24 July 2014
EMA/492068/2014
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Ozurdex

International non-proprietary name: DEXAMETHASONE

Procedure No. EMEA/H/C/001140/II/0015

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

AE	adverse event
ADR	adverse drug reaction
ANCOVA	analysis of covariance
AUC	area under the curve
BCVA	best-corrected visual acuity
BRVO	branch retinal vein occlusion
BSE	better-seeing eye
CI	confidence interval
CRVO	central retinal vein occlusion
CSR	clinical study report
DCCT	Diabetes Control and Complications Trial
DEX	dexamethasone
DEX 350	350 µg DEX PS DDS Applicator System (350 µg dexamethasone)
DEX 700	700 µg DEX PS DDS Applicator System (700 µg dexamethasone)
DEX PS DDS	dexamethasone posterior segment drug delivery system
DME	diabetic macular oedema
DR	diabetic retinopathy
EOP2	end-of-phase 2
ETDRS	Early Treatment of Diabetic Retinopathy Study
FA	fluocinolone acetonide
FDA	(United States) Food and Drug Administration
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
HbA1c	glycosylated haemoglobin
HCP	health care professionals
ICER	Institute for Clinical and Economic Review
IND	Investigational New Drug (application)
IOP	intraocular pressure
ITT	intent to treat (analysis population)
LC-MS/MS	liquid chromatography-tandem mass spectrometry method
LLOQ	lower limit of quantitation
LOCF	last observation carried forward
MedDRA	Medical Dictionary of Regulatory Activities
NDA	New Drug Application (United States)
NEI	National Eye Institute
NPDR	non-proliferative diabetic retinopathy
OCT	optical coherence tomography
PDR	proliferative diabetic retinopathy
PI	product information
PL	package leaflet
PRP	oanretinal photocoagulation
PSC	posterior subcapsular (opacities)
PT	MedDRA preferred term
RVO	retinal vein occlusion
SAE	Serious adverse event
Sham	Sham DEX PS DDS applicator system (needleless DDS applicator)
SmPC	Summary of Product Characteristics
UKPD	United Kingdom Prospective Diabetes
US(A)	United States of America
VEGF	vascular endothelial growth factor

VFQ-25	Visual Functioning Questionnaire-25
WESDR	Wisconsin Epidemiologic Study of Diabetic Retinopathy

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Allergan Pharmaceuticals Ireland submitted to the European Medicines Agency on 21 June 2013 an application for a variation including an extension of indication.

This application concerns the following medicinal product:

Medicinal product:	**International non-proprietary name:**	**Presentations:**
Ozurdex	DEXAMETHASONE	See Annex A

The following variation was requested:

Variation requested		**Type**
C.1.6 a)	Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

The MAH applied for a new indication for the treatment of adult patients with diabetic macular oedema. Consequently, the MAH proposed the update of sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC. The package leaflet (PL) was updated accordingly. In addition, the MAH proposed to reduce and consolidate the current HCP leaflet, which is provided as tear off section at the end of the PL.
The MAH also proposed this opportunity to bring the product information (PI) in line with the latest QRD template version 9.0.

The variation proposed amendments to the Summary of Product Characteristics and Package Leaflet.

CHMP Rapporteur: Greg Markey

CHMP Co-Rapporteur: Concepcion Prieto

PRAC Rapporteur: Julie Williams

Information on paediatric requirements

Not applicable.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.2. Steps taken for the assessment of the product

Submission date:	21 June 2013
Start of procedure:	26 July 2013
Rapporteur's preliminary assessment report circulated on:	16 September 2013
Co-Rapporteur's preliminary assessment report circulated on:	20 September 2013
PRAC RMP advice adopted on:	10 October 2013
Joint Rapporteur's assessment report circulated on:	10 October 2013
Joint Rapporteur's updated assessment report circulated on:	18 October 2013
Request for supplementary information and extension of timetable adopted by the CHMP on:	24 October 2013
MAH's responses submitted to the CHMP on:	16 December 2013
Rapporteur's preliminary assessment report on the MAH's responses circulated on:	20 January 2014
PRAC Rapporteur's RMP assessment report adopted on:	6 February 2014
Rapporteur's final assessment report on the MAH's responses circulated on:	17 February 2014
Request for supplementary information and extension of timetable adopted by the CHMP on:	20 February 2014
MAH's responses submitted to the CHMP on:	25 April 2014
Joint Rapporteur's preliminary assessment report on the MAH's responses circulated on:	22 May 2014
PRAC Rapporteur's RMP assessment report adopted on:	12 June 2014
An Oral explanation took place on:	25 June 2014
Request for supplementary information and extension of timetable adopted by the CHMP on:	26 June 2014
MAH's responses submitted to the CHMP on:	2 July 2014
Joint Rapporteur's preliminary assessment report on the MAH's responses circulated on:	10 July 2014
PRAC Rapporteur's RMP assessment report adopted on:	10 July 2014
CHMP opinion:	24 July 2014

2. Scientific discussion

2.1. Introduction

Ozurdex contains an extruded dosage form of 700 µg dexamethasone (DEX), in an inactive biodegradable polymer matrix, also referred to as dexamethasone posterior segment drug delivery system (DEX PS DDS). Ozurdex implants provide sustained release of dexamethasone, thereby reducing the frequency of repeated intravitreal injections. Dexamethasone is a corticosteroid that exerts anti-inflammatory properties by inhibiting oedema, fibrin deposition, capillary leakage, and phagocytic migration of the inflammatory response.

Ozurdex was granted a marketing authorisation in the European Union (EU) through the centralised procedure by Commission Decision on 27 July 2010 for the treatment of adult patients with macular oedema following either Branch Retinal Vein Occlusion (BRVO) or Central Retinal Vein Occlusion (CRVO). In 2011, Ozurdex was furthermore approved for use in a new indication of treatment of adult patients with inflammation of the posterior segment of the eye presenting as non-infectious uveitis.

Patients may receive repeated doses of Ozurdex, if, in the physician's opinion, they may benefit from retreatment without being exposed to significant risk. However, experience is limited with regards to repeat-dosing intervals less than 6 months and there is no experience of repeated administrations in uveitis or beyond 2 implants in RVO.

With this application, the MAH applied for a new indication in the treatment of adult patients with diabetic macular oedema (DME). The application was mainly supported by results from two pivotal phase 3 studies which employed the same protocol.

DME may develop as a consequence of diabetic retinopathy (DR) and can occur at any DR stage. DR is one of the most important causes of visual loss worldwide, and is the principal cause of impaired vision in patients between 25 and 74 years of age. Visual loss from diabetic retinopathy may be secondary to macular oedema (retinal thickening and oedema involving the macula), haemorrhage from new vessels, retinal detachment, or neovascular glaucoma. DME typically presents with a gradual onset of blurring of near and distant vision in patients who have other evidence of microvascular eye disease, such as peri-macular microaneurysms.

Early detection of retinopathy in individuals with diabetes is critical in preventing visual loss, but current methods of screening fail to identify a sizable number of high-risk patients. The control of diabetes associated metabolic abnormalities (i.e. hyperglycemia, hyperlipidemia, and hypertension) is also important in preserving visual function because these conditions have been identified as risk factors for both the development and progression of DR and DME.

In 1985, the Early Treatment Diabetic Retinopathy Study (ETDRS) established laser photocoagulation as the standard of care for DME. The study showed that laser photocoagulation for clinically significant macular oedema reduces the risk of moderate vision loss by one half (23% versus 12%) over three years, but gains in vision occur slowly, and only 3% of patients experience a 15-letter improvement. The risks of laser photocoagulation include foveal damage due to inadvertent macular photocoagulation when laser is performed on microaneurysms close to the fovea and postoperative expansion of treatment scars, both of which may result in a permanent decrease in visual acuity.

At the time of this report, other therapeutic options for the management of DME in addition to laser included vitrectomy surgery, steroids, and Vascular Endothelial Growth Factor (VEGF) inhibitors.

VEGF is a cytokine promoting neovascularisation and vascular permeability. VEGF is expressed at increased concentrations in the setting of macular oedema and has been shown to be extensively involved in the development and progression of DME. Corticosteroids have been shown to inhibit the expression of VEGF, and consequently may help to antagonise VEGF-mediated disease progression. Additionally, corticosteroids prevent the release of prostaglandins, some of which have been identified as mediators of cystoid macular oedema.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity / environmental risk assessment

The environmental exposure assessment was conducted to determine the predicted aquatic concentrations of the active ingredient, dexamethasone, in surface water. As Ozurdex can be prescribed for the treatment of more than one indication, the $PEC_{surface\ water}$ has been calculated as the sum all of three clinical indications RVO, uveitis and DME, taking into account prevalence data and

treatment regimens, resulting in a $PEC_{surface\ water}$ of $1.69*10^{-5}$ µg/L. This is less than the threshold of 0.01 µg/L.

Therefore and since dexamethasone is not a persistent bioaccumulative and toxic drug, as log Kow does not exceed 4.5 (2.06 ± 0.58), further risk studies have not been performed. This was considered acceptable by the CHMP.

2.3. Clinical aspects

2.3.1. Introduction

Good Clinical Practice (GCP)

The clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Study ID	No. of study centres / locations	Design	Study Posology	Study Objective	Subjects by arm entered	Duration	Gender M/F, Median Age	Diagnosis Incl. criteria	Primary Endpoint
206207-010	59 centres (including Australia, Asia, North America, Europe)	Randomised, sham-controlled, masked, parallel group	700 µg DEX PS DDS; 350 µg DEX PS DDS; Sham injection	Efficacy and safety	163, 166, 165	3 years	62% male, mean age 63 years	DME, BCVA 34-68 letters, retinal thickness ≥300 µm	BCVA average change from baseline
206207-011	72 centres (South America, North America, Europe, Asia, New Zealand)	Randomised, sham-controlled, masked, parallel group	700 µg DEX PS DDS; 350 µg DEX PS DDS; Sham injection	Efficacy and safety	188, 181, 185	3 years	60% male, mean age 62 years	DME, BCVA 34-68 letters, retinal thickness ≥300 µm	BCVA average change from baseline
206207-012	48 centres (US, Canada)	Randomised, masked, parallel group	700 µg DEX PS DDS with laser; laser alone	Efficacy and safety	126, 127	1 year	51% male, mean age 62 years	DME, BCVA 34-70, retinal thickness ≥275 µm	Proportion with BCVA improvement of ≥10 letters in study eye from baseline
206207-018	13 centres (US, Australia)	Open-label, uncontrolled	700 µg DEX PS DDS	Efficacy and safety	55	26 weeks	46% male	DME, BCVA 24-70 letters, retinal thickness ≥275 µm, history of pars plana vitrectomy	Change from baseline in central retinal thickness by OCT

2.3.2. Pharmacokinetics

The pharmacokinetic (PK) profile of the Ozurdex has been outlined in the initial marketing authorisation application. In the DME development program, no new PK studies were performed.

However, plasma samples were drawn from a small subset of patients from each of the two Phase 3 studies to investigate the PK of the DEX PS DDS 350 and 700 µg implants in patients with DME.

In Study 206207-010, PK samples were collected from 19 patients (5 patients in the DEX 700 group, 8 patients in the DEX 350 group, and 6 patients in the Sham group) at baseline (prior to dosing), days 1, 7, and 21, and at months 1.5 and 3 after the first treatment. Of the 23 PK samples collected from the 5 patients in the DEX 700 group, 20 samples (i.e. 87% of the PK samples) had plasma concentrations of dexamethasone below the lower limit of quantitation (LLOQ) of 0.05 ng/mL, and only 3 samples (i.e. 13% of samples) had concentrations that were slightly above the LLOQ. The highest observed plasma concentration of dexamethasone in this study was 0.0889 ng/mL. All samples collected from the 8 patients in the DEX 350 group and from the 6 patients in the Sham treatment group had plasma concentrations of dexamethasone below the LLOQ.

In Study 206207-011, PK samples were collected from 12 patients (5 patients in the DEX 700 group, 3 patients in the DEX 350 group, and 4 patients in the Sham group) at the same study visits as described above. A total of 93% of the PK samples collected from the patients in the DEX 700 group had plasma concentrations of dexamethasone below the LLOQ, and only 2 samples collected from 2 different patients had concentrations that were slightly above the LLOQ. The highest observed plasma concentration of dexamethasone in this study was 0.102 ng/mL (observed at 7 days post-dose). All PK samples collected from the 3 patients in the DEX 350 group and from the 4 patients in the Sham treatment group had plasma concentrations of dexamethasone below the LLOQ.

There were no apparent correlations between plasma dexamethasone concentration and age, body weight, or sex.

2.3.3. Conclusions on clinical pharmacology

The systemic exposure to dexamethasone in DME patients receiving Ozurdex was consistent with that described in the SmPC for patients with macular oedema secondary to RVO. The findings of the PK analysis did not raise any concerns.

2.4. Clinical efficacy

Data from four clinical studies were submitted in support of this application. The efficacy claim in DME was primarily based on data from two phase 3 studies, 206207-010 and 206207-011. In addition, two phase 2 studies were conducted to investigate the safety and efficacy of dexamethasone in combination with laser photocoagulation (study 206207-012) and in vitrectomised patients (study 206207-018).

2.4.1. Dose finding studies

No specific dose-response studies were performed as part of the DME development program. Reference was made by the MAH to a dose-ranging study (DC103-06) that evaluated the tableted form of DEX PS DDS inserted via surgery compared to an untreated observation group. This study included patients with persistent macular oedema due to RVO, uveitis, and Irvine-Gass syndrome, in addition to diabetic retinopathy. The study showed a dose-response effect across all efficacy parameters, with a greater therapeutic effect associated with DEX 700 than with DEX 350. Data from this study have been discussed in detail in a previous submission, including those for the subgroup of diabetic patients, and have not been resubmitted.

2.4.2. Main studies

The two Phase 3 studies, 206207-010 and -011, shared the same protocol, and the results were presented by the MAH both separately and based on an integrated analysis.

Study 206207-010/-011: A 3-Year, Phase 3, Multicenter, Masked, Randomized, Sham-Controlled Trial to Assess the Safety and Efficacy of 700 µg and 350 µg Dexamethasone Posterior Segment Drug Delivery System (DEX PS DDS) Applicator System in the Treatment of Patients with Diabetic Macular Edema

Methods

Study participants

For enrolment into the study, each patient had to meet all of the following criteria. If both eyes were eligible for the study, the eye with shorter duration of macular oedema was to be selected. The study eye was identified at the qualification/baseline visit and remained the same throughout the entire study duration. Only the study eye was treated in the study.

Main inclusion criteria

- Male or female, at least 18 years of age
- Diagnosis of diabetes mellitus (type 1 or type 2). Any 1 of the following was considered to be sufficient evidence that diabetes was present:
  - Current regular use of insulin for the treatment of diabetes.
  - Current regular use of oral hypoglycaemic agent(s) for the treatment of diabetes.
  - Diabetes defined by American Diabetes Association (ADA) guidelines:
    - Symptoms of diabetes (polyuria, polydipsia, and unexplained weight loss) plus plasma glucose concentration at any time of the day regardless of time since last meal ≥ 200 mg/dL (11.1 mmol/L) or
    - 8-hour fasting plasma glucose ≥ 126 mg/dL (7.0 mmol/L) or
    - 2-hour post-load (75 g) glucose ≥ 200 mg/dL (11.1 mmol/L) during an oral glucose tolerance test.
- Diabetic macular oedema in the study eye defined as clinically observable macular oedema involving the centre of the macula (fovea) associated with diabetic retinopathy with any of the following characteristics:
  - Prior medical therapy for DME;
  - Prior macular laser(s) for DME with the most recent laser at least 3 months prior to qualification/baseline when, in the opinion of the investigator, the patient would be able to improve 15 or more letters in best corrected visual acuity (BCVA) from baseline with the resolution of the macular oedema despite the presence of macular laser scars;
  - In the investigator's opinion the patient would not benefit from macular laser treatment;
  - The patient refused laser treatment.
- BCVA score between 34 letters (approximately 20/200 Snellen equivalent) and 68 letters (approximately 20/50 Snellen equivalent) in the study eye measured by the ETDRS method at qualification/baseline.

- Retinal thickness of ≥ 300 µm by optical coherence tomography (OCT) in the 1 mm central macular subfield of the study eye at qualification/baseline as determined by the investigator.
- Patients who had received intravitreal triamcinolone acetonide must have satisfied the following:
    - the intended dose for each injection was 4 mg or less;
    - the most recent dose was at least 6 months prior to the qualification/baseline visit;
    - no treatment-related adverse event was seen that, in the opinion of the investigator, had the potential to worsen or reoccur with study treatment.

Main exclusion criteria

- Uncontrolled systemic disease or current immunosuppressive diseases (eg, HIV or AIDS).
- Initiation of medical therapy for diabetes or a change from oral hypoglycaemic agents to insulin therapy within 4 months prior to the qualification/baseline visit.
- Blood HbA1c level greater than 10% at the qualification/baseline visit.
- Renal failure requiring haemodialysis or peritoneal dialysis within 6 months prior to the qualification/baseline visit.
- Adjusted glomerular filtration rate less than 50 mL/min based on the Modified Diet in Renal Disease formula adjusted for body surface area at the qualification/baseline visit.
- Any ocular condition in the study eye that, in the opinion of the investigator, would have prevented a 15-letter improvement in visual acuity (eg, severe macular ischemia, extensive macular laser scarring or atrophy).
- Presence of branch retinal vein occlusion, central retinal vein occlusion, uveitis, pseudophakic cystoid macular oedema, or any other condition in the study eye that could have been contributing to macular oedema.
- Presence of an epiretinal membrane or vitreoretinal interface changes in the study eye that, in the opinion of the investigator, was the primary cause of macular oedema or was severe enough to prevent improvement in visual acuity despite reduction in macular oedema.
- History of intraocular pressure (IOP) elevation in response to steroid treatment in either eye that resulted in any of the following:
    - a ≥ 10 mm Hg increase in IOP from baseline with an absolute IOP ≥ 25 mm Hg;
    - required therapy with 3 or more anti-glaucoma medications.
- History of glaucoma or optic nerve head change consistent with glaucoma damage, and/or glaucomatous visual field loss in the study eye. Patients with a history of previous angle-closure or similar conditions that have been successfully treated with either a laser or surgical peripheral iridotomy were allowed as long as the visual fields and optic nerves had been stable for > 1 year prior to study entry and the patient had been and could be safely dilated.
- Ocular hypertension in the study eye at qualification/baseline with any of the following:
    - IOP > 23 mm Hg if taking no anti-glaucoma medications;
    - IOP > 21 mm Hg if taking 1 anti-glaucoma medication;

- use of 2 or more anti-glaucoma medications (combination products were to be considered 2 medications).

Note: Anti-glaucoma medications or lack thereof must have been stable for at least 4 weeks prior to qualification/baseline.

- Aphakia or presence of anterior chamber intraocular lens in the study eye.
- Active optic disc or retinal neovascularization in the study eye at qualification/baseline.
- Active or history of choroidal neovascularization in the study eye.
- Presence of rubeosis iridis in the study eye at qualification/baseline.
- Any active ocular infection (i.e. bacterial, viral, parasitic, or fungal) in either eye at qualification/baseline.
- History of herpetic infection in the study eye or adnexa.
- Presence of active or inactive toxoplasmosis in either eye at qualification/baseline.
- Presence of visible scleral thinning or ectasia in the study eye
- Media opacity in the study eye at qualification/baseline that precluded clinical and photographic evaluation (including but not limited to pre-retinal or vitreous haemorrhage, lens opacity).
- Intraocular surgery, including cataract surgery, and/or laser of any type in the study eye within 90 days prior to qualification/baseline.
- History of central serous chorioretinopathy in either eye.
- History of pars plana vitrectomy in the study eye.
- Anticipated need for ocular surgery or laser in the study eye within 1 year following the qualification/baseline visit (eg, panretinal photocoagulation (PRP), cataract surgery).
- History of use of intravitreal steroids in the study eye other than triamcinolone acetonide.
- History of use of intravitreal bevacizumab, ranibizumab, or pegaptanib in the study eye within 3 months prior to the qualification/baseline visit.
- History of use of any intravitreal agent in the study eye other than triamcinolone acetonide, bevacizumab, ranibizumab, or pegaptanib, or intravitreal doses of triamcinolone acetonide > 4 mg, bevacizumab > 1.25 mg, ranibizumab > 0.5 mg, or pegaptanib > 0.3 mg.
- Periocular depot of steroids to the study eye within 6 months prior to qualification/baseline.
- Use of systemic steroids (eg, oral, intravenous, intra-articular, epidural, intra-bursal) within 1 month prior to the qualification/baseline visit or anticipated use at any time during the study. Inhaled and intranasal steroids were allowed.
- For patients who participated in therapeutic drug monitoring evaluation only: use of dexamethasone within 1 month prior to qualification/baseline or anticipated use during the first 90 days in any form/route of administration.
- Use of immunosuppressants, immunomodulators, antimetabolites, and/or alkylating agents within 6 months prior to qualification/baseline or anticipated use at any time during the study.

