evaluation). If needed the code can be accessed at all times.

11.1 Protection of Human Subjects

11.1.1 Subject Informed Consent

Informed consent/assent must take place before any study specific procedures are initiated. Signed and dated written informed consent must be obtained from each subject and/or from the subject's parent or legal guardian prior to enrollment into the study.

All informed consent/assent forms must be approved for use by the sponsor and receive approval/favorable opinion from an IRB/IEC prior to their use. If the consent form requires revision (e.g., due to a protocol amendment or significant new safety information), it is the investigator's responsibility to ensure that the amended informed consent is reviewed and approved by the sponsor or the designated CRO (IRW) prior to submission to the governing IRB/IEC and that it is read, signed and dated by all subjects subsequently enrolled in the study as well as those currently enrolled in the study.

11.1.2 Ethics committee Review and Approval

Ethics Committee approval as required by ICH-GCP and local regulations will be obtained prior to initiating the study.

11.2 Ethical Conduct of the Study

This study will be conducted in accordance with the ethical principles that originated with the Declaration of Helsinki.

11.3 Subject Confidentiality

All personal study subject data collected and processed for the purposes of this study should be maintained by the investigator and his/her staff with adequate precautions as to ensure that the confidentiality of the data in accordance with local, state, and federal laws and regulations.

Monitors, auditors and other authorized representatives of IRW Consulting, the sponsor, the IRB/IEC approving this study, the FDA, the DHHS, other domestic government agencies, and other foreign regulatory agencies will be granted direct access to the study subject's original medical and study records for verification of the data and/or clinical trial procedures. Access to this information will be permitted to the aforementioned individuals to the extent permitted by law.

A report of the results of this study may be published or sent to the appropriate health authorities in any country in which the investigational product may ultimately be marketed, but the subject's identity will not be disclosed in these documents.

11.4 Documentation

Source documents may include a subject's medical records, hospital charts, clinic charts, electronic records, the investigator's study subject files, as well as the results of diagnostic tests such as OCTs and laboratory tests. The investigator's copy of the Case Report Forms serves as the investigator's record of a subject's study-related data.

11.4.1 Retention of Documentation

All study related correspondence, patient records, consent forms, record of the distribution and use of all investigational products and copies of case report forms should be maintained on file for at least two years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region; or until at least two years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian.

All study results will be treated according to rules on confidentiality and anonymity. Domestic law on protection of privacy, procession and destruction of data will be followed. All investigational material will be kept by investigating doctors during the study and with the principal investigator once the study has finished. All study material will be handled with the same confidentiality as other medical records.

11.5 Labeling, Packaging, Storage, Accountability, and Return or Disposal of Investigational Product

11.5.1 Labeling/Packaging

A label will be included describing the appropriate use of the investigational product.The study medication will be packed and labeled according to ICH cGMP guidelines and to local law. This will be performed on behalf of the Sponsor by Oriola, Sweden. The study medication will be packed to avoid inadvertently unmasking and in such a way that the product is protected from deterioration during transport and storage. The labels will be translated as appropriate. The study medication will be filled into single dose vials– the

primary packaging. 10 vials will be packed in one sealed aluminum pouch, the secondary packaging, and then in a tertiary packaging (carton box) per subject.

Each aluminum foil and cardboard box will carry a label with

- Instructions on how to use the eye drops
- Sponsor name and address
- Protocol number
- Number of vials per aluminum pouch or carton box
- Expiry date
- Text regarding clinical trial
- Name and phone number of investigating physician

Both medications, Active and Vehicle, will be packaged in the same type of final packaging to respect the randomization and the masking methodology.

11.5.2 Storage of Investigational Product

The investigational product must be stored in a secure area accessible only to the investigator and his/her designees. The investigational product will be dispensed only to subjects entered into the clinical study, in accordance with the conditions specified in this protocol.

11.5.3 Accountability of Investigational Product

The investigational product is to only be prescribed by the principal investigator or his/her named sub investigator(s), and is to only be used in accordance with this protocol.

The investigator must keep an accurate accounting of the investigational product received from the supplier. This includes the amount of investigational product dispensed to subjects, amount of investigational product returned to the investigator by the subjects, and the amount returned or disposed upon the completion of the study. A detailed inventory must be completed for the investigational product.

11.5.4 Return or Disposal of Investigational Product

At the end of the study, all investigational product will be returned to the sponsor or their designee or destroyed at the study site. The return or disposal of investigational product will be specified in writing.

11.6 Recording of Data on Source Documents and Case Reports Forms (CRFs)

The investigator is responsible for ensuring that study data is completely and accurately recorded on each subject's case report form, source document, and all study-related material. All study data should also be attributable, legible, contemporaneous, and original. Recorded datum should only be corrected in a manner that does not obliterate, destroy, or render illegible the previous entry (eg, by drawing a single line through the incorrect entry and writing the revision next to the corrected data). An individual who has corrected a data entry should make clear who made the correction and when, by adding to the correction his/her initials as well as the date of the correction.

11.7 Publications

The sponsor, Oculis ehf. owns the rights to all data obtained during the conduct of the study and reserves the right to publish all data associated with this clinical study program. Authorship and manuscript composition will reflect cooperation among all parties involved in the study. Authorship will be established before writing the manuscript. The study sponsor, Oculis ehf. will have the final decision regarding the manuscript and publication.

12 Toxicology

In our previous animal studies on dexamethasone suspensions containing cyclodextrin the suspension was well tolerated after topical application to rabbits and no macroscopic signs of irritation and redness were observed (Loftsson et al. 2007; Sigurdsson et al. 2007; Loftsson et al. 2008; Jansook et al. 2010).

Dexamethasone eye drops are already on the market for more than a decade used to treat inflammation in the eyes. We refer to the summary of product characteristics for Maxidex® for list of possible side effects. Most common side effects of Maxidex® are burning in the eyes, increase IOP and ocular discomfort.

To summarize the human use of DexNP eye drops, they have been used in 60 patients treated for up to 12 weeks with up to 6 times a day frequency. No serious adverse effects have been noted. In addition 101 patients received an earlier dexamethasone cyclodextrin eye drops with no adverse effects.

The formulation contains γ-cyclodextrin which has GRAS (generally recognized as safe) recognition in food and drug industry. Cyclodextrins are already used in registered eye preparations e.g. Voltaren Ophtha® from Novartis registered in Sweden and Clorocil® eye drop solution.

Other inactive ingredients of the formulation are commonly used in eye formulations. All of them have an active monograph in the European Pharmacopoeia or USP monograph.

13 Disclosure and Confidentiality

All Unpublished information concerning the test product and research carried out by the Sponsor, including patent applications, manufacturing processes, basic scientific data, etc., is considered confidential and the sole property of the sponsor. Disclosure to third parties must be limited to those undertaking legitimate peer review of the scientific and ethical aspects of the trial and to those participating including the recipients of drugs, so that customary medical care and informed consent can be achieved.

14 Insurance Indemnity

The Sponsor agrees to indemnify (legal and financial coverage) and hold the Investigator free of harm from any claim, whether based on legal principles or on generally accepted liability standards within the pharmaceutical industry, made against him by reason of personal injury, including death, to any person arising out of or connected with the performance of the trial to the extent that the injury is not caused by:

1. failure by the Investigator to adhere to the terms of the Protocol;
2. failure by the Investigator to comply with any applicable governmental regulations;
3. malpractice, negligence or willful malfeasance by the Investigator.

The Investigator agrees to notify the Sponsor and IRW whenever he/she becomes aware of a claim or action, and to co-operate with and to authorize the Sponsor to carry out sole management of such claim or action.

The insurance also covers the Sponsor's liability under law and generally accepted liability standards within the pharmaceutical industry towards any third parties, including subjects, as Sponsor of the trial".