- Use of warfarin, enoxaparin, or heparin within 2 weeks prior to qualification/baseline or anticipated use within the 3-year study period.
- BCVA score < 34 letters (approximately 20/200 Snellen equivalent) in the non-study eye using the ETDRS method at qualification/baseline.
- Previous enrolment in a DEX PS DDS Applicator System clinical trial.

Treatments

Patients received the initial treatment with dexamethasone 700 µg (DEX 700), dexamethasone 350 µg (DEX 350), or Sham in the study eye on randomisation day (day 0), and could have received up to 6 additional retreatments of the same assigned study medication. Patients were assessed for retreatment eligibility every 3 months at a scheduled visit starting from month 6 through month 36, whereby the study treatment procedure was not to be performed more often than approximately every 6 months. Patients were eligible for retreatment if:

- Retinal thickness in the 1 mm central macular subfield by optical coherence tomography is >175 µm (determined by the site, not the central reading centre),

OR

- Upon investigator interpretation of the OCT for any evidence of residual retinal oedema consisting of intraretinal cysts or any regions of increased retinal thickening (within or outside of the centre subfield).

Patients randomised to active treatment had the study drug placed into the vitreous through the pars plana using the DEX PS DDS Applicator System. Patients randomised to Sham treatment had the needleless applicator pressed against the conjunctiva to preserve masking.

Prior to study treatment, the study eye of each patient was anesthetised with topical and subconjunctival anesthetic. Patients also received antimicrobial drops in the study eye 4 times per day for 3 days prior to the study treatment procedure, up to 4 times per day on the day of the procedure, and 4 times per day for 3 days post-operatively.

Following the 4th protocol amendment, the final allowed treatment was moved from the month 33 to the month 36 visit and the last/exit visit was re-scheduled from month 36 to month 39.

Rescue Therapy

A patient could have been treated with escape therapy (defined as any therapy for macular oedema in the study eye other than the assigned study medication) at the investigator's discretion at any time during the study. Escape therapy could have included:

- intravitreal steroids other than the study medication in the study eye;
- periocular steroids in the study eye;
- laser and/ or surgical treatments for macular oedema in the study eye;
- intravitreal anti-vascular endothelial growth factor (VEGF) therapy in the study eye;
- systemic anti-VEGF therapy;
- other pharmacologic therapies for macular oedema in the study eye.

Patients who received escape therapy in the study eye were considered study treatment failures, were no longer be eligible to receive study medication, and were withdrawn from the study based on when

they last received study treatment. If the last study treatment was less than 3 months prior to the escape therapy, the patient was followed up for adverse event information 3 months after the last study treatment.

Withdrawals

A patient who had a confirmed decrease in BCVA of 15 or more letters from baseline in the study eye attributable to macular oedema (eg, not due to cataract or media opacity) was exited from the study at the investigator's discretion and considered a treatment failure. This 15 or more letter decrease in BCVA was confirmed and documented at 2 consecutive visits at least 4 weeks apart using the ETDRS method. The patient did not receive study treatment between or during these 2 visits.

Objectives

The study objectives were:

- to evaluate the safety and efficacy of the 700 µg DEX PS DDS Applicator System (700 µg dexamethasone) and 350 µg DEX PS DDS Applicator System (350 µg dexamethasone) compared with a Sham DEX PS DDS Applicator System (needleless applicator) in patients with DME.
- to evaluate the safety and efficacy of the 700 µg DEX PS DDS Applicator System (700 µg dexamethasone) compared with the 350 µg DEX PS DDS Applicator System (350 µg dexamethasone) in patients with DME.

Outcomes/endpoints

The primary efficacy endpoint was BCVA average change from baseline during the study using observed data in the study eye (AUC approach). BCVA was measured using the ETDRS method in the study eye at the qualification/baseline visit and each follow-up visit. BCVA measurements were performed following manifest refraction, except at days 1, 7, and 21, after the study treatment or retreatment. At days 1, 7, and 21 after a treatment or retreatment, visual acuity evaluations were performed using refraction obtained at baseline or at the preceding retreatment visit, respectively.

Secondary efficacy analyses of BCVA included:

- mean change from baseline;
- proportion of patients with improvement of 10 or more letters from baseline;
- proportion of patients with improvement of 15 or more letters from baseline;
- categorical change from baseline;
- proportion of patients with worsening of 15 or more letters from baseline.

Secondary efficacy analyses of central subfield retinal thickness using OCT included:

- average change from baseline (AUC approach);
- mean change from baseline.

OCT was performed in both eyes at the qualification/baseline visit, and in only the study eye every 3 months. The mean retinal thickness in the 1 mm central subfield was captured. OCT images were collected and submitted for evaluation to a central reading centre using standardised procedures by graders masked to the study group assignment.

Secondary efficacy analyses of diabetic retinopathy severity level based on fundus photography included:

- proportion of patients at each severity category by visit;
- time to first diabetic retinopathy 3–step progression;
- time to first diabetic retinopathy 2–step progression.

Fundus photography was performed in both eyes when fluorescein angiography was required. A central reading centre assessed fundus photographs for macular oedema and diabetic retinopathy severity. The ratings were condensed to 9 severity categories based on ETDRS Final Retinopathy Severity Scale: diabetic retinopathy absent, microaneurysms only, mild non-proliferative diabetic retinopathy (NPDR), moderate NPDR, moderately severe NPDR, severe NPDR, mild proliferative diabetic retinopathy (PDR), moderate PDR, and high risk or advanced PDR.

Secondary efficacy analyses of contrast sensitivity using the Pelli-Robson chart: Change from baseline number of letters read correctly.

Other endpoints:

- Baseline and change from baseline retinal thickness in the centre point and macular volume (mm^3) in the study eye evaluated using OCT.
- Presence of retinal thickening within the grid of the study eye as evaluated using fundus photography including clinically significant macular oedema, area of hard exudates, cyst size, and centre retinal thickness.
- Raw values and change from baseline in calculated total disk areas of fluorescein leakage at the centre, inner, and outside subfield. Fluorescein angiography was performed in both eyes to provide angiographic evidence of leakage at the qualification/baseline visit and evidence of change over time. The central reading centre analysed fluorescein leakage, capillary non-perfusion, and cystoid changes.
- Patient reported outcomes using the National Eye Institute (NEI) Visual Functioning Questionnaire 25 (VFQ-25), SF-36™ Health Survey version 1 (SF-36v1), and EuroQol 5 Dimensions Health Questionnaire (EQ-5D).

Sample size

The sample size calculation was based on the primary efficacy analysis of the BCVA average change from baseline in the study eye comparing each DEX PS DDS dose and Sham. From 2 single-dose studies in RVO, the observed BCVA average change from baseline during the study at month 6 was 6.9 and 2.9 letters for the DEX 700 and Sham groups, respectively. The observed standard deviation was 10 letters. Therefore, for the DME studies, assuming a 4-letter mean difference in the BCVA average change from baseline during the study for DEX 700 over Sham, and an increase of 20% in the standard deviation to 12.0 letters due to increased variation for multiple injections and longer study duration, the planned sample size of 170 patients per arm (510 patients total) would have a power of 86% (2-sided alpha of 0.05).

Randomisation

Sites used either the interactive voice response system (IVRS) or the interactive web response system (IWRS) to assign to each qualified patient a randomisation number. Patients were randomised in a 1:1:1 ratio to DEX 700, DEX 350, or Sham.

Blinding (masking)

Patients were masked to the study treatments for the duration of the trial. The study treatment procedure and post-injection safety evaluations (except BCVA) were performed by the treating investigator. The treating investigator also evaluated the quality of the OCT prints, fundus photographs, and/or fluorescein angiograms obtained during the qualification/baseline visit. He/she had overall responsibility for the safety of the patient, and did not participate in the efficacy evaluations. Treating investigators were to keep study medication information confidential unless sharing this information was in the best interest of the patient for safety reasons.

The follow-up investigator did not participate in study treatment procedures. The treating investigators and follow-up investigators were to maintain their roles throughout the study. Any unscheduled visits necessary within 30 days after a study treatment procedure were performed by the treating investigator. All other unscheduled visits were performed by the follow-up investigator.

Individuals collecting BCVA, contrast sensitivity, OCT, fundus photographs, and fluorescein angiography data were masked to patient treatments. BCVA technicians only performed measurements of BCVA, manifest refraction, and contrast sensitivity.

A central reading centre was used to evaluate OCT, fundus photographs, and fluorescein angiography and the grader was masked from study treatments.

The study medications were supplied in identically appearing packages. The assembled DEX PS DDS Applicator System and the needleless DDS applicator without study treatment were individually packaged in identical pouches and carton with a unique identifier.

Statistical methods

Analysis populations

The **intent-to-treat (ITT) population** was defined as all randomised patients. The ITT analysis was performed based on the treatment to which the patient was randomised, and was used for the analysis of baseline characteristics, efficacy variables, and health outcome variables.

The **per protocol (PP) population** was defined as randomised patients with no major protocol violations. The PP population was used for the analysis of selected efficacy variables, based on the treatment which the patient received. The PP population was determined by clinical, medical, and biostatistics prior to database lock. In addition, patients who missed their last retreatment opportunity were also to be excluded from the PP population.

The **safety population** was defined as all patients who were treated. Safety analyses were performed based on the treatment which the patient received, and all safety variables were analysed using the safety population.

Primary Efficacy Analyses

The primary analysis of BCVA average change from baseline was performed using an AUC (area under the concentration-effect curve) approach based on analysis of covariance (ANCOVA) with treatment as a fixed effect and the baseline BCVA as a covariate in the ITT population. The primary comparisons between DEX 700 and Sham, and between DEX 350 and Sham were performed in a pairwise fashion using contrasts from the ANCOVA model. A gate-keeping procedure was used to control the overall type I error at 5% for the 2 between-group comparisons. The comparison of DEX 700 versus Sham was considered significant if the p-value was $\leq$0.05. Only if the comparison of DEX 700 versus Sham was significant at the 0.05 level was the comparison of DEX 350 versus Sham to be performed, at a

significance level of 0.05. If the comparison of DEX 700 versus Sham was not statistically significant, the comparison of DEX 350 versus Sham was not to be considered statistically significant regardless of its p-value. In addition, 2-sided 95% confidence intervals (CIs) were constructed for the 3 between-group differences based on the ANCOVA model.

No imputation was performed for missing values. BCVA assessments after escape therapy were set to missing.

Other analyses of BCVA average change from baseline included:

- based on observed data in the PP population
- based on multiple imputation for missing values
- based on "as is" observed data
- subgroups of patients defined by duration of diabetes, duration of DME, baseline HbA1c, prior laser treatment, treatment-naïve patients, lens status at baseline, non-proliferative diabetic retinopathy (NPDR) severity at baseline, and country

Secondary Efficacy Analyses

Unless stated otherwise, all of the secondary efficacy analyses were performed on the data with missing value imputed by last observation carried forward (LOCF) in the ITT population.

Efficacy variables involving change from baseline in BCVA, retinal thickness or contrast sensitivity were analysed using ANCOVA with treatment as a fixed effect and baseline values as covariate. This approach was also applied to the raw values and change from baseline in calculated total disk areas of fluorescein leakage. Responder endpoints were analysed using Pearson's chi-square test. For categorical changes, including presence of retinal thickening within the grid of the study eye, the Wilcoxon rank-sum test was used. Time to DR progression was analysed using the Kaplan-Meier method and log-rank test.

Sensitivity analyses were performed using multiple imputation methodology for the change from baseline in BCVA.

Results

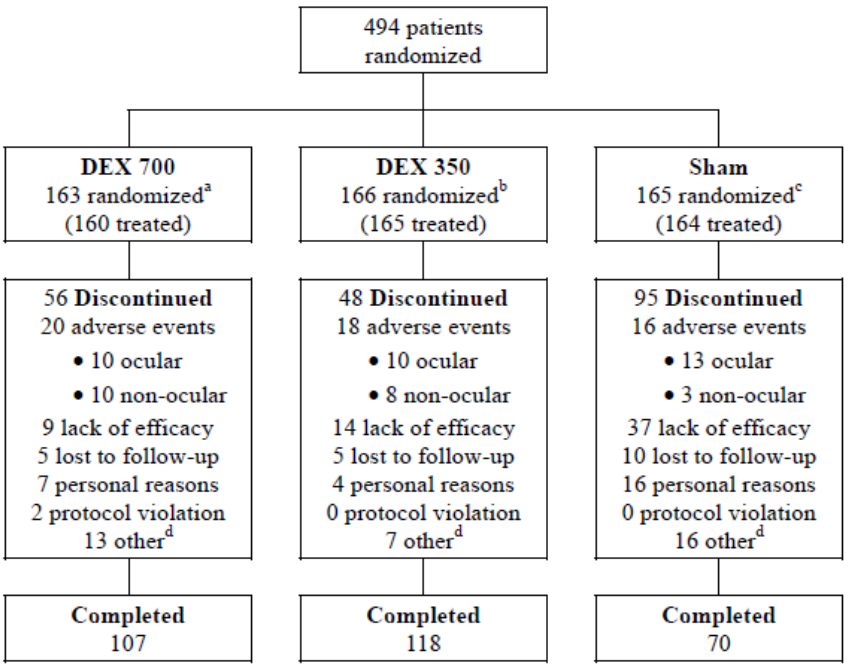
Participant flow

In study **206207-010**, 929 patients were screened and 46.9% (436/929) were considered to be screen failures. The reasons for screen failure were: failure to meet exclusion criteria (50.5%), failure to meet inclusion criteria (39.9%), other reasons (13.1%), and serious medical event (0.5%). One patient that was counted as a screen failure was actually randomised by error but never received study treatment.

A total of 494 patients were randomised and enrolled into the study: 163 in the DEX 700 group,166 in the DEX 350 group, and 165 in the Sham group (see Figure 1).

In study **206207-011**, 961 patients were screened and 42.4% (407/961) did not meet the entry criteria. The reasons for screen failure were: failure to meet exclusion criteria (56.3%), failure to meet inclusion criteria (32.7%), and other reasons (12.5%).

A total of 554 patients were randomised and enrolled into the study: 188 in the DEX 700 group, 181 in the DEX 350 group, and 185 in the Sham group (see Figure 2).



ITT = intent-to-treat

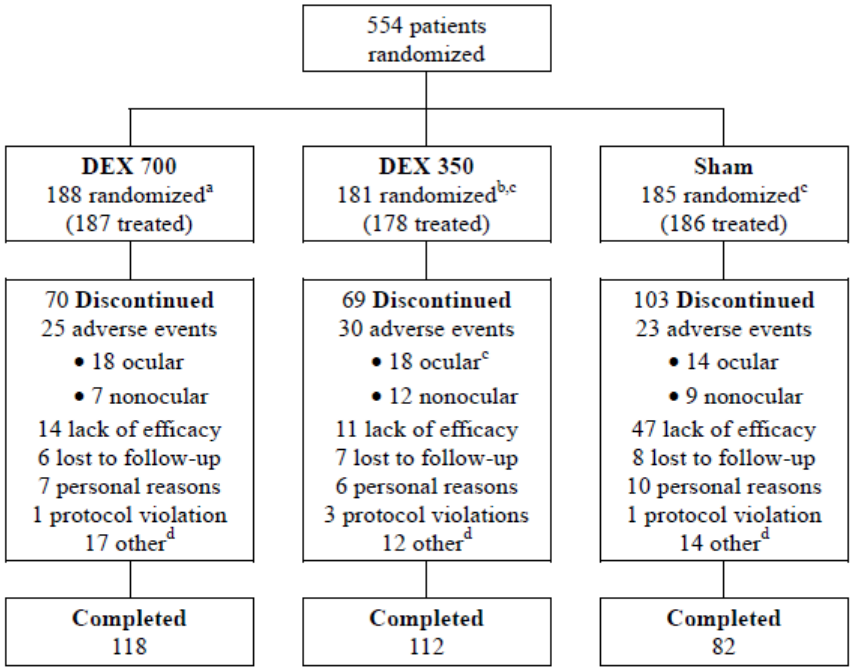
[a] Three patients (4368-4784, 4449-4268, and 8093-4766) were randomized to DEX 700 but never received treatment.

[b] One patient (4451-4278) was randomized to DEX 350 but never received treatment.

[c] One patient (4431-4098) was randomized to Sham but never received treatment.

[d] "Other" reasons for patient discontinuation included site closure, patient withdrawal of consent, poor compliance from patient, sponsor request, patient participation in other trial, etc; see Listing 16.2.1-2 for complete details.

Figure 1 - Disposition of Patients in Study 206207-010 (ITT Population)



ITT = intent-to-treat

[a] One patient (4406-7060) was randomized to DEX 700 but never received any treatment.

[b] Two patients (0469-7856 and 5099-7160) were randomized to DEX 350 but never received any treatment.

[c] One patient (5941-8189) was randomized to DEX 350 but actually received Sham. This patient discontinued the study due to a serious adverse event of macular fibrosis in the study eye after Sham treatment. The patient is counted in the DEX 350 group for analyses based on the ITT population and in the Sham group for analyses based on the safety population.

[d] "Other" reasons for patient discontinuation included patient withdrawal of consent, patient relocation, site closure, etc; see Listing 16.2.1-2 for complete details.

Figure 2 - Disposition of Patients in Study 206207-011 (ITT Population)

Discontinuation rates were high in both studies: DEX 700 (35.9%), DEX 350 group (33.7%), and Sham (56.6%). The largest number occurred in the Sham group due to lack of efficacy, mostly by the end of Year 1. Discontinuation rates over time are summarised in the following table.

Table 1 – Cumulative discontinuation rates

Time-point	Study 206207-010			Study 206207-011		
	DEX 700	DEX 350	Sham	DEX 700	DEX 350	Sham
Month 12	16.6%	9.6%	38.2%	17.0%	14.4%	35.7%
Month 24	25.8%	18.7%	51.5%	29.3%	28.7%	49.2%
Month 39	34.4%	28.9%	57.6%	37.2%	38.1%	55.7%

Recruitment

For study 206207-010, recruitment was initiated on 28 February 2005 (First Patient Enrolled) and the study was completed (Last Patient Completed) on 1 June 2012. The study recruited patients in 6 centres in Australia, 3 centres in Canada, 7 centres in the Czech Republic, 5 centres in Germany, 7 centres in Israel, 1 centre in the Philippines, 1 centre in Portugal, 4 centres South Africa, 4 centres in Spain and 21 centres in the US.

Recruitment for study 206207-011 started on 31 May 2005 (First Patient Enrolled) and finished on 29 May 2012 (Last Patient Completed). The study involved 8 centres in Brazil, 1 centre in Canada, 1 centre in Colombia, 4 centres in France, 1 centre in Hungary, 5 centres in India, 10 centres in Italy, 1 centre in New Zealand, 2 centres in Poland, 1 centre in Singapore, 3 centres in South Korea, 3 centres in Taiwan, 3 centres in the United Kingdom and 29 centres in the US.

Conduct of the study

The original protocol (approved on 19 November 2004) of study 206207-010 and -011 was amended five times:

1. October 2005: addition of an inclusion criterion regarding criteria for patients who had received intravitreal triamcinolone acetonide, modified wording of several exclusion criteria, addition of endothelial cell density measurements at selected sites as a response measure, and an increase in the number of sites from approximately 40 to approximately 80.
2. May 2007: changes that clarified or modified wording of several inclusion and exclusion criteria, added the exclusion criterion regarding history of use of intravitreal agents, deleted the exclusion criterion regarding use of carbonic anhydrase inhibitors, and revised the study schedule regarding 3-field fundus photographs and glomerular filtration rate (GFR) assessments. In addition, changes to the statistical section included indicating that analyses would be performed at 24 rather than 12 months and modifying the primary efficacy endpoint for the US FDA to the proportion of patients with a BCVA improvement of 15 or more letters from baseline in the study eye at 24 months (2 years).
3. February 2009: sample size calculation modified, revising the total number of patients to 510. The original sample size was estimated using preliminary results from a phase 2 study (DC103-06), and was revised following the then more recent results of intravitreal triamcinolone in DME patients (Gillies et al, 2006).

4. May 2010: a new (seventh) treatment was added to the month 36 visit and a new visit (month 39/exit) was added to accommodate the new treatment and associated procedures. Retreatment criteria regarding retinal thickness changed from OCT > 225 microns to OCT > 175 microns. An analysis and submission for approval when all patients complete 24 months was removed; the study was to continue until all patients exited or completed 36 months.
5. November 2011: primary endpoint revised to BCVA average change from baseline during the study (AUC approach) that takes into account the effect of multiple treatments and multiple observation times during the entire 3-year study period. This change was based on changes in the standard of care for DME over the course of the study, and applied to countries/regions other than the US.

Protocol deviations

A total of 52 and 63 patients were excluded from analyses of the PP population in study 206207-010 and study 206207-011, respectively due to protocol deviations including failure of meeting inclusion and exclusion criteria, lack of treatment or mistreatment and missing of last retreatment opportunity.

Baseline data

The baseline demographics and disease characteristics of the 2 pivotal trials are summarised in Table 2 and Table 3.

Patients had a mean age of 62.4 years (range 25 to 88 years) and more males (60.7%) than females (39.3%) were recruited. The majority of subjects were Caucasian, though Study 206207-011 did contain a higher proportion of Asian and Hispanic subjects. The average duration of diabetes was around 16 years, with the majority having type 2 diabetes and around two-thirds of subjects had a baseline HbA1c of ≤8%. Average duration of DME was around 2 years, though the variability of this parameter was large. Around 60-70% of subjects had received prior laser treatment for DME, with a slightly higher proportion in Study 206207-010. Average macular thickness was over 450 µm in both studies. Over 70% of subjects were phakic at baseline, and mean IOP was around 15 mmHg.

Table 2 - Demographic Characteristics (ITT population)

	206207-010 (N = 494)			206207-011 (N = 554)		
Characteristic Attribute	DEX 700 (N = 163)	DEX 350 (N = 166)	Sham (N = 165)	DEX 700 (N = 188)	DEX 350 (N = 181)	Sham (N = 185)
Age (years)						
Mean (SD)	63.1 (8.01)	63.3 (9.01)	62.6 (9.10)	61.9 (8.57)	61.3 (9.34)	62.4 (9.85)
Range	33 to 84	27 to 82	26 to 83	40 to 85	25 to 84	29 to 88
< 45, n (%)	4 (2.5)	5 (3.0)	7 (4.2)	2 (1.1)	8 (4.4)	6 (3.2)
45 to 65, n (%)	89 (54.6)	97 (58.4)	95 (57.6)	116 (61.7)	109 (60.2)	108 (58.4)
> 65, n (%)	70 (42.9)	64 (38.6)	63 (38.2)	70 (37.2)	64 (35.4)	71 (38.4)
Sex, n (%)						
Male	102 (62.6)	100 (60.2)	102 (61.8)	111 (59.0)	106 (58.6)	115 (62.2)
Female	61 (37.4)	66 (39.8)	63 (38.2)	77 (41.0)	75 (41.4)	70 (37.8)
Race, n (%)						
Caucasian	138 (84.7)	140 (84.3)	134 (81.2)	96 (51.1)	94 (51.9)	99 (53.5)
Non-Caucasian	25 (15.3)	26 (15.7)	31 (18.8)	92 (48.9)	87 (48.1)	86 (46.5)
Black	7 (4.3)	7 (4.2)	13 (7.9)	9 (4.8)	9 (5.0)	7 (3.8)
Asian[b]	12 (7.4)	14 (8.4)	13 (7.9)	42 (22.3)	42 (23.2)	40 (21.6)
Hispanic	1 (0.6)	2 (1.2)	2 (1.2)	34 (18.1)	32 (17.7)	31 (16.8)
Japanese	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	2 (1.1)	1 (0.5)
Other[c]	5 (3.1)	3 (1.8)	3 (1.8)	6 (3.2)	2 (1.1)	7 (3.8)
Iris color, n (%)						
Light	69 (42.3)	74 (44.6)	73 (44.2)	58 (30.9)	47 (26.0)	53 (28.6)
Dark	94 (57.7)	92 (55.4)	92 (55.8)	130 (69.1)	134 (74.0)	132 (71.4)
Weight (kg)						
Mean (SD)	84.3 (17.79)	85.1 (20.43)	82.2 (16.95)	81.2 (22.60)	79.0 (20.11)	78.9 (18.10)
Range	48 to 144	43 to 155	50 to 150	41 to 204	43 to 160	45 to 135
Height (cm)						
Mean (SD)	167.2 (9.30)	167.3 (10.12)	167.0 (8.84)	163.8 (9.39)	164.5 (9.74)	165.0 (9.51)
Range	146 to 188	139 to 191	142 to 188	137 to 196	135 to 186	133 to 190

Table 3 – Baseline Disease Characteristics (ITT population)

Study 206207-010				Study 206207-011			
Characteristic Attribute	DEX 700 (N = 163)	DEX 350 (N = 166)	Sham (N = 165)	Characteristic Attribute	DEX 700 (N = 163)	DEX 350 (N = 166)	Sham (N = 165)
Diabetes duration (years)				Diabetes duration (years)			
N	162	166	164	N	187	181	184
Mean (SD)	17.2 (9.21)	16.2 (9.20)	15.3 (8.30)	Mean (SD)	15.9 (8.85)	15.5 (9.49)	16.4 (9.79)
Median (Range)	16.0 (2 to 51)	15.5 (2 to 57)	15.5 (1 to 37)	Median (Range)	16.0 (1 to 43)	15.0 (1 to 61)	16.0 (1 to 54)
Diabetes Type, n (%)				Diabetes Type, n (%)			
Type 1	13 (8.0)	13 (7.8)	16 (9.7)	Type 1	21 (11.2)	9 (5.0)	12 (6.5)
Type 2	148 (90.8)	153 (92.2)	149 (90.3)	Type 2	166 (88.3)	172 (95.0)	173 (93.5)
HbA1c				Missing	1 (0.5)	0 (0.0)	0 (0.0)
N	161	165	164	HbA1c			
Mean (SD)	7.5 (1.11)	7.5 (1.09)	7.5 (1.07)	N	186	180	185
Median (Range)	7.4 (5 to 10)	7.4 (5 to 10)	7.4 (5 to 10)	Mean (SD)	7.6 (1.19)	7.6 (1.16)	7.5 (1.04)
≤ 8%	115 (70.6)	119 (71.7)	112 (67.9)	Median (Range)	7.5 (4 to 10)	7.5 (5 to 10)	7.2 (5 to 10)
> 8%	46 (28.2)	46 (27.7)	52 (31.5)	≤ 8%	118 (62.8)	118 (65.2)	137 (74.1)
DME duration (months)				> 8%	68 (36.2)	62 (34.3)	48 (25.9)
N	162	166	164	Missing	2 (1.1)	1 (0.6)	0 (0.0)
Mean (SD)	24.0 (26.24)	24.9 (29.26)	27.2 (29.59)	DME duration (months)			
Median (Range)	15.0 (0 to 160)	14.0 (0 to 191)	16.0 (0 to 152)	Mean (SD)	23.2 (25.78)	25.5 (33.27)	24.8 (25.05)
DME subtype based on fluorescein angiography, n (%)[b]				Median (Range)	15.0 (0 to 163)	17.0 (0 to 299)	19.0 (0 to 187)
None	1 (0.6)	2 (1.2)	0 (0.0)	DME subtype based on fluorescein angiography, n (%)[b]			
Focal	53 (32.5)	66 (39.8)	68 (41.2)	None	4 (2.1)	0 (0.0)	4 (2.2)
Intermediate	64 (39.3)	60 (36.1)	59 (35.8)	Focal	74 (39.4)	70 (38.7)	74 (40.0)
Diffuse	34 (20.9)	26 (15.7)	35 (21.2)	Intermediate	70 (37.2)	64 (35.4)	63 (34.1)
Diabetic retinopathy severity of the study eye, n (%)[c]				Diffuse	35 (18.6)	34 (18.8)	37 (20.0)
Moderately severe NPDR or better	89 (54.6)	90 (54.2)	86 (52.1)	Missing	5 (2.7)	13 (7.2)	7 (3.8)
Severe NPDR or worse	62 (38.0)	65 (39.2)	68 (41.2)	Diabetic retinopathy severity of the study eye, n (%)[c]			
Prior treatment for DME in the study eye, n (%)				Moderately severe NPDR or better	84 (44.7)	80 (44.2)	88 (47.6)
Laser	115 (70.6)	116 (69.9)	122 (73.9)	Severe NPDR or worse	89 (47.3)	86 (47.5)	81 (43.8)
Intravitreal injection of steroid	28 (17.2)	30 (18.1)	23 (13.9)	Missing	15 (8.0)	15 (8.3)	16 (8.6)
Anti-VEGF	17 (10.4)	20 (12.0)	13 (7.9)	Prior treatment for DME in the study eye, n (%)			
No prior treatment for DME	40 (24.5)	40 (24.1)	38 (23.0)	Laser	116 (61.7)	108 (59.7)	121 (65.4)
Study eye was better-seeing eye (BSE), n (%)	36 (22.1)	37 (22.3)	34 (20.6)	Intravitreal injection of steroid	30 (16.0)	39 (21.5)	38 (20.5)
Lens status in the study eye at baseline, n (%)				Anti-VEGF	8 (4.3)	19 (10.5)	13 (7.0)
Phakic eye	119 (73.0)	119 (71.7)	115 (69.7)	No prior treatment for DME	64 (34.0)	58 (32.0)	51 (27.6)
Aphakic eye	0 (0.0)	0 (0.0)	0 (0.0)	Study eye was better-seeing eye (BSE), n (%)	41 (21.8)	39 (21.5)	49 (26.5)
Pseudophakic eye	44 (27.0)	47 (28.3)	50 (30.3)	Lens status in the study eye at baseline, n (%)			
BCVA in study eye at baseline (letters)				Phakic eye	146 (77.7)	140 (77.3)	134 (72.4)
Mean (SD)	56.2 (10.05)	55.9 (9.64)	56.8 (8.66)	Aphakic eye	0 (0.0)	0 (0.0)	0 (0.0)
Median (Range)	59.0 (34 to 95)	58.0 (34 to 74)	58.0 (34 to 74)	Pseudophakic eye	42 (22.3)	41 (22.7)	51 (27.6)
IOP in study eye at baseline (mm Hg)				BCVA in study eye at baseline (letters)			
Mean (SD)	15.3 (2.71)	15.8 (2.97)	15.4 (3.07)	Mean (SD)	55.9 (9.83)	55.2 (9.69)	57.0 (8.76)
Median (Range)	15.0 (9 to 22)	16.0 (10 to 23)	15.0 (8 to 22)	Median (Range)	59.0 (34 to 72)	56.0 (34 to 90)	59.0 (36 to 82)
Systolic blood pressure (mm Hg)				IOP in study eye at baseline (mm Hg)			
N	161	164	161	Mean (SD)	15.4 (2.54)	15.5 (2.62)	15.2 (3.04)
Mean (SD)	142.6 (17.09)	140.9 (16.97)	138.3 (17.20)	Median (Range)	15.0 (9 to 23)	16.0 (10 to 26)	16.0 (9 to 28)
Median (Range)	140.0 (100 to 195)	140.0 (100 to 189)	139.0 (90 to 193)	Systolic blood pressure (mm Hg)			
Diastolic blood pressure (mm Hg)				N	188	181	184
N	161	164	161	Mean (SD)	138.5 (17.39)	137.5 (17.90)	136.3 (17.27)
Mean (SD)	78.8 (10.79)	79.1 (9.13)	78.7 (10.32)	Median (Range)	139.0 (100 to 200)	138.0 (90 to 217)	133.5 (100 to 190)
Median (Range)	80.0 (50 to 114)	80.0 (50 to 101)	80.0 (50 to 104)	Diastolic blood pressure (mm Hg)			
OCT retinal thickness at center subfield				N	188	180	184
N	162	165	165	Mean (SD)	79.7 (9.46)	79.0 (9.75)	78.4 (10.05)
Mean (SD)	436.7 (145.88)	457.4 (158.09)	468.7 (129.61)	Median (Range)	80.0 (59 to 110)	80.0 (59 to 117)	80.0 (47 to 112)
Median (Range)	419.0 (53 to 875)	435.0 (55 to 1439)	449.0 (181 to 892)	OCT retinal thickness at center subfield (microns)			
				N	186	179	177
				Mean (SD)	486.0 (163.12)	475.4 (160.70)	453.7 (135.36)
				Median (Range)	461.0 (149 to 1102)	463.0 (142 to 1064)	446.0 (131 to 835)

Numbers analysed

Study 206207-010

The ITT population included 163 patients in the DEX 700 group, 166 patients in the DEX 350 group, and 165 patients in the Sham group.

The PP population included 144, 155 and 143 patients in the DEX 700, DEX 350 and Sham group, respectively.

The safety population consisted of 160 patients in the DEX 700 group, 165 patients in the DEX 350 group, and 164 patients in the Sham group.

Study 206207-011

The ITT population included 188 subjects in the DEX 700 group, 181 subjects in the DEX 350 group, and 185 subjects in the Sham group.

The PP population included 170, 159 and 162 patients in the DEX 700, DEX 350 and Sham group, respectively.

The safety population included 187 patients in the DEX 700 group, 178 patients in the DEX 350 group, and 186 patients in the Sham group.

Outcomes and estimation

Primary endpoint

The results for the mean BCVA average change from baseline (AUC approach) by study as well as based on the integrated analysis are provided in Table 4.

Table 4 - BCVA Average Change from Baseline During the Study (AUC Approach)

	Study 206207-010			Study 206207-011			Pooled Studies 206207-010 and -011		
	DEX 700	DEX 350	Sham	DEX 700	DEX 350	Sham	DEX 700	DEX 350	Sham
Statistic	(N = 163)	(N = 166)	(N = 165)	(N = 188)	(N = 181)	(N = 185)	(N = 351)	(N = 347)	(N = 350)
Mean	4.1*	4.3*	1.9	2.9	2.9	2.0	3.5*	3.6*	2.0
SD	8.26	8.49	7.74	8.55	7.67	8.20	8.43	8.09	7.98
Median	4.5	4.0	1.2	3.1	2.7	2.1	3.9	3.5	1.6

* indicates statistically significant ($p \leq 0.05$) difference between DEX 700 or DEX 350 versus Sham
AUC = area under the curve, BCVA = best-corrected visual acuity, ITT = intent-to-treat, SD = standard deviation
Note: Average change calculated using AUC approach based on observed data. Missing values were not imputed. For the by-study analyses, p-values were based on an analysis of covariance (ANCOVA) with treatment as a factor and baseline value as a covariate. For the pooled analysis, p-values were based on an ANCOVA with treatment and study as factors, and baseline value as a covariate.

In Study 206207-010 the mean BCVA average change from baseline (AUC approach) was statistically significantly greater with DEX 700 compared to Sham (difference of 2.1 letters, 95% CI: 0.4 to 3.8, p = 0.016) and with DEX 350 compared to Sham (difference of 2.3 letters, 95% CI: 0.5 to 4.0, p = 0.010).

In study 206207-011 the mean BCVA average change from baseline was 2.9 letters with DEX 700 compared to 2.0 letters with Sham (difference of 0.8 letters, 95% CI: -0.9 to 2.4, p = 0.366). The average change was 2.9 letters with DEX 350 compared to 2.0 letters with Sham (difference of 0.7 letters, 95% CI: -0.9 to 2.4, p = 0.396). The differences were not statistically significant.

Secondary endpoints

- BCVA change from baseline

Mean BCVA change from baseline over time is summarised in Table 5 and Figure 3.

Table 5 - Mean BCVA Change from Baseline

	Study 206207-010			Study 206207-011			Pooled Studies 206207-010 and -011		
Visit	DEX 700 (N = 163)	DEX 350 (N = 166)	Sham (N = 165)	DEX 700 (N = 188)	DEX 350 (N = 181)	Sham (N = 185)	DEX 700 (N = 351)	DEX 350 (N = 347)	Sham (N = 350)
Baseline	56.2	55.9	56.8	55.9	55.2	57.0	56.1	55.5	56.9
Month 1.5	5.9*	5.8*	2.8	6.5*	6.2*	2.2	6.2*	6.0*	2.5
Month 3	5.9*	6.0*	2.4	6.5*	6.8*	2.4	6.2*	6.4*	2.4
Month 4.5	4.5*	5.6*	2.4	5.2*	4.9*	1.3	4.9*	5.2*	1.8
Month 6	4.6*	3.7	2.0	3.6*	2.2	1.1	4.1*	3.0	1.5
Month 7.5	5.8*	6.2*	1.6	5.6*	4.7*	1.4	5.7*	5.4*	1.5
Month 9	5.5*	6.2*	1.4	4.6*	4.3*	0.9	5.0*	5.2*	1.1
Month 10.5	4.2*	5.2*	1.2	2.4	3.8*	0.6	3.2*	4.5*	0.9
Month 12	3.3	3.7*	1.2	1.9	1.9	0.7	2.5	2.8*	0.9
Month 15	4.6*	4.5*	0.8	2.1	3.1	0.5	3.3*	3.8*	0.6
Month 18	2.3	2.1	1.1	-1.0	0.1	-0.2	0.5	1.0	0.4
Month 21	4.0*	3.4	1.0	-0.2	0.8	0.4	1.7	2.1	0.7
Month 24	1.5	2.3	1.1	-1.2	-1.6	-0.5	0.1	0.3	0.3
Month 27	3.1	2.9	1.2	0.1	-0.1	-0.4	1.5	1.3	0.3
Month 30	2.3	2.3	1.3	0.1	-0.4	-0.1	1.1	0.9	0.5
Month 33	3.5	4.2*	1.0	1.0	-0.1	-0.3	2.2	1.9	0.3
Month 36	3.7	5.1*	1.0	0.7	0.4	-0.1	2.1	2.7	0.4
Month 39/Final	4.1*	5.0*	0.8	1.3	1.4	-0.0	2.6	3.2*	0.4

* indicates statistically significant ($p \leq 0.05$) difference between DEX 700 or DEX 350 versus Sham
BCVA = best-corrected visual acuity, ITT = intent-to-treat
Note: Missing values were imputed by last observation carried forward at the follow-up visits. For the by-study analyses, p-values were based on analysis of covariance (ANCOVA) with treatment as a factor and baseline value as a covariate. For the pooled analysis, p-values were based on an ANCOVA with treatment and study as factors, and baseline value as a covariate.

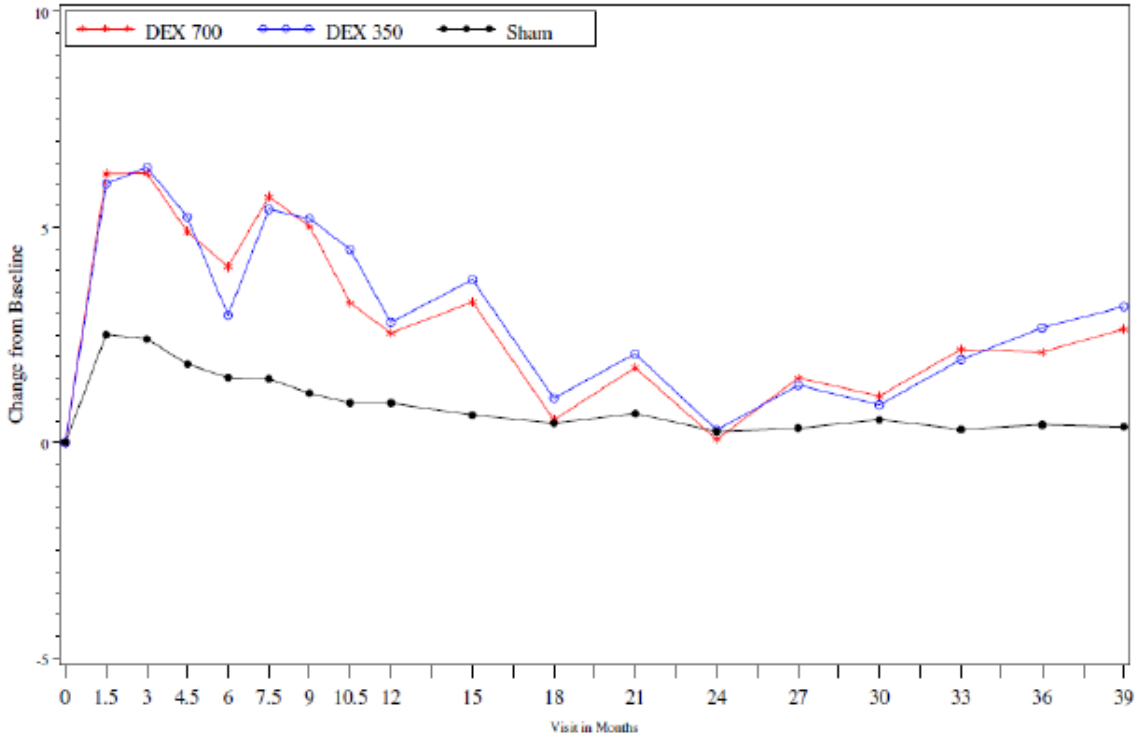


Figure 3 - Mean BCVA Change From Baseline (Pooled Studies)

- Proportion of patients with improvement of ≥10 OR ≥15 letters from baseline

In study 206207-010 the proportion of patients with BCVA improvement of ≥ 10 letters was significantly higher with DEX 700 (38.7%) and DEX 350 (34.3%) compared with Sham (23.0%) at the end of the 3-year study (p = 0.002 and p = 0.023), respectively.