15 Trial Agreements

The Principal Investigator at the investigational site must comply with all the terms, conditions, and obligations of the Clinical Trial Agreement (CTA) for this trial. In the event of any inconsistency between the Trial Protocol and the CTA, the trial agreement shall prevail.

A separate Financial Agreement between /Sponsor/ and the Principal Investigator and/or institution will be filed in the Investigator's File and the Trial Master File.

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Appendix 1: Schedule of Visits and Measurements

Schedule of Visits and Measurements

7 visits over the course of 16 weeks:

Study visit schedule

- Screening Visit (Day -1 to -28)
- Baseline (Day 1)
- Week 2
- Week 4
- Week 8
- Week 12 - Primary end point
- Week 16 - final visit

(visit window is ± 3 days)

	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7
Procedure	Screening	Day 1	Week 2	Week 4	Week 8	Week 12	Week 16
Informed Consent	X						
Randomisation		X					
Demographic Data		X					
Medical and Ophthalmology History	X	X					
Medication History and Update	X	X	X	X	X	X	X
Visual Acuity	X	X	X	X	X	X	X
Biomicroscopy	X	X	X	X	X	X	X
IOP	X	X	X	X	X	X	X
Ophthalmoscopy	X	X				X	X
OCT	X	X	X	X	X	X	X
Cataract evaluation		X				X	
Blood test	X						X
Blood pressure	X	X	X	X	X	X	X
Urine pregnancy test	X*						
VFQ-25		X				X	
Investigational Product Dispensed		X		X	X		
Investigational Product Returned				X	X	X	
Adverse Events		X	X	X	X	X	X
Exit from Study							X

*if applicable

Appendix 2: NEI-VFQ-25 questionnaire

PB/IA

National Eye Institute
Visual Functioning Questionnaire - 25
(VFQ-25)

version 2000

(INTERVIEWER ADMINISTERED FORMAT)

January 2000

Instructions:

I'm going to read you some statements about problems which involve your vision or feelings that you have about your vision condition. After each question I will read you a list of possible answers. Please choose the response that best describes your situation.

Please answer all the questions as if you were wearing your glasses or contact lenses (if any).

Please take as much time as you need to answer each question. All your answers are confidential. In order for this survey to improve our knowledge about vision problems and how they affect your quality of life, your answers must be as accurate as possible. Remember, if you wear glasses or contact lenses for a particular activity, please answer all of the following questions as though you were wearing them.

Visual Functioning Questionnaire - 25

PART 1 - GENERAL HEALTH AND VISION

1. In general, would you say your overall health is*:

	(Circle One)
READ CATEGORIES:	
Excellent	1
Very Good	2
Good	3
Fair	4
Poor	5

2. At the present time, would you say your eyesight using both eyes (with glasses or contact lenses, if you wear them) is excellent, good, fair, poor, or very poor or are you completely blind?

	(Circle One)
READ CATEGORIES:	
Excellent	1
Good	2
Fair	3
Poor	4
Very Poor	5
Completely Blind	6

* Skip Question 1 when the VFQ-25 is administered at the same time as the SF-36 or RAND 36-Item Health Survey 1.0

3. How much of the time do you worry about your eyesight?

READ CATEGORIES:	(Circle One)
None of the time	1
A little of the time	2
Some of the time	3
Most of the time	4
All of the time?	5

4. How much pain or discomfort have you had in and around your eyes (for example, burning, itching, or aching)? Would you say it is:

READ CATEGORIES:	(Circle One)
None	1
Mild	2
Moderate	3
Severe, or	4

PART 2 - DIFFICULTY WITH ACTIVITIES

The next questions are about how much difficulty, if any, you have doing certain activities wearing your glasses or contact lenses if you use them for that activity.