In study 206207-011 the proportion of patients with ≥ 10 letters BCVA improvement was significantly higher with DEX 700 (34.6%) compared with Sham (24.9%) at the end of the 3-year study (p = 0.040), but not with DEX 350 (29.8%) compared with Sham (24.9%) at the year 3/final visit (p = 0.286).

The results for improvement in BCVA by 15 or more letters are provided in Table 6 and Figure 4.

In both studies the proportion of patients with ≥ 15 letters BCVA improvement was significantly higher with DEX 700 compared to Sham at the year 3 visit. With regards to DEX 350, only study 206207-011 showed statistical superiority to Sham.

Table 6 - Number (%) of Patients with ≥15 Letter Improvement in BCVA

	Study 206207-010			Study 206207-011			Pooled Studies 206207-010 and -011		
Visit	DEX 700 (N = 163)	DEX 350 (N = 166)	Sham (N = 165)	DEX 700 (N = 188)	DEX 350 (N = 181)	Sham (N = 185)	DEX 700 (N = 351)	DEX 350 (N = 347)	Sham (N = 350)
Month 1.5	20 (12.3)*	18 (10.8)*	6 (3.6)	21 (11.2)*	23 (12.7)*	3 (1.6)	41 (11.7)*	41 (11.8)*	9 (2.6)
Month 3	23 (14.1)*	23 (13.9)*	10 (6.1)	22 (11.7)*	26 (14.4)*	5 (2.7)	45 (12.8)*	49 (14.1)*	15 (4.3)
Month 4.5	25 (15.3)*	21 (12.7)	11 (6.7)	22 (11.7)*	23 (12.7)*	7 (3.8)	47 (13.4)*	44 (12.7)*	18 (5.1)
Month 6	23 (14.1)	17 (10.2)	13 (7.9)	16 (8.5)*	11 (6.1)	6 (3.2)	39 (11.1)*	28 (8.1)	19 (5.4)
Month 7.5	26 (16.0)*	26 (15.7)*	13 (7.9)	27 (14.4)*	24 (13.3)	14 (7.6)	53 (15.1)*	50 (14.4)*	27 (7.7)
Month 9	31 (19.0)*	30 (18.1)*	14 (8.5)	29 (15.4)*	26 (14.4)*	13 (7.0)	60 (17.1)*	56 (16.1)*	27 (7.7)
Month 10.5	26 (16.0)*	29 (17.5)*	13 (7.9)	26 (13.8)	26 (14.4)	16 (8.6)	52 (14.8)*	55(15.9)*	29 (8.3)
Month 12	22 (13.5)	25 (15.1)	15 (9.1)	24 (12.8)	18 (9.9)	18 (9.7)	46 (13.1)	43 (12.4)	33 (9.4)
Month 15	25 (15.3)*	27 (16.3)*	12 (7.3)	24 (12.8)	26 (14.4)	18 (9.7)	49 (14.0)*	53 (15.3)*	30 (8.6)
Month 18	28 (17.2)	16 (9.6)	18 (10.9)	23 (12.2)	19 (10.5)	17 (9.2)	51 (14.5)	35 (10.1)	35 (10.0)
Month 21	27 (16.6)*	25 (15.1)	15 (9.1)	29 (15.4)	17 (9.4)	19 (10.3)	56 (16.0)*	42 (12.1)	34 (9.7)
Month 24	23 (14.1)	25 (15.1)	18 (10.9)	34 (18.1)*	17 (9.4)	19 (10.3)	57 (16.2)*	42 (12.1)	37 (10.6)
Month 27	33 (20.2)	32 (19.3)	21 (12.7)	31 (16.5)	22 (12.2)	19 (10.3)	64 (18.2)*	54 (15.6)	40 (11.4)
Month 30	27 (16.6)	33 (19.9)*	19 (11.5)	35 (18.6)*	22 (12.2)	19 (10.3)	62 (17.7)*	55 (15.9)	38 (10.9)
Month 33	36 (22.1)*	29 (17.5)	19 (11.5)	35 (18.6)*	26 (14.4)	18 (9.7)	71 (20.2)*	55 (15.9)*	37 (10.6)
Month 36	34 (20.9)*	33 (19.9)	21 (12.7)	37 (19.7)*	30 (16.6)	20 (10.8)	71 (20.2)*	63 (18.2)*	41 (11.7)
Month 39/Final	36 (22.1)*	31 (18.7)	22 (13.3)	42 (22.3)*	33 (18.2)*	20 (10.8)	78 (22.2)*	64 (18.4)*	42 (12.0)

* indicates statistically significant ($p \leq 0.05$) difference between DEX 700 or DEX 350 versus Sham
BCVA = best-corrected visual acuity, ITT = intent-to-treat
Note: Missing values are imputed by last observation carried forward at the follow-up visits. For the by-study analyses, p-values were based on the chi-square test. For the pooled analysis, p-values were based on the Cochran-Mantel-Haenszel (CMH) general association test stratified by study.

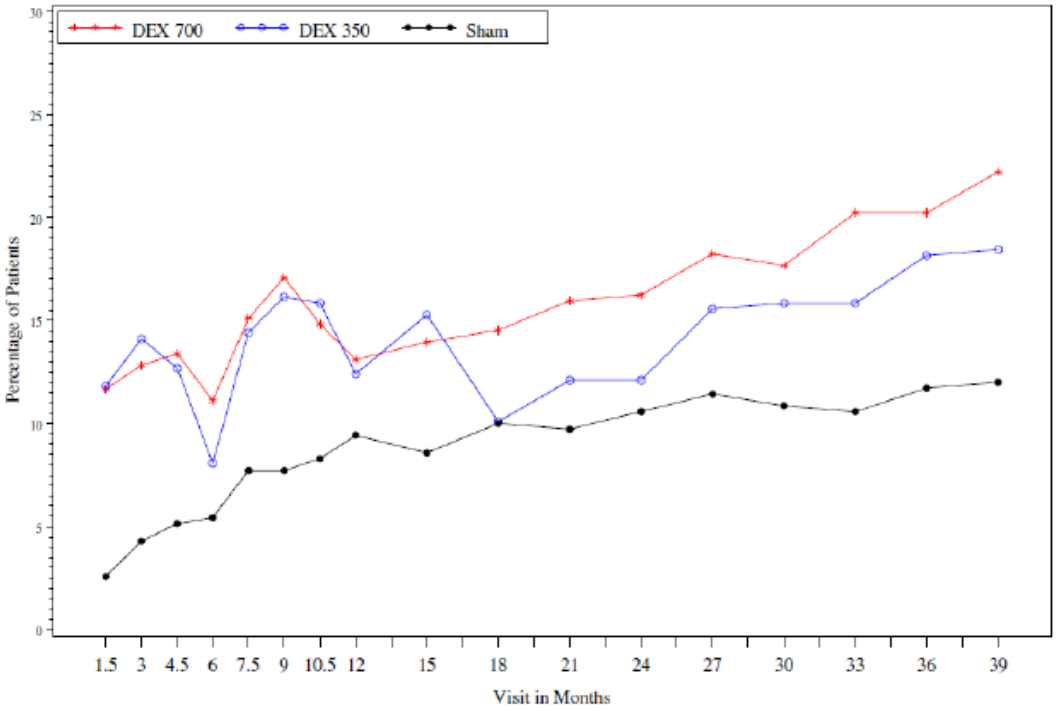


Figure 4 - Proportion of Patients with ≥15 Letters Improvement in BCVA (Pooled Studies)

- BCVA categorical change from baseline

BCVA change from baseline in the number of letters read correctly for the study eye was classified into the following 5 categories: (1) ≥ 15 letters improvement, (2) ≥ 5 and < 15 letters improvement, (3) no change (i.e. change between -5 to +5 letters [not including either -5 or +5]), (4) ≥ 5 and < 15 letters worsening, and (5) ≥ 15 letters worsening. The results for ≥ 15 letters improvement and ≥ 15 letters worsening are presented separately (see above and below).

In study 206207-010 at the year 3/final visit, the proportion of patients with 5 or more letters improvement was higher with DEX 700 (57.1% [93/163]) compared to Sham (33.9% [56/165]), and the proportion of patients with 5 or more letters worsening was similar with DEX 700 (21.5% [35/163]) compared to Sham (24.8% [41/165]). Similar results were achieved with DEX 350 with regards to the proportion of patients with 5 or more letters improvement, which was higher with DEX 350 (54.8% [91/166]), however, the proportion of patients with 5 or more letters worsening was less with DEX 350 (16.3% [27/166]) compared to Sham (24.8% [41/165]).

In study 206207-011 at the year 3/final visit, the proportion of patients with 5 or more letters improvement was higher with DEX 700 (47.9% [90/188]) compared to Sham (38.9% [72/185]), but the proportion of patients with 5 or more letters worsening was similar with DEX 700 (28.2% [53/188]) compared to Sham (26.5% [49/185]). Similar results were observed with DEX 350 (proportion of patients with 5 or more letters improvement was higher with DEX 350: 49.2% [89/181]; proportion of patients with 5 or more letters worsening was similar with DEX 350: 29.8% [54/181]).

- Proportion of patients with BCVA worsening of 15 or more letters from baseline

In study 206207-010, across all visits, the proportion of patients with BCVA worsening of 15 or more letters from baseline was similar in the DEX groups and the Sham group, with no statistically significant differences between the active groups and Sham. At the year 3/final visit, the proportion

was 9.2% (15/163) in the DEX 700 group, 6.0% (10/166) in the DEX 350 group, and 10.3% (17/165) in the Sham group.

Similar results were obtained in study 206207-011. Across all visits, the proportion of patients with BCVA worsening of 15 or more letters from baseline was similar in the DEX groups and Sham, with no statistically significant between group differences, except for months 4.5, 18 through 24, and 30. At the year 3/final visit, the proportion was 16.5% (31/188) in the DEX 700 group, 14.4% (26/181) in the DEX 350 group, and 11.9% (22/185) in the Sham group.

- Change from baseline in retinal thickness of the central subfield during the study

In study 206207-010, the mean average decrease from baseline during the study in central subfield retinal thickness (AUC approach) was significantly greater with DEX 700 (101.1 µm) and DEX 350 (103.9 µm) compared to Sham (37.8 µm), $p < 0.001$. Mean decreases in retinal thickness at the centre subfield were consistently greater with DEX than with Sham throughout the study. Statistically significant improvements with DEX 700 compared to Sham were observed at every visit during the 3-year study period ($p \leq 0.010$).

In study 206207-011, the mean average decrease from baseline during the study in central subfield retinal thickness (AUC approach) was significantly greater with DEX 700 (120.7 µm) and DEX 350 (111.6 µm) versus Sham (45.8 µm), $p < 0.001$. Mean decreases in retinal thickness were consistently greater with DEX than with Sham throughout the study.

Figure 5 depicts the mean changes in retinal thickness over time based on the results of the integrated analysis of both studies.

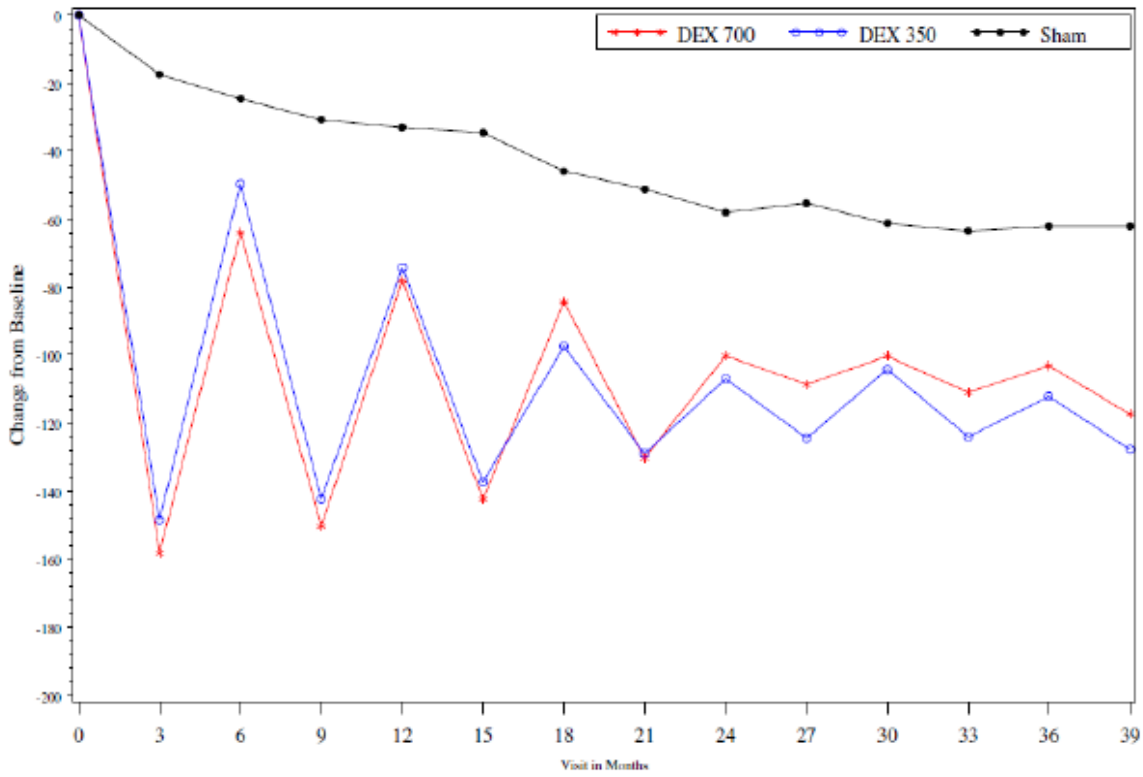


Figure 5 - Mean Change From Baseline in Central Subfield Retinal Thickness (µm) (Pooled Studies)

- 2-Step or 3-Step Progression of Diabetic Retinopathy Severity from Baseline

The majority of patients in study 206207-010 were rated as “moderately severe NPDR” or less throughout the study, while in study 206207-011 most patients in each treatment group had “mild PDR” or less throughout the study. There were no statistically significant differences between the treatment groups in the distribution of the severity categories at any visit in neither study.

In each of the phase 3 studies and the pooled analysis, less than 10% of patients had a 2-step progression in their diabetic retinopathy severity score throughout the 3-year studies. Time to diabetic retinopathy 2-step progression cumulative response curves were consistently lower in the DEX groups compared to Sham, indicating that treatment with dexamethasone delayed the progression of diabetic retinopathy. However, the differences were not statistically significant in neither of the studies.

In each of the phase 3 studies and the pooled analysis, no more than 3% of patients in any treatment group showed a 3-step progression. There were no statistically significant differences between the treatment groups in the 3-step progression rates at any visit in either study or the pooled analyses.

- Contrast Sensitivity

In study 206207-010 mean decreases from baseline in number of letters read correctly were observed only in the DEX treatment groups. In study 206207-011 small mean decreases from baseline in number of letters read correctly were observed in all 3 treatment groups.

- Visual Functioning Questionnaire-25

There were no consistent statistically significant differences between DEX and Sham on health outcomes measures in the ITT population (VFQ-25 composite and subscale scores) for average change from baseline (AUC approach), or the proportion of patients with 10-point improvement.

Ancillary analyses

Results from additional analyses of the primary efficacy endpoint using the PP population or “as is” observed data (BCVA data recorded after escape therapy were also used) were generally similar to the observed data in the ITT population. However, there was a notable difference between the results obtained from the primary analysis and those using multiple imputation for missing values, whereby the mean BCVA average change compared to baseline in Study 206207-010 and 206207-011 was 2.9 and -0.1 letters with DEX 700 compared to 0.2 and 0.4 letters with Sham, respectively. The differences between DEX 700 and Sham were not statistically significant.

- **Pre-specified subgroup analyses**

Subgroups of patients were defined by duration of diabetes, duration of DME, baseline HbA1c, prior laser treatment, treatment-naïve patients, lens status at baseline, non-proliferative diabetic retinopathy (NPDR) severity at baseline, and country. The results are summarised in Table 7 and Table 8.

Table 7 - Efficacy in the Study Eye by Subgroups (Study 206207-010)

	Mean BCVA average change from baseline during study (AUC approach), mean difference (p-value)[a]		BCVA 15 or more letters improvement from baseline at year 3/final, % difference (p-value)[b]	
	DEX 700 vs Sham	DEX 350 vs Sham	DEX 700 vs Sham	DEX 350 vs Sham
Diabetes duration ≤ 15 years (N = 76, 83, 82)	3.0 (0.014)	2.9 (0.017)	15.0% (0.006)	12.0% (0.018)
Diabetes duration > 15 years (N = 86, 83, 82)	1.4 (0.277)	1.7 (0.175)	2.5% (0.693)	-1.5% (0.815)
DME duration ≤ 1.5 years (N = 89, 99, 86)	3.0 (0.017)	2.1 (0.082)	8.6% (0.121)	7.6% (0.158)
DME duration > 1.5 years (N = 73, 67, 78)	1.2 (0.344)	2.6 (0.038)	9.3% (0.154)	2.5% (0.683)
HbA1c ≤ 8% (N = 115, 119, 112)	2.8 (0.006)	2.8 (0.007)	9.3% (0.059)	10.2% (0.038)
HbA1c > 8% (N = 46, 46, 52)	0.2 (0.891)	0.9 (0.589)	6.6% (0.418)	-6.4% (0.363)
Prior laser treatment (N = 115, 116, 122)	2.3 (0.024)	3.0 (0.004)	9.4% (0.049)	8.4% (0.075)
No prior laser treatment (N = 48, 50, 43)	1.3 (0.440)	0.2 (0.905)	6.4% (0.462)	-2.6% (0.740)
Any prior treatment (N = 123, 126, 127)	2.6 (0.011)	3.2 (0.002)	10.9% (0.020)	9.6% (0.036)
No prior treatment (N = 40, 40, 38)	0.3 (0.857)	-0.6 (0.723)	1.4% (0.877)	-8.6% (0.311)
Phakic study eye at baseline (N = 119, 119, 115)	0.7 (0.492)	1.5 (0.144)	5.5% (0.241)	8.0% (0.097)
Pseudophakic study eye at baseline (N = 44, 47, 50)	5.9 (< 0.001)	4.1 (0.007)	18.1% (0.042)	-1.1% (0.880)
Severe NPDR or worse at baseline (N = 62, 65, 68)	3.3 (0.023)	3.3 (0.018)	15.4% (0.017)	9.6% (0.104)
Moderately severe NPDR or better at baseline (N = 89, 90, 86)	1.4 (0.242)	1.1 (0.352)	2.8% (0.638)	0.3% (0.953)

Note: N values correspond to the following order of treatment groups: DEX 700, DEX 350, and Sham.

AUC = area under the curve, BCVA = best corrected visual acuity, DME = diabetic macular edema, HbA1c = hemoglobin A1c, ITT = intent-to-treat, NPDR = non-proliferative diabetic retinopathy

[a] P-value based on a ANCOVA with treatment as a factor and baseline value as a covariate. Estimated difference was from least-squares means.

[b] P-value was from chi-square test.

Table 8 - Efficacy in the Study Eye by Subgroups (Study 206207-011)

	Mean BCVA average change from baseline during study (AUC approach), mean difference (p-value)[a]		BCVA 15 or more letters improvement from baseline at year 3/Final, % difference (p-value)[b]	
	DEX 700 vs Sham	DEX 350 vs Sham	DEX 700 vs Sham	DEX 350 vs Sham
Diabetes duration ≤ 15 years (N = 93, 93, 90)	-0.4 (0.746)	1.0 (0.425)	13.7% (0.014)	10.4% (0.050)
Diabetes duration > 15 years (N = 94, 88, 94)	2.1 (0.065)	0.5 (0.653)	9.6% (0.077)	4.2% (0.410)
DME duration ≤ 1.5 years (N = 107, 93, 91)	0.3 (0.843)	0.2 (0.901)	11.1% (0.048)	9.4% (0.097)
DME duration > 1.5 years (N = 81, 88, 94)	1.0 (0.348)	1.2 (0.285)	11.2% (0.031)	5.1% (0.269)
HbA1c ≤ 8% (N = 118, 118, 137)	1.1 (0.322)	0.9 (0.415)	12.9% (0.007)	7.8% (0.084)
HbA1c > 8% (N = 68, 62, 48)	0.5 (0.725)	0.6 (0.673)	9.3% (0.152)	7.8% (0.224)
Prior laser treatment (N = 116, 108, 121)	0.4 (0.686)	0.8 (0.469)	9.2% (0.060)	1.5% (0.738)
No prior laser treatment (N = 72, 73, 64)	1.2 (0.404)	0.5 (0.705)	15.8% (0.013)	16.8% (0.008)
Any prior treatment (N = 124, 123, 134)	0.7 (0.495)	0.8 (0.409)	9.8% (0.032)	3.4% (0.410)
No prior treatment (N = 64, 58, 51)	0.7 (0.679)	0.4 (0.811)	15.2% (0.036)	16.1% (0.031)
Phakic study eye at baseline (N = 146, 140, 134)	-0.1 (0.892)	-0.4 (0.684)	12.7% (0.007)	5.9% (0.181)
Pseudophakic study eye at baseline (N = 42, 41, 51)	3.6 (0.018)	4.3 (0.005)	6.0% (0.461)	11.2% (0.104)
Severe NPDR or worse at baseline (N = 89, 86, 81)	3.0 (0.010)	1.1 (0.334)	13.8% (0.014)	6.5% (0.198)
Moderately severe NPDR or better at baseline (N = 84, 80, 88)	-0.4 (0.756)	1.3 (0.321)	8.9% (0.118)	10.0% (0.087)

Note: N values correspond to the following order of treatment groups: DEX 700, DEX 350, and Sham.

AUC = area under the curve, BCVA = best corrected visual acuity, DME = diabetic macular edema, HbA1c = hemoglobin A1c, ITT = intent-to-treat, NPDR = non-proliferative diabetic retinopathy

[a] P-value based on ANCOVA with treatment as a factor and baseline value as a covariate. Estimated difference was from least-squares means.

[b] P-value was from Chi-square test.

Patients with prior DME treatment

With regards to the subpopulation of patient with prior treatment of DME, in the pooled analysis, the mean BCVA average change from baseline during the study (AUC approach) was significantly greater with DEX 700 (3.2 letters) compared to Sham (1.5 letters), p = 0.024. Likewise, the proportion of patients with 15 or more letters improvement in BCVA from baseline was significantly higher with DEX 700 (21.5%) compared with Sham (11.1%) at the year 3/final visit, p = 0.002.

The mean change from baseline in BCVA was 2.7 in the DEX 700 group and 0.1 in the Sham group at year 3/final visit, p = 0.055, and the mean average decrease from baseline in OCT central subfield retinal thickness (AUC approach) was significantly greater with DEX 700 (126.1 µm) compared to Sham (39.0 µm), p < 0.001.

Pseudophakic patients

Among the 275 patients with a pseudophakic study eye at baseline, treatment with dexamethasone injections was significantly more effective than with Sham (see Figure 6 for the pooled analysis as well as Table 7 and Table 8 for the outcome in each individual study). For the primary endpoint of mean

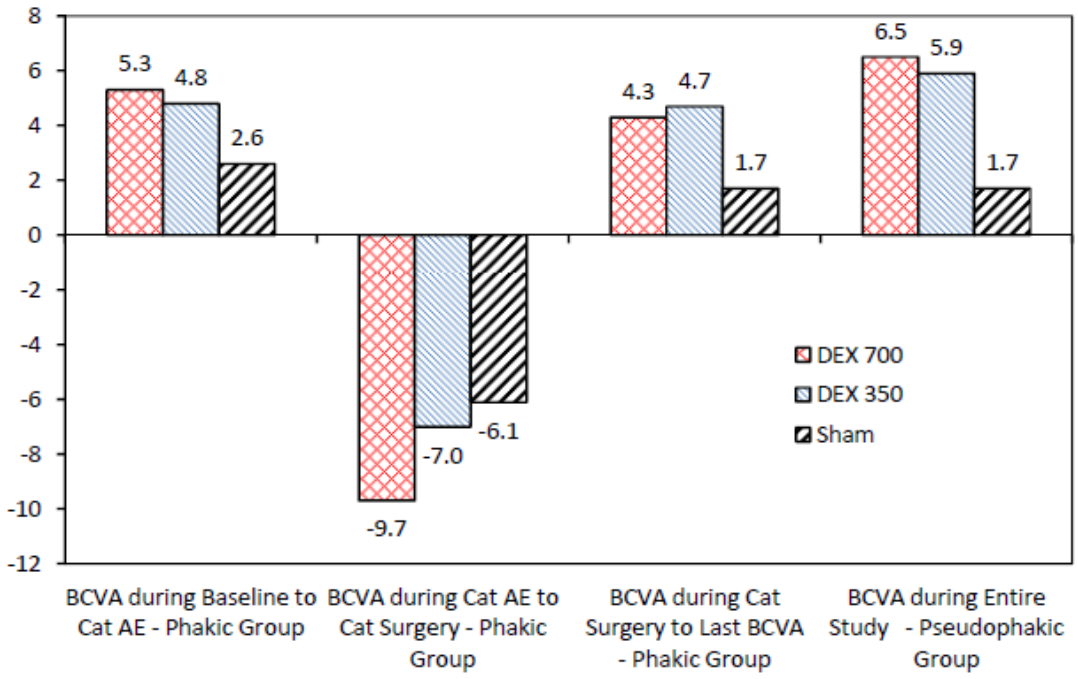
average change in vision over the 3-year study period, a gain of 8 letters was experienced by DEX 700 subjects in study 206207-010 (a sham-adjusted effect size of 6 letters), compared with a 5 letter gain in study 206207-011 (sham-adjusted effect size of 3.6 letters). The proportion of pseudophakic patients gaining 15 letters in study 206207-011 and -010 was 12% and 34% in patients receiving DEX 700 compared to 6% and 16% in sham treated patients, respectively.

- **Other Analyses**

The MAH performed post-hoc analyses taking into account the impact of cataract adverse events and cataract surgery as confounding factors to the efficacy outcomes.

Among the 773 patients with a phakic study eye at baseline who reported a cataract adverse event (see section 0for details), the median time from 'baseline to cataract adverse event' was 16.0 months, 14.8 months, and 10.7 months in the DEX 700, DEX 350, and Sham groups, respectively. The median time from 'cataract adverse event to cataract surgery' was 5.8 months, 5.7 months, and 4.0 months in the DEX 700, DEX 350, and Sham groups, respectively.

In phakic patients with cataract event, an improved effect was achieved in the DEX 700 and DEX 350 groups after surgery with a mean average BCVA gain of 4.3 and 4.7, respectively, compared to 1.7 letters with Sham (see Figure 6).



AE = adverse event, AUC = area under the curve, BCVA = best-corrected visual acuity, Cat = cataract, ITT = intent-to-treat
Note: BCVA during baseline to Cat AE is the period from baseline to the study visit prior to reporting of cataract AE.
Sample sizes for the DEX 700, DEX 350, and Sham groups are as follows for each time interval:
Baseline to cataract AE for baseline phakic study eyes (N =176, 159, 42)
Cataract AE to cataract surgery + 30 days for baseline phakic study eyes (N = 132, 118, 14)
Day of cataract surgery + 30 days to last BCVA for baseline phakic study eyes (N = 142, 123, 17)
Pseudophakic study eyes (N = 86, 88, 101)

Figure 6 – Mean BCVA Average Change From Baseline (AUC Approach) in Phakic Study Eyes for Time Intervals Between Baseline, Cataract Adverse Event, Cataract Surgery, and Last BCVA Measurement and in Pseudophakic Study Eyes for the Entire Study Duration (Pooled Analysis)

The effect size was even greater (6.7 letters gain for DEX 700 compared to 2.1 letters with Sham) in patients who experienced cataract and cataract surgery early in the study and hence had sufficient time to fully recover (>12 month).

Furthermore, in patients with a phakic study eye at baseline with no cataract adverse events reported and no posterior subcapsular opacity ≥ 1-grade worsening (N = 53, 57, 172 in the DEX 700, DEX 350, and Sham groups, respectively), similar results were achieved to those seen in patients post cataract surgery. The mean BCVA average change from baseline was 4.7, 4.4, and 2.2 in the DEX 700, DEX 350, and Sham groups, respectively.

Summary of main study(ies)

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 9 - Summary of Efficacy for pooled analysis of studies 206207-010 and 206207-011

Title for both studies: A 3-Year, Phase 3, Multicenter, Masked, Randomized, Sham-Controlled Trial to Assess the Safety and Efficacy of 700 µg and 350 µg Dexamethasone Posterior Segment Drug Delivery System (DEX PS DDS) Applicator System in the Treatment of Patients with Diabetic Macular Edema			
Study identifier	Studies 206207-010 and 206207-011		
Design	Multicentre, Masked, Randomised, Sham-Controlled, Parallel Group		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	3 years N/A N/A	
Hypothesis	Superiority		
Treatments groups	DEX 700	700 µg dexamethasone in DEX PS DDS, 351 patients enrolled	
	DEX 350	350 µg dexamethasone in DEX PS DDS, 347 patients enrolled	
	Sham	Needleless applicator, 350 patients enrolled	
Endpoints and definitions	Primary endpoint	Mean BCVA average change from baseline during the study using observed data in the study eye (AUC approach)	Primary endpoint in EU
	Secondary endpoint (1)	Mean BCVA change from baseline	using ANCOVA with treatment as a fixed effect and baseline BCVA as a covariate
	Secondary endpoint (2)	Proportion of patients with improvement of ≥10 letters from baseline	using Pearson's chi-square test
	Secondary endpoint (3)	Proportion of patients with improvement of ≥15 letters from baseline	using Pearson's chi-square test; Primary endpoint in US
	Secondary endpoint (4)	Categorical change in BCVA from baseline	using Wilcoxon rank-sum test
	Secondary endpoint (5)	Proportion of patients with worsening of ≥15 letters from baseline	using Pearson's chi-square test

	Secondary endpoint (6)	Average change from baseline in retinal thickness of the central subfield during the study (AUC approach, observed cases)	using ANCOVA with treatment as a fixed effect and baseline central subfield retinal thickness as a covariate
	Secondary endpoint (7)	Mean change from baseline in central subfield retinal thickness	using ANCOVA with treatment as a fixed effect and baseline central subfield retinal thickness as a covariate
	Secondary endpoint (8)	Change from baseline in number of letters read correctly evaluated using contrast sensitivity	using ANCOVA with treatment as a fixed effect and baseline number of letters read correctly as a covariate

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to treat; Year 3 (Month 39)			
Descriptive statistics and estimate variability	**Treatment group**	**DEX 700**	**DEX 350**	**Sham**
	Number of subjects	*351*	*347*	*350*
	Mean BCVA average change from baseline in letters (SD)	3.5 (8.43)	3.6 (8.09)	2.0 (7.98)
	Difference vs. sham (95% CI; *p* value)	1.4 (0.2, 2.6; *p* = 0.023)	1.4 (0.2, 2.6; *p* = 0.019)	
Analysis description	**Secondary analysis**			
Descriptive statistics and estimate variability	**Treatment group**	**DEX 700**	**DEX 350**	**Sham**
	Number of subjects	*351*	*347*	*350*
	Mean BCVA change from baseline in letters (SD)	2.6 (15.69)	3.2 (13.83)	0.4 (13.85)
	Difference vs. sham (95% CI, *p* value)	2.1 (0.0, 4.2; *p* = 0.054)	2.5 (0.3, 4.6; *p* = 0.024)	
	Proportion of patients with improvement of ≥10 letters from baseline (%)	36.5	32.0	24.0
	Difference vs. sham (95% CI, *p* value)	12.5 (5.7, 19.2; *p* < 0.001)	8.0 (1.3, 14.6; *p* = 0.019)	
	Proportion of patients with improvement of ≥15 letters from baseline (%)	22.2	18.4	12.0
	Difference vs. sham (95% CI, *p* value)	10.2 (4.7, 15.7; *p* < 0.001)	6.4 (1.1, 11.8; *p* = 0.018)	
	Categorical change in BCVA from baseline (%) ▪ ≥5 to <15 letter improvement ▪ -5 to +5 letter change ▪ ≥5 to <15 letter worsening	 29.9 22.8 12.0	 33.4 24.8 13.0	 24.6 37.7 14.6

	Proportion of patients with worsening of ⩾15 letters from baseline	13.1	10.4	11.1
	Difference vs. sham (95% CI)	2.0 (-2.9, 6.8)	-0.8 (-5.4, 3.8)	
	Mean average change from baseline in retinal thickness of the central subfield during the study in microns (SD)	-111.6 (134.10)	-107.9 (135.78)	-41.9 (116.00)
	Difference vs. sham (95% CI, *p* value)	-68.6 (-84.8, - 52.4; *p* < 0.001)	-63.2 (-79.4, - 47.0; *P* < 0.001)	
	Mean change from baseline in central subfield retinal thickness in microns (SD)	-117.3 (208.13)	-127.8 (196.65)	-62.1 (180.11)
	Difference vs. sham (95% CI)	-54.2 (-81.1, -27.3)	-62.7 (-89.7, -35.8)	
	Change from baseline in number of letters read correctly evaluated using contrast sensitivity (SD)	-0.8 (8.22)	-0.8 (7.11)	-0.4 (5.78)
	Difference vs. sham (95% CI)	-0.6 (-1.6, 0.4)	-0.6 (-1.6, 0.4)	

Analysis performed across trials (pooled analyses and meta-analysis)

Results from the pooled analyses for studies 206207-010 and 206207-011 are summarised in Table 9.

Supportive study(ies)

Study 206207-012

Study 206207-012 was a 52-week, masked, multicentre, randomised, sham-controlled trial (with up to 13 weeks additional follow-up) to assess the safety and efficacy of DEX 700 in combination with laser photocoagulation (hereafter referred to as Combination Therapy) compared to laser photocoagulation alone (hereafter referred to as Laser Alone) in patients with diffuse DME. The study was conducted at 48 centres in the US and Canada, between 2007 and 2010. Subjects were recruited on the basis of a diagnosis of diffuse DME in at least one eye, with a BCVA score of ≥34 to ≤70 letters and mean retinal thickness by OCT in the 1 mm central macular subfield ≥275 microns. Pseudophakic patients and those who had previously received intravitreal steroids were excluded. Subjects were randomised in a 1:1 ratio to Combination Therapy or Laser Alone, stratified according to baseline BCVA score (≥34 to ≤49 letters or ≥50 to ≤70 letters).

After initial treatment on day 0, a maximum of 3 additional laser treatments could be performed at intervals of no less than 13 weeks, and a maximum of 1 additional treatment with DEX 700/Sham could be given with a minimum interval of 26 weeks. To be eligible for retreatment, patients must have met all of the 4 following:

1. Mean retinal thickness in the 1 mm central macular subfield of ≥250 microns by OCT in the study eye
2. The patient was not at significant risk from a retreatment in the opinion of the investigator
3. The patient may have benefited from a retreatment in the opinion of the investigator
4. The following intervals between treatments in the study eye must have been followed:
    a. For laser retreatment, at least 13 weeks had passed since the last laser treatment

b. For DEX/Sham DEX retreatment, at least 26 weeks had passed since the last DEX/Sham DEX treatment

A total of 253 patients were randomised and included in the ITT population: 126 Combination Therapy and 127 Laser Alone.

The primary efficacy endpoint was the proportion of patients with a BCVA improvement of 10 or more letters from baseline in the study eye at 12 months. Combination Therapy was more effective than Laser Alone in improving vision up to month 4 in the ITT population. The effect of repeated treatment was observed for the Combination Therapy group up to 3 months after retreatment with DEX 700 (month 9 visit). The benefit was however not maintained at 6 months (month 12 visit) after retreatment, the primary time point of the study. At this primary time point, the difference (95% CI) between Combination Therapy and Laser Alone was 4.1 (-6.7 to 15.0), p = 0.453.

Statistically significant increases in the mean BCVA change from baseline were shown in favour of Combination Therapy over Laser Alone from month 1 through month 9. At these visits, the maximum mean increase was 2.8 letters with Laser Alone compared to 7.7 letters with Combination Therapy.

The BCVA categorical change from baseline in the study eye favoured Combination Therapy over Laser Alone from month 1 through month 9. The proportion of patients with a BCVA improvement of 15 or more letters from baseline was generally higher with Combination Therapy than with Laser Alone, while the proportion of patients with a BCVA worsening of 15 or more letters was generally lower in the Combination Therapy group than with Laser Alone.

The change from baseline BCVA in the number of letters read correctly for the study eye also demonstrated an early but not persistent advantage of Combination Therapy over Laser in the ITT population.

Central subfield mean thickness, total macular volume, average lesion thickness, and central point thickness (manual reading) assessed by OCT each showed statistically significant decreases with Combination Therapy compared to Laser Alone following the initial treatment at month 1 and month 4, but not at month 6. The effect of repeated treatment was observed for the Combination Therapy group at month 9, but not at month 12.

Diffuse leakage area assessed by fluorescein angiography showed statistically significant mean decreases with Combination Therapy compared to Laser Alone at each visit through month 12. There were no statistically significant between-group differences in focal leakage area.

There were no statistically significant between-group differences in the number of additional DEX 700/Sham implants or additional laser treatments, nor in the time to retreatment with DEX 700/Sham. Approximately 90% of subjects received a retreatment at Month 6.

In summary, this Phase 2 study failed on its primary efficacy endpoint of demonstrating a benefit of Ozurdex plus laser over laser alone in terms of the proportion of subjects achieving a gain of at least 10 letters of vision at 12 months. Similarly, the mean change in vision from baseline at 12 months did not differ between the treatment groups. The study did demonstrate that the implants seem to have a peak effect between 1-3 months after insertion. However, comparisons of the long term effect of Ozurdex versus laser treatment cannot be made due to the short duration of the study, and the longer term nature of the effects of laser treatment for DME.

Study 206207-018

Study 206207-018 was a 26-week, open-label trial to assess the safety and efficacy of DEX 700 in patients with DME who had had pars plana vitrectomy in the study eye at least 3 months prior to enrolment. Patients received a single treatment only, and were followed for up to 26 weeks after

treatment. The study was conducted in the US and Australia, in 2009. A total of 56 patients were enrolled and included in the ITT population, and 55 of these patients received treatment.

The primary efficacy endpoint was the change from baseline in central retinal thickness in the study eye at week 26 as assessed by OCT. Statistically significant mean decreases were found at weeks 1, 4, 8, 13, 20, and the primary time point of week 26. Mean BCVA increased after treatment from 54.5 letters at baseline to a high of 60.5 letters at week 8. Statistically significant increases from baseline in BCVA were seen at all time points except for day 2. Most patients experienced an increase in BCVA during the study compared to baseline.

The percentage of patients experiencing improvements in BCVA of ≥ 5 letters increased from week 8 onwards compared to earlier time points. The number and percentage of patients with a change in BCVA ≥ 10 letters reached a peak at weeks 8 and 13. The number and percentage of patients with BCVA ≥ 15 letters reached a maximum at week 8 that was maintained up until week 26. At week 8, 32.1% of patients experienced an improvement of ≥ 5 to < 10 letters, and 30.4% of patients experienced an improvement of ≥ 10 letters. These improvements were maintained until week 20.

At baseline, 96.4% (54/56) of patients had fluorescein leakage indicating retinal capillary leakage in the macula of the study eye compared to 79.2% (42/53) at week 26. Of the patients with leakage at week 26, the leakage had improved (i.e. area of leakage decreased by ≥ 10% from baseline) in 33.3% (14/42) of patients, was unchanged (i.e. area of leakage decreased by < 10% from baseline) in 57.1% (24/42) of patients, and had worsened (i.e. area of leakage increased by ≥ 10% from baseline) in 9.5% (4/42) of patients.