5. How much difficulty do you have reading ordinary print in newspapers? Would you say you have:

(READ CATEGORIES AS NEEDED)

	(Circle One)
No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

6. How much difficulty do you have doing work or hobbies that require you to see well up close, such as cooking, sewing, fixing things around the house, or using hand tools? Would you say:

(READ CATEGORIES AS NEEDED)
(Circle One)

No difficulty at all..... 1
A little difficulty..... 2
Moderate difficulty..... 3
Extreme difficulty..... 4
Stopped doing this because of your eyesight..... 5
Stopped doing this for other reasons or not.....
interested in doing this 6

7. Because of your eyesight, how much difficulty do you have finding something on a crowded shelf?

(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all..... 1
A little difficulty..... 2
Moderate difficulty..... 3
Extreme difficulty..... 4
Stopped doing this because of your eyesight..... 5
Stopped doing this for other reasons or not.....
interested in doing this 6

8. How much difficulty do you have reading street signs or the names of stores?

(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all..... 1
A little difficulty..... 2
Moderate difficulty..... 3
Extreme difficulty..... 4
Stopped doing this because of your eyesight..... 5
Stopped doing this for other reasons or not.....
interested in doing this 6

9. Because of your eyesight, how much difficulty do you have going down steps, stairs, or curbs in dim light or at night?

(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all..... 1
A little difficulty..... 2
Moderate difficulty..... 3
Extreme difficulty..... 4
Stopped doing this because of your eyesight..... 5
Stopped doing this for other reasons or not.....
interested in doing this 6

10. Because of your eyesight, how much difficulty do you have noticing objects off to the side while you are walking along?

(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all..... 1
A little difficulty..... 2
Moderate difficulty..... 3
Extreme difficulty..... 4
Stopped doing this because of your eyesight..... 5
Stopped doing this for other reasons or not.....
interested in doing this 6

11. Because of your eyesight, how much difficulty do you have seeing how people react to things you say?

(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all..... 1
A little difficulty..... 2
Moderate difficulty..... 3
Extreme difficulty..... 4
Stopped doing this because of your eyesight..... 5
Stopped doing this for other reasons or not.....
interested in doing this 6

12. Because of your eyesight, how much difficulty do you have picking out and matching your own clothes?

(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all..... 1
A little difficulty..... 2
Moderate difficulty..... 3
Extreme difficulty..... 4
Stopped doing this because of your eyesight.... 5
Stopped doing this for other reasons or not interested in doing this 6

13. Because of your eyesight, how much difficulty do you have visiting with people in their homes, at parties, or in restaurants ?

(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all..... 1
A little difficulty..... 2
Moderate difficulty..... 3
Extreme difficulty..... 4
Stopped doing this because of your eyesight.... 5
Stopped doing this for other reasons or not interested in doing this 6

14. Because of your eyesight, how much difficulty do you have going out to see movies, plays, or sports events?

(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all..... 1
A little difficulty..... 2
Moderate difficulty..... 3
Extreme difficulty..... 4
Stopped doing this because of your eyesight.... 5
Stopped doing this for other reasons or not interested in doing this 6

15. Now, I'd like to ask about driving a car. Are you currently driving, at least once in a while?

(Circle One)
Yes ..... 1 *Skip To Q 15c*
No.....2

15a. IF NO, ASK: Have you never driven a car or have you given up driving?

(Circle One)
Never drove ..... 1 *Skip To Part 3, Q 17*
Gave up..... 2

15b. IF GAVE UP DRIVING: Was that mainly because of your eyesight, mainly for some other reason, or because of both your eyesight and other reasons?

(Circle One)
Mainly eyesight ..... 1 *Skip To Part 3, Q 17*
Mainly other reasons ..... 2 *Skip To Part 3, Q 17*
Both eyesight and other reasons .... 3 *Skip To Part 3, Q 17*

15c. IF CURRENTLY DRIVING: How much difficulty do you have driving during the daytime in familiar places? Would you say you have:

(Circle One)
No difficulty at all..... 1
A little difficulty..... 2
Moderate difficulty..... 3
Extreme difficulty..... 4

16. How much difficulty do you have driving at night? Would you say you have: (READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all..... 1
A little difficulty..... 2
Moderate difficulty..... 3
Extreme difficulty..... 4
Have you stopped doing this because.....
of your eyesight..... 5
Have you stopped doing this for other.....
reasons or are you not interested in.....
doing this 6

16a. How much difficulty do you have driving in difficult conditions, such as in bad weather, during rush hour, on the freeway, or in city traffic?