In conclusion, central retinal thickness and visual acuity both improved after treatment, with the peak effect occurring at week 8. Intravitreal DEX 700 was effective in reducing central retinal thickness and macular leakage, and resulted in improved BCVA until 26 weeks in patients with vitrectomy.

In summary, this short, uncontrolled Phase 2 study of Ozurdex in patients with DME and a history of vitrectomy showed a benefit of treatment up to 6 months after implantation in terms of reduction of macular thickness and increase in BCVA. However, limited conclusions can be made due to the uncontrolled nature of the study.

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

Evidence for the efficacy of Ozurdex in diabetic macular oedema (DME) is based mainly on data from two Phase 3 studies (studies 206207-010 and 206207-011) with an identical design, differing only in terms of the location of the study centres. The studies recruited subjects with type 1 or 2 diabetes mellitus, and DME of a severity that would be amenable to treatment, with macular thickness of at least 300 µm and visual acuity between 20/50 and 20/200 (34-68 ETDRS letters). Patients were also recruited on the basis that they had either previously received medical treatment for DME (i.e. triamcinolone or a VEGF inhibitor), or had received laser treatment but still had the potential to gain 15 letters of vision, or that they would not benefit from further laser or had refused laser. An upper limit on HbA1c of 10% was applied to exclude those patients with very poorly controlled diabetes.

A total of 1048 patients with DME were enrolled to a high or low strength Ozurdex implant (DEX 700 or DEX 350), or to sham treatment. Laser treatment was not used as a comparator in the studies in an attempt to minimise bias from complications of laser and allow assessment of the benefits and risks of Ozurdex in relation to no treatment. However, this was viewed by the CHMP as a deficiency in the design of the studies, since it resulted in a large number of withdrawals by sham-subjects due to lack of efficacy. Rescue treatment with other types of steroid, laser, or intravitreal VEGF injections could be

given, but subjects who were rescued were considered treatment failures and were withdrawn from the study (see also discussions below). Unfortunately, as rescue therapy after discontinuation was not captured in the studies, very little information is available on the outcome of such patients.

Discontinuation rates were generally high in both studies: DEX 700 (35.9%), DEX 350 group (33.7%), and Sham (56.6%). Since no imputation methods were applied for missing data in the primary efficacy analysis this was of concern (see discussions under 'efficacy data and additional analyses' below).

Patients were followed for 3 years, and could receive up to 6 additional treatments from month 6 if they had macular thickness over 175 µm or on the basis of any evidence of residual retinal oedema on the investigator's interpretation of the OCT scan. In the posology recommendations, retreatment is advised after approximately 6 months in case of decreased vision and/or macular oedema, together with general advice to consider the patient's initial response and likelihood to benefit from additional treatment as well as the associated risks. Although visual acuity was not used as a criterion for retreatment in the clinical studies, the CHMP considered that both visual and anatomic criteria were important to ensure optimal maintenance of visual function. Overall, the recommendations were considered by the CHMP to be in line with clinical practice. The lack of experience beyond repeated administration of 7 implants was also reflected in the posology recommendations.

The primary efficacy endpoint was BCVA average change from baseline during the 3 year study period using observed data in the study eye. The CHMP considered the choice of efficacy measures in principle appropriate both with regards to visual acuity, which is an accepted functional endpoint in DME studies, and with regards to retinal thickness as a supportive anatomic outcome measure. However, the area under the curve (AUC) approach for assessing visual acuity over an extended period (primary endpoint) has advantages and disadvantages. Its advantages include the ability to minimise the variability in vision during the study and to capture the average gain in vision experienced by subjects over the entire study period. However, in a scenario where a large proportion of treated subjects are likely to experience an event (such as cataract) that temporarily reduces vision during the study, the AUC approach may fail to show a significant effect of treatment. A responder analysis of the proportion gaining a certain level of vision, or the mean change in vision at the end of the study may show a different outcome in such a scenario, but in the case of a treatment with a 6 month lifespan and a peak effect at 1-3 months, the timing of the end of the study relative to the last treatment administration would clearly be of relevance.

The demographics were as expected for the population of DME patients. Demographics and disease characteristics of subjects both within and between each study were broadly comparable with the exception that study 206207-011 recruited a higher proportion of Hispanic and Asian subjects. Furthermore, subjects in study 206207-011 (in particular active-treatment subjects compared to those receiving sham) may have had slightly more severe diabetic eye disease and less well-controlled diabetes, reflected by the proportion with HbA1c >8%, the proportion with severe NPDR or worse, and baseline macular thickness. Overall, a limited number of patients with type I diabetes and this limitation was reflected in the SmPC.

Efficacy data and additional analyses

With respect to the primary endpoint, study 206207-010 demonstrated a small but statistically significant increase of 2.1 letters in the mean average change from baseline in BCVA over the 3 year study period for DEX 700 over sham. Study 206207-011 failed to demonstrate a difference between treatments. In the pooled analysis the difference between DEX 700 and sham was 1.4 letters, with a 95% confidence interval of 0.2 to 2.6 letters. The clinical relevance of this degree of average vision gain over 3 years is questionable.

Furthermore, the different baseline characteristics of participants in the trials raised questions on whether pooling of the data was appropriate. However, additional analyses performed by the MAH suggested that the difference in the two studies was primarily due to a more pronounced impact of cataract events on visual acuity outcomes in study 206207-011 (see below for discussions on the impact of steroid-induced cataract events on the efficacy results). The discrepancy between studies decreased when the subgroup of phakic patients with cataract or worsening in lens opacity but without operation was excluded from the data analysis.

With respect to the secondary endpoint of mean change in BCVA from baseline, DEX 700 subjects in study 206207-010 experienced a gain of 3.3 letters over sham subjects, whilst for those in study 206207-011 the figure was 1.3 letters. In both studies, the proportion of DEX 700 subjects who gained at least 15 letters of vision by Year 3 was 22%, a 9% increase over sham in Study 206207-010 ($p = 0.038$), and a 12% increase in Study 206207-011 ($p = 0.003$). The difference in mean average decrease in macular thickness from baseline to Year 3 between DEX 700 and sham was 63 µm in Study 206207-010, and 75 µm in Study 206207-011. No relevant effect of treatment was observed for the VFQ-25 patient-reported outcome.

By way of indirect comparison, in the RESTORE study, monthly injections of ranibizumab, a VEGF inhibitor approved for DME treatment, demonstrated a 5 letter increase over laser control treatment in mean average change in BCVA from Month 1 to Month 12, and 23% of subjects achieved a gain of at least 15 letters by the end of Year 1, a 14% increase over the laser control group. Long-term outcome data from studies with ranibizumab also showed an effect size greater than that observed with Ozurdex. Furthermore, in the FAME studies, 29% of subjects treated with fluocinolone acetonide (a long-acting intravitreal steroid implant) gained at least 15 letters at Year 3 versus 19% of controls; but in the subgroup of patients with chronic DME (duration ≥ 3 years), for which fluocinolone acetonide is approved, the proportions were 34% versus 13%, and the mean change from baseline in BCVA was 6 letters greater than in the Sham group. In both of these studies, control subjects were allowed laser treatment, unlike control subjects in the Ozurdex studies. Since the beneficial effect of laser photocoagulation was not accounted for in the pivotal trials with Ozurdex, the effect size might be even less impressive when compared to existing DME treatments. Nevertheless, the CHMP noted the limitations of such indirect comparison and that no head-to-head data were available.

Visual acuity varied markedly throughout the studies, due to the 6 month lifespan of each implant, and due to the effects of cataract on vision midway through the studies (see below for discussions on cataract). Visual response was seen to peak at around 1-3 months after treatment, declining thereafter. The effect was largely lost by the 6 month time-point after each injection. This was particularly apparent in the early phases of the studies when (re-)treatments of patients were better aligned. While the MAH argued that the effect on vision-related quality of life and vision related tasks would be limited provided good vision in the fellow eye, as supported by VFG-25 scores, the issue remained a concern for the CHMP in particular since diabetic patients are at risk of developing bilateral DR/DME. Overall, the results suggest that a more frequent injection schedule may improve the effect of Ozurdex on visual acuity over sham treatment. However, this would also presumably have increased the risks. As these assumptions were not supported by data, the CHMP considered that the posology recommendations should be based on the regimen studied in the pivotal trials. Furthermore, the CHMP recommended that the MAH should conduct a post-approval study to further investigate the optimal posology in terms of the frequency of retreatment.

An increase in the risk of cataract is a known side effect of ocular steroids (see also section 2.5.), and the increased incidence of cataract in patients treated with Ozurdex is likely to have confounded the visual efficacy outcomes, in particular the mean average change in vision from baseline, which reflects the average level of vision over the 3 year study period. In phakic patients with cataract event, an improved effect was seen after cataract surgery with a mean average BCVA gain of 4.3 and 4.7 letters

in the DEX 700 and DEX 350 groups, respectively, compared to 1.7 letters with Sham. The effect size was even higher in the subgroup of patients who experienced cataract and cataract surgery early in the study and hence had sufficient time to fully recover (>12 month; mean average BCVA gains of 6.7 and 2.1 letters in DEX 700 and Sham groups, respectively). This is in line with the effect seen in pseudophakic patients. However, while pseudophakic subjects in study 206207-010 experienced improved outcomes compared to those with a natural lens at baseline, the effects seen for this subgroup were lower in study 206207-011 (see also discussion on subgroup analyses below).

Multiple imputation was used in the secondary analysis and there was a notable difference with the results from the primary analysis, where no imputation methods were applied for missing data. Upon request of the CHMP, the MAH provided further sensitivity analyses based on a revised imputation strategy with LOCF being either the value in the middle of the last treatment cycle (peak) or at the end of a treatment cycle (trough) to better understand the impact of missing data on the study results. The MAH also provided a revised analysis accounting for cataract adverse events. This led to a more consistent set of data and similar conclusions were reached across the different types of analyses.

No specific dose-response studies were performed for the DME indication. The doses (350 µg and 700 µg) and dose frequency selected for the Phase 3 studies were based on the posologies tested for other indications (BRVO, uveitis) and data from a subgroup of diabetic patients included in a previous study. Although some results (those related to the responder analyses) seem to be more favourable for the 700 µg dose, this dose did not show a clear clinical benefit over the lower dose of 350 µg. The MAH justified the selection of the higher strength as the recommended dose for DME treatment as it is the available dose in the market for the other already approved indications. Given that from a safety perspective the low dose did not represent an obvious advantage (see also discussions in section 0) the selection of the 700 µg dose was considered acceptable.

Pre-specified subgroup analyses were conducted for the primary endpoint and for the proportion of subjects gaining at least 15 letters based on a range of baseline characteristics. These did not reveal a significant effect of the majority baseline factors on the study outcome, though in both studies there was a trend towards improved efficacy in patients with lower HbA1c and severe non-proliferative diabetic retinopathy at baseline.

A subgroup analysis in pseudophakic patients was presented by the MAH with a view to identifying a suitable target population for Ozurdex. For the primary endpoint of mean average change in vision over the 3-year study period, a sham-adjusted effect size of 6 letters was observed in the DEX 700 group in study 206207-010, compared with a Sham-adjusted 3.6 letter gain in this group in study 206207-011. A similar trend of greater effect in study 206207-010 compared with 206207-011 was also observed for the secondary endpoints. The proportion of pseudophakic patients gaining 15 letters in the DEX 700 group in study 206207-011 was low with a sham-adjusted effect size of 6%, which is lower than the proportion of sham-treated subjects gaining 15 letters in study 206207-010 (16%). The MAH attributed the difference between the two studies to the small sample size of the subpopulation. The CHMP agreed that the sample size might have contributed to the difference between the studies and furthermore noted that difference in the baseline demographic and disease characteristics suggested that patients in study 206207-011 may have been more severely affected compared to those recruited in study 206207-010.

Further consideration was given to subgroup analyses in patients with prior DME treatments to support an indication in patients insufficiently responsive to, or unsuitable for non-corticosteroid therapy. This subgroup comprised around three-quarters of subjects, many of whom will have received more than one type of treatment prior to study start. Over 90% of these patients had previously received laser, around a quarter a steroid injection, and around one in ten an injection with an anti-VEGF agent. For the primary endpoint of mean average change in vision over the 3-year study period, a modest sham-

adjusted effect size of 3 letters was observed in the DEX 700 group in study 206207-010, compared with a 1 letter sham-adjusted gain in this group in study 206207-011. The data were generally similar to the overall population, with a trend of greater effect for all endpoints in study 206207-010 compared with 206207-011 and taking into account that visual outcomes were affected by the occurrence of cataract events in the majority of patients. Nevertheless, the CHMP acknowledged that no treatment options other than steroids existed for these patients. Whilst a longer-acting steroid implant (fluocinolone acetonide) was available in many EU countries for use in DME at the time of this report, there would be some benefits in having the choice of an alternative steroid treatment with a shorter duration of effect.

2.4.4. Conclusions on the clinical efficacy

The clinical efficacy of Ozurdex in the broad indication of treatment of patients with DME was considered by the CHMP to be insufficiently demonstrated , on the basis that one of the two pivotal phase 3 studies failed in its primary endpoint, the effect size observed in the other study was very modest and of uncertain clinical relevance, and the effects of treatment on vision were not consistent over the lifespan of the implant. The derived loss of visual acuity related to the cataract progression and the need of cataract surgery in a relevant proportion of treated patients needs to be taken into consideration in the overall analysis of the product. In addition, the failure to use laser as control, which would presumably have further reduced the effect size observed, affected the interpretation of the results of the studies.

However, improved results were seen in pseudophakic patients due to the absence of cataract events as a confounding factor for visual outcomes. Furthermore, the CHMP considered that, despite the modest effect size in the overall population and the subgroup of patients with prior DME treatment, there were some benefits in having the choice of an alternative steroid treatment with a short duration of effect in patients insufficiently responsive to, or unsuitable for non-corticosteroid therapy.

With the submission of the final reports of studies 206207-010 and 206207-011, the MAH also fulfilled the requirement in the risk management plan to submit these studies (post-authorisation measure MEA-004).

2.5. Clinical safety

2.5.1. Introduction

The safety evaluation of this application was based on data from the two pivotal phase 3 studies in DME, studies 206207-010 and 206207-011. Owing to differences in design, treatment paradigm, study duration, and patient populations of the phase 2 studies, the related safety data was not pooled with the phase 3 data.

A description of the study design and methodologies including the analyses sets is provided in section 2.4.

Patient exposure

Overall, 1040 patients with DME received at least 1 study treatment in the phase 3 studies and were included in the safety population: 347 patients in the DEX 700 group, 343 patients in the DEX 350 group, and 350 patients in the Sham group.

Table 10 – Patient Exposure

	Total patients enrolled	Total patients exposed	Patients exposed to DEX 700	Duration of treatment
Sham-controlled				
Study 206207-010	494	489	160	36 months
Study 206207-011	554	551	187	36 months
Total (phase 3 studies):	*1048*	***1040***	***347***	
Study 206207-012 (phase 2 study)		252	125	52 weeks
Open label (study 206207-018)	56	55	55	26 weeks
Post marketing (from 17 June 2009 to 31 January 2013)		45,018 patient years		

Overall, the average cumulative exposure to study treatment for patients in the Sham group was 22% less than for patients in the DEX treatment groups, due to more patient discontinuations after the second treatment primarily due to lack of efficacy. Therefore discussion of adverse event rates includes both the absolute incidence (number of patients reporting event/total number of patients) as well as the rates adjusted for study exposure (per 100 patient years). Cumulative study exposure (i.e. patient years) in the pooled phase 3 studies was 853.9, 880.2 and 665.5 patient years in the DEX 700, DEX 350 and the Sham group, respectively.

The number of patients exposed over 36 months was 139 (40.1%) for DEX 700, 145 (42.3%) for DEX 350 and 93 (26.6%) for Sham.

The number (percentage) of patients who received 1 to 7 treatments (DEX 700, DEX 350, or Sham) during the phase 3 studies is provided in Table 11. In the pooled phase 3 studies, during the course of the 3-year study period, a total of 3037 study retreatments were administered.

Table 11 - Number (%) of Patients Who Received 1-7 Treatments over the 3-Years Study Duration (Pooled Analysis, Safety Population)

Total Number of Treatment(s)	DEX 700 (N = 347)	DEX 350 (N = 343)	Sham (N = 350)
1	44 (12.7)	34 (9.9)	106 (30.3)
2	54 (15.6)	45 (13.1)	63 (18.0)
3	39 (11.2)	41 (12.0)	41 (11.7)
4	42 (12.1)	40 (11.7)	26 (7.4)
5	49 (14.1)	41 (12.0)	29 (8.3)
6	88 (25.4)	105 (30.6)	50 (14.3)
7	31 (8.9)	37 (10.8)	35 (10.0)

Adverse events

A higher proportion of patients in the DEX groups experienced ocular and non-ocular adverse events compared with Sham. The incidences of adverse events between DEX 700 and DEX 350 groups were generally similar.

The number (percentage) of patients who experienced one or more adverse events, treatment-related adverse events, and serious adverse events, and patients who died or discontinued the study due to one or more adverse events during the study period are summarised by treatment group in Table 12.

Table 12 - Overall Summary of Number (%) of Patients with Adverse Events

Event/Relationship	DEX 700 (N = 347)	DEX 350 (N = 343)	Sham (N = 350)
All adverse events	333 (96.0)	334 (97.4)	281 (80.3)
Ocular	314 (90.5)	312 (91.0)	228 (65.1)
Study eye	296 (85.3)	303 (88.3)	203 (58.0)
Non-study eye	198 (57.1)	200 (58.3)	157 (44.9)
Non-ocular	241 (69.5)	237 (69.1)	207 (59.1)
Treatment-related adverse events	244 (70.3)	227 (66.2)	90 (25.7)
Ocular	244 (70.3)	226 (65.9)	89 (25.4)
Study eye	244 (70.3)	226 (65.9)	89 (25.4)
Applicator/insertion	106 (30.5)	107 (31.2)	52 (14.9)
DEX PS DDS	212 (61.1)	186 (54.2)	43 (12.3)
Non-study eye	0 (0.0)	0 (0.0)	0 (0.0)
Non-ocular	3 (0.9)	1 (0.3)	1 (0.3)
Deaths	9 (2.6)	15 (4.4)	5 (1.4)
Serious adverse events	115 (33.1)	120 (35.0)	83 (23.7)
Ocular	33 (9.5)	19 (5.5)	16 (4.6)
Study eye	24 (6.9)	14 (4.1)	4 (1.1)
Non-study eye	15 (4.3)	11 (3.2)	12 (3.4)
Non-ocular	94 (27.1)	108 (31.5)	70 (20.0)
Treatment-related serious adverse events	16 (4.6)	10 (2.9)	1 (0.3)
Ocular	16 (4.6)	10 (2.9)	1 (0.3)
Study eye	16 (4.6)	10 (2.9)	1 (0.3)
Applicator/insertion	2 (0.6)	0 (0.0)	0 (0.0)
DEX PS DDS	14 (4.0)	10 (2.9)	1 (0.3)
Non-study eye	0 (0.0)	0 (0.0)	0 (0.0)
Non-ocular	0 (0.0)	0 (0.0)	0 (0.0)
Discontinuations due to adverse events	45 (13.0)	47 (13.7)	40 (11.4)

Note: Ocular adverse events include those noted by investigator as right or left eye, or coded in the eye System Orga Class. Within each type of relationship, a subject is counted at most once. All adverse events include all reported events, regardless of relationship to treatment. Treatment-related adverse events include those in the investigator's opinion may have been caused by the study medication with reasonable possibility.

Non-ocular adverse events

In the pooled phase 3 studies, the overall incidence of non-ocular adverse events was higher in the DEX 700 group (69.5%) and DEX 350 group (69.1%) compared to Sham (59.1%). However, when the data were adjusted for study exposure, the rates (per 100 patient years) were similar between the groups: 28.2, 26.9, and 31.1 events per 100 patient years in the DEX 700, DEX 350, and Sham groups, respectively.

The most common non-ocular adverse events (> 4% in any treatment group) were anaemia, nasopharyngitis, bronchitis, urinary tract infection, upper respiratory tract infection, fall, hypercholesterolaemia, and hypertension. Only hypertension showed a higher incidence in the DEX treatment groups compared to Sham: 6.1, 5.7, and 4.1 rates per 100 patient years in the DEX 700, DEX 350, and Sham groups, respectively. There was also an imbalance in serious adverse events of cellulitis, pneumonia, gastroenteritis and urinary tract infections for dexamethasone-treated subjects.