Would you say you have:

(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all..... 1
A little difficulty..... 2
Moderate difficulty..... 3
Extreme difficulty..... 4
Have you stopped doing this because.....
of your eyesight..... 5
Have you stopped doing this for other.....
reasons or are you not interested in...
doing this 6

PART 3: RESPONSES TO VISION PROBLEMS

The next questions are about how things you do may be affected by your vision. For each one, I'd like you to tell me if this is true for you all, most, some, a little, or none of the time.

READ CATEGORIES:	All of the time	Most of the time	Some of the time	A little of the time	None of the time
	(Circle One On Each Line)				
17. Do you accomplish less than you would like because of your vision?	1	2	3	4	5
18. Are you limited in how long you can work or do other activities because of your vision?	1	2	3	4	5
19. How much does pain or discomfort in or around your eyes, for example, burning, itching, or aching, keep you from doing what you'd like to be doing? Would you say:	1	2	3	4	5

For each of the following statements, please tell me if it is definitely true, mostly true, mostly false, or definitely false for you or you are not sure.

	(Circle One On Each Line)				
	Definitely True	Mostly True	Not Sure	Mostly False	Definitely False
20. I stay home most of the time because of my eyesight.....	1	2	3	4	5
21. I feel frustrated a lot of the time because of my eyesight.....	1	2	3	4	5
22. I have much less control over what I do, because of my eyesight.	1	2	3	4	5
23. Because of my eyesight, I have to rely too much on what other people tell me..	1	2	3	4	5
24. I need a lot of help from others because of my eyesight.	1	2	3	4	5
25. I worry about doing things that will embarrass myself or others, because of my eyesight.....	1	2	3	4	5

That's the end of the interview. Thank you very much for your time and your help.

Appendix of Optional Additional Questions

SUBSCALE: GENERAL HEALTH

A1. How would you rate your overall health, on a scale where zero is as bad as death and 10 is best possible health?

(Circle One)

0	1	2	3	4	5	6	7	8	9	10
Worst										Best

SUBSCALE: GENERAL VISION

A2. How would you rate your eyesight now (with glasses or contact lens on, if you wear them), on a scale of from 0 to 10, where zero means the worst possible eyesight, as bad or worse than being blind, and 10 means the best possible eyesight?

(Circle One)

0	1	2	3	4	5	6	7	8	9	10
Worst										Best

SUBSCALE: NEAR VISION

A3. Wearing glasses, how much difficulty do you have reading the small print in a telephone book, on a medicine bottle, or on legal forms?

Would you say:

(READ CATEGORIES AS NEEDED)

	(Circle One)
No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

A4. Because of your eyesight, how much difficulty do you have figuring out whether bills you receive are accurate?

(READ CATEGORIES AS NEEDED)

	(Circle One)
No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

A5. Because of your eyesight, how much difficulty do you have doing things like shaving, styling your hair, or putting on makeup?

(READ CATEGORIES AS NEEDED)

	(Circle One)
No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

SUBSCALE: DISTANCE VISION

A6. Because of your eyesight, how much difficulty do you have recognizing people you know from across a room?

(READ CATEGORIES AS NEEDED)

	(Circle One)
No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

A7. Because of your eyesight, how much difficulty do you have taking part in active sports or other outdoor activities that you enjoy (like golf, bowling, jogging, or walking)?