The only treatment-related non-ocular adverse event was headache, reported for 3 patients in the DEX 700 group, 1 in the DEX 350 group, and 1 in the Sham group.

There was no evidence of increased risk of arterial thromboembolic events (eg, nonfatal stroke, nonfatal myocardial infarction, or vascular death including death of unknown causes) following repeated treatment with DEX.

- Hypertension

Overall, 71.4% (748/1048) of patients in the pooled phase 3 studies reported a medical history of hypertension, which was similar to reports in the scientific literature (National Institute of Diabetes and Digestive and Kidney Diseases, 2011). There were no differences between the treatment groups: 69.5% in the DEX 700 group, 70.9% in the DEX 350 group, and 73.7% in the Sham group.

Although there were individual patients reporting hypertension as adverse events, there were no obvious trends in systolic or diastolic blood pressure recordings during the studies (see laboratory values below).

In the subgroup of patients who reported hypertension adverse events during the pooled phase 3 studies (N = 128 overall, 52 in the DEX 700 group, 49 in the DEX 350 group, and 27 in the Sham group), there was no apparent temporal relationship between the onset of the individual adverse event of hypertension and the timing of DEX injection(s). More than 50% of the hypertension adverse events occurred 3 months or later after DEX injection overall and in each treatment group when the drug exposure should have diminished.

Ocular adverse events

An overview of all adverse events reported in more than 2% of patients in the phase 3 studies is provided in Table 13.

Table 13 - Number (%) of Patients with Ocular Adverse Events in the Study Eye That Occurred in > 2% in Any Treatment Group – Entire Study Period

Adverse Event Preferred Term[a]	DEX 700 (N = 347)	DEX 350 (N = 343)	Sham (N = 350)
Overall	296 (85.3)	303 (88.3)	203 (58.0)
Cataract[b]	131 (37.8)	111 (32.4)	34 (9.7)
Intraocular pressure increased[c]	107 (30.8)	103 (30.0)	12 (3.4)
Conjunctival haemorrhage	73 (21.0)	89 (25.9)	45 (12.9)
Cataract subcapsular[b]	41 (11.8)	41 (12.0)	12 (3.4)
Visual acuity reduced	29 (8.4)	28 (8.2)	14 (4.0)
Vitreous haemorrhage	24 (6.9)	45 (13.1)	25 (7.1)
Dry eye	21 (6.1)	19 (5.5)	9 (2.6)
Ocular hypertension[c]	21 (6.1)	17 (5.0)	5 (1.4)
Macular fibrosis[d]	20 (5.8)	37 (10.8)	10 (2.9)
Conjunctival hyperaemia	20 (5.8)	30 (8.7)	19 (5.4)
Conjunctivitis	19 (5.5)	15 (4.4)	8 (2.3)
Eye pain	18 (5.2)	24 (7.0)	13 (3.7)
Cataract nuclear[b]	18 (5.2)	15 (4.4)	8 (2.3)
Macular oedema	18 (5.2)	13 (3.8)	19 (5.4)
Vitreous detachment	17 (4.9)	23 (6.7)	8 (2.3)
Vitreous floaters	17 (4.9)	9 (2.6)	7 (2.0)
Lenticular opacities[b]	16 (4.6)	11 (3.2)	4 (1.1)
Conjunctival oedema	15 (4.3)	17 (5.0)	4 (1.1)
Retinal haemorrhage	14 (4.0)	20 (5.8)	15 (4.3)
Retinal exudates	14 (4.0)	14 (4.1)	15 (4.3)
Posterior capsule opacification	13 (3.7)	13 (3.8)	7 (2.0)
Punctate keratitis	12 (3.5)	11 (3.2)	9 (2.6)
Diabetic retinopathy	12 (3.5)	8 (2.3)	7 (2.0)
Vitreous opacities	11 (3.2)	5 (1.5)	3 (0.9)
Retinal aneurysm	10 (2.9)	11 (3.2)	6 (1.7)
Corneal abrasion	10 (2.9)	10 (2.9)	6 (1.7)
Blepharitis	10 (2.9)	5 (1.5)	16 (4.6)
Lacrimation increased	8 (2.3)	10 (2.9)	9 (2.6)
Cataract cortical[b]	7 (2.0)	13 (3.8)	9 (2.6)
Retinal neovascularisation	4 (1.2)	14 (4.1)	18 (5.1)

[a] System organ classes and preferred terms based on MedDRA, version 15.0
[b] Calculation of the proportion of patients who experienced cataract adverse events did not consider the patient's lens status (phakic or pseudophakic study eye). For discussion on cataract adverse events in patients who had a phakic study eye at baseline, see Section 2.7.4.4.4.1.
[c] Elevated intraocular pressure adverse events are further discussed in Section 2.7.4.4.3.1.
[d] Macular fibrosis included the investigator terms macular fibrosis, macular puckering, epiretinal membrane, premacular gliosis, preretinal fibrosis etc.

- Increased intraocular pressure (IOP)

Change in IOP during the study was analysed based upon MedDRA preferred terms (PT) associated with elevated IOP adverse events. In addition, actual IOP measurements (≥25 mm Hg or ≥35 mm Hg) and change from baseline in IOP measurements (≥10 mm Hg in change from baseline) were taken into account.

The incidence of elevated IOP adverse events across the entire study period in the DEX 700, DEX 350, and Sham was 36.0% (125/347), 34.1% (117/343), and 5.1% (18/350), respectively. When adjusted for exposure time in the treatment groups, the rate per 100 patient years was 12.5 and 11.7 in the DEX 700 and DEX 350 groups, respectively, compared with 1.8 in the Sham group.

The incidence of elevated IOP adverse events did not increase over time in the DEX groups, the magnitude of the IOP elevation following treatment with dexamethasone did not increase upon repeated injection, and the proportion of patients using IOP-lowering medications in the study eye remained similar from year to year. These data suggested that there was no cumulative effect of DEX on IOP.

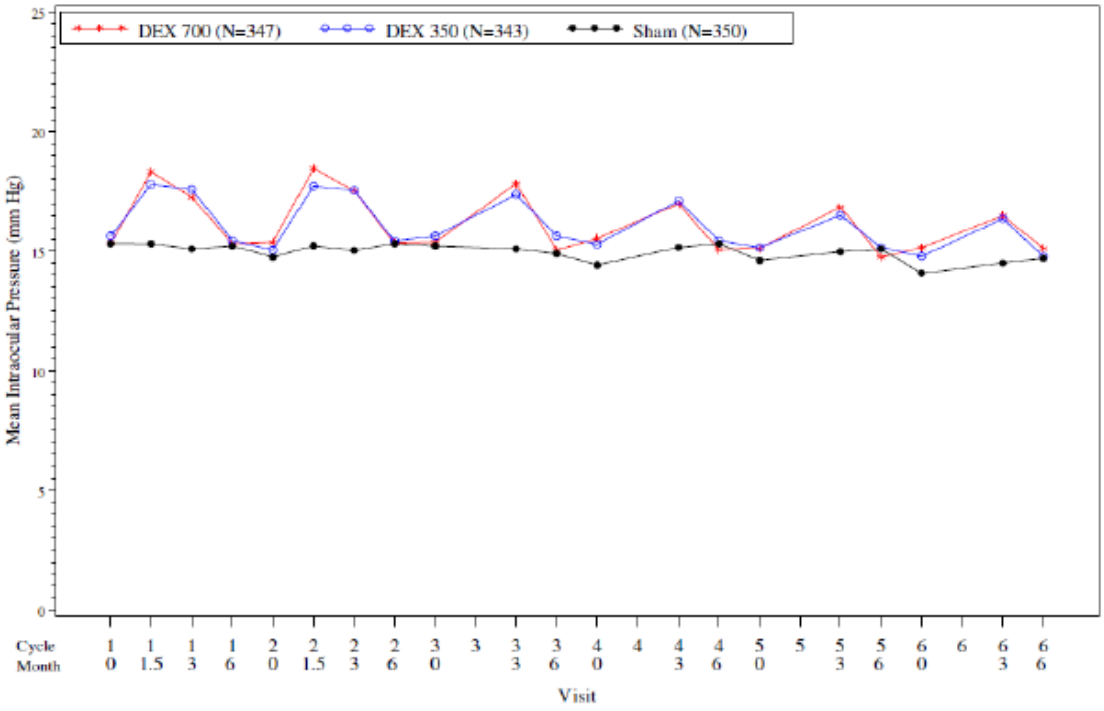


Figure 7 - Mean Intraocular Pressure in the Study Eye by Visit Within Each Treatment Cycle

In the pooled phase 3 studies, 32.0% of patients in the DEX 700 group, 27.4% in the DEX 350 group, and 4.3% in the Sham group had IOP values ≥25 mm Hg in the study eye at one or more visits during the study. At month 6 after each treatment, less than 1% of patients in each group had IOP ≥25 mm Hg.

Furthermore, 6.6% of patients in the DEX 700 group, 5.2% in the DEX 350 group, and 0.9% in the Sham group had IOP ≥35 mm Hg in the study eye at one or more visits during the study. At month 6 after each treatment, no more than 1 patient in each group had IOP ≥35 mm Hg.

Overall, 27.7% of patients in the DEX 700 group, 24.8% in the DEX 350 group, and 3.7% in the Sham group had a ≥10 mm Hg IOP increase from baseline at one or more visits during the study. At month 6 after each treatment, ≤1% of patients in each group had a ≥10 mm Hg IOP increase from baseline.

Use of IOP-lowering mediations in the study eye is summarised below.

Table 14 - Number (%) of Patients Using IOP-lowering Medication in the Study Eye

Visit	DEX 700 (N = 347)	DEX 350 (N = 343)	Sham (N = 350)	Total (N = 1040)
Baseline[a]	12/347 (3.5)	26/343 (7.6)	14/350 (4.0)	52/1040 (5.0)
Baseline to Month 12	114/347 (32.9)	99/343 (28.9)	23/350 (6.6)	236/1040 (22.7)
Month 12 to Month 24	90/305 (29.5)	89/314 (28.3)	11/241 (4.6)	190/860 (22.1)
Month 24 to Month 39/Final	75/261 (28.7)	75/269 (27.9)	12/176 (6.8)	162/706 (22.9)
Year 3/Final Visit[b]	56/261 (21.5)	49/269 (18.2)	6/176 (3.4)	111/706 (15.7)
Ever Used During the Study[c]	144/347 (41.5)	129/343 (37.6)	32/350 (9.1)	305/1040 (29.3)

IOP = intraocular pressure

Note: IOP-lowering medications included beta blocking agents, sympathomimetics, prostaglandins, carbonic anhydrase inhibitors, brimonidine, and combination agents.

[a] Baseline refers to medications used prior to the first treatment.

[b] Year 3/Final Visit includes only those medications marked as "ongoing" on the year 3 case report form.

[c] Ever Used includes those who ever used IOP-lowering medications in the study eye at any time during the study.

No patient required a removal of the implant by vitrectomy to control IOP. Only 2 patients required incisional surgery (i.e. trabeculectomy) to manage the steroid-induced IOP elevation (1 in the DEX 700 group and 1 in the DEX 350 group). Six additional patients had concurrent procedures in the study eye for the treatment of IOP elevation. One patient (DEX 700) had a trabeculectomy owing to anterior chamber fibrin blocking the aqueous outflow leading to increased IOP followed by an iridotomy, 2 patients (1 in the DEX 700 group and 1 in the Sham group) had an iridectomy, 2 patients (both in the DEX 350 group) had a trabeculoplasty, and 1 patient (DEX 700) had an iridotomy.

- Cataract

In patients with a phakic study eye at baseline (262 in the DEX 700 group, 256 in the DEX 350 group, and 250 in the Sham group), the incidence of cataract adverse events in the study eye was higher in the DEX groups compared with Sham overall and within each year. The total incidence of cataract adverse events was 67.9%, 64.1%, and 20.4% in the DEX 700, DEX 350, and Sham groups, respectively. The incidence of cataract adverse events increased during year 2, but subsequently declined in year 3, possibly due to cataract surgery.

Amongst the cataract adverse events reported in the DEX groups, the majority (one quarter) were of the subcapsular type, followed by nuclear cataract, lenticular opacities and cortical cataract.

In patients with a phakic study eye at baseline, there was a higher incidence of cataract surgery in the study eye for DEX-treated patients compared to Sham: 59.2% in the DEX 700 group, 52.3% in the DEX 350 group, and 7.2% in the Sham group during the study.

- Vitreous haemorrhage

In the pooled phase 3 studies, there were 94 patients with vitreous haemorrhage reported as an adverse event in the study eye during the study period: 6.9% of patients in the DEX 700 group, 13.1% in the DEX 350 group, and 7.1% in the Sham group. Treatment-related vitreous haemorrhage adverse events were reported in 26 patients (all events were in the study eye): 3.5% (12/347), 4.1% (14/343), and 0.0% (0/350) of patients in the DEX 700, DEX 350, and Sham groups, respectively.

Vitreous haemorrhage was reported as a serious adverse event in 20 patients: 2.9%, 1.5%, and 1.4% of patients in the DEX 700, DEX 350, and Sham groups, respectively. Four of these cases occurred in the study eye with 2 each in the DEX 700 group and the DEX 350 group. All 4 events were severe and none were considered by the investigator to be related to the study treatment. All 4 patients received vitrectomy and 3 events resolved without sequelae and 1 event was on-going. Seven cases of vitreous

haemorrhage adverse events (all in the study eye) led to patient discontinuation from the study: 2 in the DEX 700 group and 5 in the DEX 350 group.

The number of patients who used anticoagulant/antithrombotic medications during the study was small (N = 84). In each treatment group, the overall incidence of haemorrhagic adverse events in the study eye was slightly higher for patients with concomitant use of anticoagulant/antithrombotic medications compared with patients without concomitant anticoagulant/antithrombotic medications. The incidence of vitreous haemorrhage in the study eye was higher for patients with concomitant use of anticoagulant/antithrombotic medications (11.4%, 22.2%, and 9.1% in the DEX 700, DEX 350, and Sham groups, respectively) compared with patients without such medications (6.4%, 12.3%, and 7.0% in the DEX 700, DEX 350, and Sham groups, respectively).

- Retinal detachment/tear

There were 4 patients with retinal detachment reported as an adverse event in the study eye (2 in the DEX 700 group and 2 in the Sham group). All of these events occurred a considerable time after receiving the latest study drug treatment (i.e. 72 days or more). Three of these events were considered by the investigator to be unrelated to the study treatment. One event of retinal detachment in a patient in the DEX 700 group was regarded as related to the applicator/insertion by the investigator. This event was also a serious adverse event.

There were 11 patients with retinal tear reported as an adverse event, all in the study eye (5 in the DEX 700, 3 in the DEX 350 group, and 3 in the Sham group). Eight of the 11 patients had retinal tears that occurred approximately 1 month or later after receiving treatment (range: 29 to 732 days). Three events (occurring 52, 84, and 99 days after the prior study treatment) were regarded as related to the applicator/insertion by the investigator. All other retinal tears were considered by the investigator as unrelated to the study treatment. All events were mild or moderate in severity.

- Endophthalmitis

Across the 2928 cumulative number of DEX injections throughout the pooled phase 3 studies (1427 DEX 700 injections and 1501 DEX 350 injections), there were 2 reports of endophthalmitis in the study eye, both in the DEX 700 group.

One event occurred 8 days following cataract surgery, required vitrectomy, and resolved in 15 days. The patient was discontinued from the study. The event was regarded by the investigator as unrelated to the study treatment. The other event occurred 186 days after the first treatment and 4 days after the second DEX 700 injection. The event lasted for 5 days and resolved after vitrectomy, and the patient was discontinued from the study. The event was regarded by the investigator as related to the applicator/insertion.

- Hypotony of Eye/Vitreous loss

In the pooled phase 3 studies, there were 2 cases of hypotony of eye, 1 case of intraocular pressure decreased, and 1 case of vitreous loss, all in the study eye and all in the DEX 700 group.

- Retinitis Secondary to Reactivation of Latent Viral or Other Ophthalmic Infections

The MedDRA PTs for retinitis secondary to reactivation of latent viral or other ophthalmic infections included: candida retinitis, chorioretinitis, cytomegalovirus chorioretinitis, fungal retinitis, necrotising retinitis, retinitis, retinitis histoplasma, and retinitis viral.

In the pooled phase 3 studies, there was 1 case of necrotising retinitis, in the DEX 700 group. The event occurred in the study eye 267 days from the first DEX 700 treatment and 93 days from the prior DEX 700 treatment. This case of necrotising retinitis was treated with vitrectomy, intravenous acyclovir, oral prednisone, and ophthalmic prednisolone, moxifloxacin, and atropine. The patient had

no known history of herpes or human immunodeficiency virus infection; however, the investigator considered herpes to be the most likely cause of the retinal necrosis. The event was severe (sequela of blindness in the left eye) and was regarded as related to DEX PS DDS by the investigator.

- Complication of Device Insertion (DEX PS DDS Implant Misplacement)

The MedDRA PT for DEX PS DDS implant misplacement was complication of device insertion. In the pooled phase 3 studies, 1 patient in the DEX 700 group and 1 patient in the DEX 350 group had complication of device insertion reported as an adverse event in the study eye.

- Other ocular adverse events

In the DEX 700 and 350 groups, the rate of conjunctival haemorrhage was higher than in the Sham group (21.0%, 25.9%, versus 12.9, respectively). This event, along with conjunctival oedema and anterior chamber inflammation (including PTs anterior chamber inflammation, anterior chamber cell and, anterior chamber flare), which occurred in ≤5% of patients across treatment groups, was associated with the intravitreal injection procedure.

In the pooled studies, 6 patients treated with Ozurdex experienced glaucoma compared to 2 patients in the Sham group. One of the treated patients required incisional surgery to manage glaucoma.

The incidence of macular fibrosis (including investigator terms epiretinal membrane [which accounted for the majority of cases], macular puckering, premacular gliosis, macular or preretinal fibrosis and others) was higher in the DEX groups than in the Sham group: 5.8%, 10.8%, and 2.9% in the DEX 700, DEX 350, and Sham groups, respectively (3.6% in the pooled non-study eyes). In the exposure-adjusted dataset, the rates per 100 patient years for macular fibrosis were 2.3, 4.2, and 1.5 in the DEX 700, DEX 350, and Sham groups, respectively (1.5 in the pooled non-study eyes). All macular fibrosis cases were considered unrelated to the study treatment by the investigator except for one.

The incidence of visual acuity reduced was higher in the DEX groups compared with Sham: 8.4%, 8.2%, and 4.0% in the DEX 700, DEX 350, and Sham groups, respectively (3.1% in the pooled non-study eyes). In the exposure-adjusted dataset, the rates per 100 patient years for visual acuity reduced were 3.4, 3.2, and 2.1 in the DEX 700, DEX 350, and Sham groups, respectively (1.3 in the pooled non-study eyes). Review of individual cases showed that the majority of patients in the DEX groups who reported visual acuity reduced also reported cataract in the study eye prior to reporting visual acuity reduced adverse events. The incidence of visual acuity reduced was similar among treatment groups in patients who did not report cataract adverse events: 3.0% (5/164), 4.5% (8/177), and 3.7% (11/296) in the DEX 700, DEX 350, and Sham groups, respectively. In addition to cataracts, other adverse events reported by patients who experienced visual acuity reduced included macular oedema worsening, vitreous or retinal haemorrhage and IOP elevation (DEX group only).

The incidence of dry eye was higher in the DEX group compared with Sham: 6.1%, 5.5%, and 2.6% in the DEX 700, DEX 350, and Sham groups, respectively (4.4% in the pooled non-study eyes). In the exposure-adjusted dataset, the rates per 100 patient years for dry eye were 2.5, 2.2, and 1.4 in the DEX 700, DEX 350, and Sham groups, respectively (1.9 in the pooled non-study eyes). None of the dry eye adverse events reported during the pooled phase 3 studies were considered to be treatment-related by the investigator and most of these events were mild or moderate in intensity.

Serious adverse event / deaths / other significant events

The overall incidence of serious adverse events (including those with an outcome of death) for the pooled phase 3 studies was higher with DEX 700 (33.1%) and DEX 350 (35.0%) compared with Sham (23.7%). However, when adjusted for exposure time the overall incidence of serious adverse events was similar across all 3 treatment groups: the exposure-adjusted overall rates per 100 patient year of

all serious adverse events were 13.5, 13.6, and 12.5 cases per 100 patient years in the DEX 700, DEX 350, and Sham groups, respectively.