(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all..... 1
A little difficulty..... 2
Moderate difficulty..... 3
Extreme difficulty..... 4
Stopped doing this because of your eyesight.... ... 5
Stopped doing this for other reasons or not.....
interested in doing this 6

A8. Because of your eyesight, how much difficulty do you have seeing and enjoying programs on TV?

(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all..... 1
A little difficulty..... 2
Moderate difficulty..... 3
Extreme difficulty..... 4
Stopped doing this because of your eyesight..... 5
Stopped doing this for other reasons or not.....
interested in doing this 6

SUBSCALE: SOCIAL FUNCTION

A9. Because of your eyesight, how much difficulty do you have entertaining friends and family in your home?

(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all..... 1
A little difficulty..... 2
Moderate difficulty..... 3
Extreme difficulty..... 4
Stopped doing this because of your eyesight..... 5
Stopped doing this for other reasons or not.....
interested in doing this 6

SUBSCALE: DRIVING

A10.[This items, "driving in difficult conditions", has been included as item

16a as part of the base set of 25 vision-targeted items.]

SUBSCALE: ROLE LIMITATIONS

A11.The next questions are about things you may do because of your vision. For each item, I'd like you to tell me if this is true for you all, most, some, a little, or none of the time.

(READ CATEGORIES AS NEEDED)

READ CATEGORIES:	All of the time	Most of the time	Some of the time	A little of the time	None of the time
				(Circle One On Each Line)	
a. Do you have more help from others because of your vision?	1	2	3	4	5
b. Are you limited in the kinds of things you can do because of your vision?	1	2	3	4	5

SUBSCALES: WELL-BEING/DISTRESS (#A12) and DEPENDENCY (#A13)

The next questions are about how you deal with your vision. For each statement, please tell me if it is definitely true, mostly true, mostly false, or definitely false for you or you don't know.

	(Circle One On Each Line)				
	Definitely True	Mostly True	Not Sure	Mostly False	Definitely False
A12.I am often irritable because of my eyesight.....	1	2	3	4	5
A13.I don't go out of my home alone, because of my eyesight.....	1	2	3	4	5

Appendix 3: Sponsor and IRW Approvals

Protocol Title:	Efficacy and safety of dexamethasone nanoparticles eye drops in diabetic macular edema.
Protocol Number:	DX211
Final Date:	13 APR 2017

This clinical study protocol was subject to critical review and has been approved by the sponsor. The following personnel contributed to writing and/or approving this protocol.

Signed: _____ Date: 25/4/2017
Dr. Einar Stefánsson
Professor Ophthalmology, University Iceland
Chief Medical Officer/Co-founder Oculis ehf.

Signed: _____ Date: 20. April 2017
Rene Ruckert, MD., MBA
Chief Operating Officer, Oculis ehf.

Signed: _____ Date: 19 April 2017
Guðrún Marta Ásgrímsdóttir, M.Sc.
Chief R&D Officer, Oculis ehf.

Signed: _____ Date: April 23, 2017
Michael Larsen, MD, DMSc,
Professor of Clinical Ophthalmology
Department of Ophthalmology,
Rigshospitalet-Glostrup and University of Copenhagen

Signed: _____ Date: 26APR 2017
Maria Löök Santesson
CRM, Clinical Team Leader
IRW Consulting AB

Signed: _____ Date: 26/APR/2017
Ola Jeppsson
Vice President
IRW Consulting AB

Appendix 4: Investigator's Signature

Protocol Title:	Efficacy and safety of dexamethasone nanoparticles eye drops in diabetic macular edema.
Protocol Number:	DX211
Final Date:	13APR2017

I agree to implement and conduct the study diligently and in strict compliance with the protocol, good clinical practices and all applicable laws and regulations. I agree to maintain all information supplied by IRW and the sponsor in confidence and, when this information is submitted to an Institutional Review Board (IRB), Ethical Review Committee (ERC) or another group, it will be submitted with a designation that the material is confidential.

I have read this protocol in its entirety, including the above statement, and I agree to all aspects.

Name: _____

Signed:_____

Date:_____