Serious ocular adverse events in the study eye were reported for 6.9% of patients in the DEX 700 group, 4.1% in the DEX 350 group, and 1.1% in the Sham group. The most commonly reported serious ocular adverse events were cataracts (in 10, 9, and 3 patients in the DEX 700, DEX 350, and Sham groups, respectively) and vitreous haemorrhage (in 10, 5, and 5 patients in the DEX 700, DEX 350, and Sham groups, respectively). Treatment-related serious ocular adverse events all occurred in the study eye, and included cataract (8, 8, and 1 patients in the DEX 700, DEX 350, and Sham groups, respectively); and subcapsular cataract (2, 2, and 0 patients in the DEX 700, DEX 350, and Sham groups, respectively). Lens dislocation, macular oedema, necrotising retinitis, retinal detachment, vitreous adhesions, and endophthalmitis were reported in the DEX 700 group by 1 patient each.

There were 29 deaths in the pooled phase 3 studies: 9 in the DEX 700 group, 15 in the DEX 350 group, and 5 in the Sham group. None of the deaths were due to ocular adverse events and none were considered by the investigator to be related to the study treatment.

Laboratory findings

Mean values for HbA1c at study baseline were similar among the 3 treatment groups. In general, mean changes from study baseline at each study visit were small. No clinically relevant changes in laboratory values over time were observed within any of the treatment groups. There was a trend toward increasing HbA1c values during the course of the study.

Blood samples for serum creatinine were collected at the qualification/baseline visit for calculating adjusted glomerular filtration rate (GFR). Mean values for GFR at study baseline were similar among the 3 treatment groups. In general, mean changes from baseline at each study visit were small. No clinically relevant changes over time were observed within any of the treatment groups. There was a trend toward decreasing GFR during the course of the study, which reflects the progression of the underlying diabetes.

In each of the phase 3 studies, mean systolic blood pressure, diastolic blood pressure, and pulse rate at baseline were similar across the treatment groups. There were no clinically significant changes from study baseline for any of the vital signs at any visit within each treatment group. Although there were some minor differences in mean values among treatment groups at some visits for all the vital sign variables, there were no signs of any consistent trend from visit to visit and the observed differences were not considered to be clinically relevant. Thus, although there were individual patients reporting hypertension as adverse events, no obvious trends were observed in the laboratory values.

In the pooled studies, corneal endothelial cell density was measured at selected sites only (a total of 206 patients). At baseline, mean endothelial cell density was 2408.7 cells/mm^2 in the DEX 700 group, 2385.1 cells/mm^2 in the DEX 350 group, and 2451.5 cells/mm^2 in the Sham group. Within each treatment group, endothelial cell density decreased from baseline over time in the study eye. At month 36, mean decreases from baseline in endothelial cell density were notably greater with DEX 700 (288.5 cells/mm^2) and DEX 350 (325.8 cells/mm^2) compared to Sham (61.3 cells/mm^2). In the non-study eye, the mean decrease from baseline in endothelial cell density at month 36 was 64.6 cells/mm^2.

Safety in special populations

The analyses of adverse event rates and pattern did not identify any patient characteristics that would indicate a safety concern or need to individualise DEX PS DDS therapy or patient management because of safety considerations.

The same pattern of higher incidences of selected events (eg, increased IOP) with DEX compared to Sham was seen in each demographic subgroup as compared to the overall population, and there were no difference between the 700 and 350 µg doses. The safety profile was comparable for mid-age (45 to 65 years) patients and the elderly (> 65 years) as well as for the other demographic characteristic including gender, ethnicity, HbA1c levels, duration of diabetes, and previous DME treatment.

In the subpopulation with pseudophakic study eye at baseline, the incidence of ocular adverse events in the study eye was higher in the DEX 700 group (74.1% [63/85]) compared with Sham group (61.0% [61/100]). Differences in the incidence of adverse events associated with elevated IOP between the DEX 700 group (29.4%) and the Sham group (9.0%) contributed to a large part to the overall difference in ocular adverse events between the 2 groups. Overall, 33% of pseudophakic patients required IOP-lowering medication during the studies. Rates of ocular adverse events and treatment-related ocular adverse events were higher in patients who had a phakic study eye at baseline than those with pseudophakic study eye due to cataract-related adverse events in phakic patients. Cataract and posterior capsule opacification was reported in 5 and 4 pseudophakic patients in the DEX 700 group compared to 2 and 6 events in pseudophakic patients receiving Sham. The events of cataract in the DEX 700 group all related to secondary cataract with posterior capsule involvement and the incidence was similar to that in the Sham group. Furthermore, the incidence of serious adverse events was similar in the DEX 700 group (36.5%) and the Sham group (36%).

In the subpopulation of patients with any prior treatment, the incidence of ocular adverse events in the study eye was higher in the DEX 700 group (86.2% [213/247]) compared with Sham (57.1% [149/261]). Differences in the incidence of adverse events associated with elevated IOP between the DEX 700 group (38.1%) and the Sham group (4.6%), and cataract related adverse events between the DEX 700 group (70.3%) and the Sham group (20.1%), contributed in part to the overall difference in ocular adverse events between the 2 groups. Overall, 42% of the patients required IOP-lowering medication, 1% required an IOP-lowering procedure and 60% underwent cataract surgery. Serious ocular adverse events in the study eye were reported for 6.9% (17/247) of patients in the DEX 700 group and 0.8% (2/261) in the Sham group.

Safety related to drug-drug interactions and other interactions

No drug-drug interaction studies have been performed.

Discontinuation due to adverse events

The numbers of adverse events leading to discontinuation from the phase 3 studies were similar for DEX 700 (13.0%), DEX 350 (13.7%), and Sham (11.4%). The exposure-adjusted rates of patient discontinuation from the study in rates per 100 patient years showed that the overall discontinuation rates due to one or more adverse events were similar across all 3 treatment groups: 5.3, 5.3, and 6.0 in the DEX 700, DEX 350, and Sham groups, respectively.

A total of 12 patients discontinued from the study due to treatment-related adverse events: 8 in the DEX 700 group (due to the adverse events of cataract [2 patients], endophthalmitis, lens dislocation, necrotising retinitis, open angle glaucoma, retinal detachment, and vitreous adhesions [1 patient each]) and 4 in the DEX 350 group (due to cataract [2 patients], macular fibrosis, and ocular hypertension [1 patient each]). No patient in the Sham group discontinued the study due to a treatment-related adverse event.

Safety findings from supportive studies

Study 206207-012

Study 206207-012 aimed at investigating the safety and efficacy of DEX 700 in combination with laser photocoagulation (Combination Therapy) compared to laser photocoagulation alone (Laser Alone) in patients with diffuse DME over a duration of 52 weeks. A total of 252 patients were treated with DEX 700/Sham and included in the safety population: 125 Combination Therapy and 127 Laser Alone.

The overall incidence of adverse events was higher in the Combination Therapy group (92.8%) compared with Laser Alone (82.7%). Ocular adverse events in the study eye were likewise more commonly reported with Combination Therapy (73.6%) than with Laser Alone (58.3%). The rate of non-ocular adverse events was similar between the 2 treatment groups. The same patterns were observed for treatment-related events.

The incidence of IOP increased was higher in the study eye with Combination Therapy (20.0%) than with Laser Alone (1.6%). This applied to all scheduled visits and for the categories ≥35 mm Hg, ≥30 mm Hg, and ≥25 mm Hg with the exception of month 12 where IOP in the study eye was <25 mm Hg for all patients. Across all scheduled visits, 15.2% of patients in the Combination Therapy group experienced an increase in IOP of ≥10 mm Hg in the study eye compared with 1.6% with Laser Alone. There were however between-group differences at any individual visit. During the study, 15.9% (20/126) of patients in the Combination Therapy group received IOP-lowering medications compared to 1.6% (2/127) in the Laser Along group. No patient required surgery for IOP elevation.

Nearly 80% of patients reported a history of cataracts in the study eye at baseline. The overall incidence of cataract adverse events in the study eye was higher with Combination Therapy (17.6%) compared with Laser Alone (7.1%). Cataract surgery was performed on 6 patients in the Combination Therapy group and 5 patients in the Laser Alone group. The surgeries were in both eyes for 5 patients, in the non-study eye for 2 patients, and in the study eye for 4 patients.

There were 6 deaths in the study, 2 in the Combination Therapy group and 4 in the Laser Alone group. None were considered to be related to the study treatments. Serious adverse events were reported for 18.4% (23/125) of patients in the Combination Therapy group and 21.3% (27/127) in the Laser Alone group, none of which were considered related to the study treatments.

Adverse events leading to discontinuation were reported for 7.2% (9/125) of patients in the Combination Therapy group and 9.4% (12/127) in the Laser Alone group. None of the events were considered to be related to the study treatments.

There were no between-group differences for any individual biomicroscopy/ophthalmoscopy finding with at least 2 severity grades increase from baseline (deemed clinically significant) aside from a higher incidence of conjunctival haemorrhage in the Combination Therapy group (28.0%) compared with Laser Alone (15.0%). Other findings with clinically significant changes from baseline were less common, and included vitreous haemorrhage, opacity impact on visual acuity, subcapsular cataract, vitreous opacities, and conjunctival hyperaemia.

Study 206207-018

Study 206207-018 was a 6-month, open-label trial to assess the safety and efficacy of DEX 700 in patients with DME who had pars plana vitrectomy in the study eye. Patients received a single treatment only. A total of 56 patients were randomised and 55 received treatment.

A total of 90.9% (50/55) of patients experienced adverse events. Most adverse events were ocular events involving the study eye (81.8% [45/55]). Non-ocular events were reported for 43.6% (24/55)

of patients. A total of 63.6% (35/55) of patients had treatment-related adverse events, mostly associated with the applicator insertion.

Ocular adverse events in the study eye occurring in ≥10% of patients included conjunctival haemorrhage (52.7% [29/55]), conjunctival hyperaemia (20.0% [11/55]), eye pain (16.4% [9/55]), intraocular pressure increased (16.4% [9/55]), conjunctival oedema (12.7% [7/55]), and vitreous haemorrhage (10.9% [6/55]). There were no severe ocular adverse events.

A total of 12 patients had adverse events related to increased IOP. In 9 of these patients, the adverse events occurred in the study eye and in 6 of these patients, the events were considered to be related to study treatment. None of these adverse events were severe, and in 5 patients, the events resolved without additional treatment. Modest increases in mean IOP in the study eye relative to baseline were seen at each post-baseline visit, with the largest increase occurring at week 8 (mean change from baseline was 3.4 mm Hg) and mean values returning to near baseline by week 26. No patients had a change from baseline ≥10 mm Hg at week 26. Similarly, a transient increase in the percentage of patients with an actual value ≥25 mm Hg was seen at week 8 (9.3% [5/54]) but no patient had an actual value ≥25 mm Hg at week 26.

One patient (1.8%) had worsening of cataracts in both the study eye and non-study eye. A second patient (1.8%) had an increase in both a nuclear cataract and a posterior subcapsular cataract in the study eye. None of these events were considered to be related to study treatment.

A total of 25.5% (14/55) of patients had serious adverse events. There were no serious treatment-related adverse events and there were no serious ocular adverse events. One patient receiving DEX 700 discontinued due to an adverse event (anoxic encephalopathy), from which she later died.

A total of 92.7% (51/55) of patients had at least a 1-grade increase in the severity of biomicroscopy/ophthalmoscopy findings from baseline. Clinically significant (defined as at least a 2-grade increase in severity from baseline at any follow-up visit) biomicroscopy/ophthalmoscopy findings in the study eye included conjunctival haemorrhage in 10.9% (6/55) of patients, vitreous haemorrhage in 7.3% (4/55), anterior chamber cells in 3.6% (2/55), and conjunctival hyperaemia in 3.6% (2/55).

Post marketing experience

Ozurdex was first approved on 17 June 2009 in the USA and on 27 July 2010 in the EU for the treatment of macular oedema following retinal vein occlusion (RVO). At the time of this application, Ozurdex was approved in 56 countries for this indication and marketed in 37 countries. The indication was later extended to include the treatment of non-infectious posterior segment uveitis, which was approved in 46 countries worldwide at the time of the DME application.

With regards to the exposure estimates, 31 January 2013 was used as the cut-off date. The cumulative post-marketing distribution during this period was 154,348 units of Ozurdex, translating into an estimated 45,018 patient-years of exposure, assuming that treatment with Ozurdex involves, on average, 1.2 units (since Ozurdex is being administered in some circumstances to both eyes at the same treatment session), the average months of effect/treatment were calculated at 4.2 and the number of treatments in a year at 2.85.

As of 27 January 2013, 4 periodic safety update reports (PSURs) of Ozurdex have been reviewed globally covering the time period from 17 June 2009 to 27 July 2012. The fifth PSUR was still under review at the time of this report. The cumulative post-marketing experience with Ozurdex is subject to this PSUR assessment.

Integrated safety analysis across indications

Upon request by the CHMP, the MAH presented results from an integrated safety analysis across indication to support one single ADR table for SmPC section 4.8. The studies included in the analysis were 5 pivotal phase 3 studies in three indications as follows:

Study 206207-008 and 009 (BRVO/CRVO): Six-month, Phase 3, Multicenter, Masked, Randomized, Sham-Controlled Trial (With Six-Month Open-Label Extension) to Assess the Safety and Efficacy of 700 µg and 350 µg Dexamethasone Posterior Segment Drug Delivery System (DEX PS DDS) Applicator System in the Treatment of Patients with Macular Edema Following Central Retinal Vein Occlusion or Branch Retinal Vein Occlusion

206207-014 (Uveitis) : An 8-week, Multicenter, Masked, Randomized Trial (with an 18-Week Masked Extension) to Assess the Safety and Efficacy of 700 µg and 350 µg Dexamethasone Posterior Segment Drug Delivery System (DEX PS DDS) Applicator System Compared With Sham DEX PS DDS Applicator System in the Treatment of Non Infectious Ocular Inflammation of the Posterior Segment in Patients with Intermediate Uveitis

206207-010 and 011 (DME): A 3 Year, Phase 3, Multicenter, Masked, Randomized, Sham Controlled Trial to Assess the Safety and Efficacy of 700 µg and 350 µg Dexamethasone Posterior Segment Drug Delivery System (DEX PS DDS) Applicator System in the Treatment of Patients with Diabetic Macular Edema

For the pooled analysis, MedDRA, the medical coding dictionary used to code adverse events, was up-versioned for BRVO/CRVO (v11.0) and Uveitis (v11.1) studies to MedDRA v15.0 which was used for the DME studies.

All adverse drug reactions (ADRs, events with a reasonable possibility caused by OZURDEX) listed for the approved BRVO/CRVO and uveitis indications as well as ADRs identified from the DME studies were included in the combined ADR list. The frequency of the clinical ADRs were re-calculated based on the pooled data. The frequency of the majority of the ADRs remained unchanged. However, the frequency for migraine, anterior chamber cells, retinal detachment, abnormal sensation in the eye, eyelid pruritus and sclera hyperaemia changed from common to uncommon in the pooled analysis.

The ADRs previously listed under post-marketing experience in SmPC section 4.8 were also integrated in the combined ADR list and frequencies were calculated based on the occurrence in clinical trial, where possible. The post marketing ADR of device dislocation (implant migration from vitreous to anterior chamber) with or without corneal oedema has never been observed in the pivotal studies. Therefore, its frequency was calculated based on the rule of three, which is 3 divided by 844, the total number of patients who received OZURDEX in the 5 pivotal studies, resulting in a frequency of 0.4% (uncommon).

2.5.2. Discussion on clinical safety

At the time of this report, Ozurdex was approved for marketing in the EU for the treatment of macular oedema following retinal vein occlusion, as well as posterior uveitis. The safety profile in these indications was considered by the CHMP to be reasonably well established. However, there was limited information on the safety of chronic use of Ozurdex.

The safety evaluation of patients with DME exposed to Ozurdex was mainly based on the pooled analysis of the two Phase 3 studies, 206207-010 and 206207-011. Overall, 347 patients were exposed in these studies to treatment with DEX 700 and 343 to DEX 350 for up to 39 months. Although the number of subject withdrawals was high, cumulative exposure data for up to 33 months were available

for at least two-thirds of Ozurdex subjects. Around half of the Sham-treated subjects had exited by 24 months into the studies.

On the whole, given that diabetes mellitus is a chronic and progressive condition, the number of DME patients exposed to dexamethasone with long term safety data was considered sufficient for an adequate safety assessment. However, patients with DME may require treatment for an undefined period of time which would interfere with the external validity of the results.

Overall in the phase 3 trials, 81 patients ≥ 75 years were included. No safety concern was raised in this age group.

Supportive data were furthermore available from the two Phase 2 studies, in which 125 patients were exposed to 1 or 2 Ozurdex implants plus laser for up to 12 months (study 206207-012), and 55 vitrectomised patients with DME were exposed to a single Ozurdex implant for up to 6 months (study 206207-018). The safety observations from these studies did not highlight any additional concerns to what was seen in the phase 3 studies (see discussion below). The safety of Ozurdex in combination with laser and as a single implant in vitrectomised patients with DME appeared to be acceptable.

Non-ocular adverse events were unlikely to be a significant feature with Ozurdex, due to the low systemic exposure to dexamethasone, and the events that did occur were generally reported with a similar frequency in the active and the control groups. The most common non-ocular adverse events were anaemia, nasopharyngitis, bronchitis, urinary tract infection, upper respiratory tract infection, fall, hypercholesterolaemia, and hypertension, which were not unexpected in an aging diabetic population. The only treatment-related non-ocular adverse event was headache. There was also an imbalance in serious adverse events of cellulitis, pneumonia, gastroenteritis and urinary tract infections for dexamethasone-treated subjects, but the number of these events was small.

With regards to hypertension, whilst there was a notably higher rate of events in the dexamethasone groups, the disproportion between the exposure-adjusted rates per 100 years in active versus sham patients was relatively small, and there were no obvious trends in systolic or diastolic blood pressure recordings during the studies. In this context it was noted that systemic exposure with corticosteroids may cause fluid retention which can result in hypertension (Clyburn and DiPette, 1995; Ferrari, 2003). However, in the pooled phase 3 studies, there were only 3 adverse events of 'weight increased' (all in the DEX 350 group) and there were no adverse events indicative of fluid retention. In addition, more than 50% of the hypertension adverse events occurred 3 months or later after DEX injection in each treatment group as well as overall, when the drug exposure should have diminished. Therefore and since the systemic exposure after intravitreal injection of the Ozurdex implant was minimal, the CHMP considered it unlikely that the observed adverse events of hypertension were associated with any potential systemic corticosteroid effect. Nevertheless, the CHMP considered that there was a degree of uncertainty remaining as to whether systemic exposure and related adverse reactions represented a potential risk of Ozurdex in diabetic patients. It was therefore agreed to retain it as a safety concern in the risk management plan (RMP) and spontaneous post-marketing reports should be targeted for follow-up.

The commonest ocular adverse events that occurred in the Phase 3 studies (cataract and increased IOP) were expected and were known adverse reactions already listed in the SmPC for other indications. Other frequently-reported events, such as conjunctival haemorrhage and eye pain, were expected responses to intravitreal injection, and were already listed in the SmPC as well.

IOP-related events were reported in 36% of the patients treated with DEX 700, and in 5% with Sham, and 28% of DEX 700-subjects had an IOP increase from baseline of at least 10 mmHg at some point in the trial. A total of 42% of subjects receiving DEX 700 required IOP-lowering medication during the study (though 4% were using medication at baseline). In addition, 7 subjects (1%) required a surgical

or laser procedure to control the IOP, including two trabeculectomies. In conclusion, the rise in IOP was generally manageable with IOP-lowering medication and the CHMP agreed to reflect this information in SmPC.

The rates of IOP events and subjects requiring medication for IOP were similar to those observed in the FAME studies for fluocinolone acetonide. However, the surgical/laser intervention rate for dexamethasone was lower. This was not unexpected, since the duration of action of Ozurdex is much shorter compared to the fluocinolone acetonide implant (up to 3 years), and subjects were unlikely to have been retreated if their IOP was uncontrollable with medication. The CHMP furthermore noted that 6 patients treated with Ozurdex experienced glaucoma compared to 2 patients in the Sham group and that one of the treated patients required incisional surgery to manage glaucoma. It was agreed that glaucoma should be added as an uncommon adverse drug reaction in SmPC section 4.8.

In the context of IOP-related events, the CHMP noted that the safety evaluations in the Phase 3 studies were conducted by an unmasked investigator for the first 30 days after study treatment procedures. Whilst certain assessments, such as biomicroscopy and indirect ophthalmoscopy, would probably have indeed anyways led to unblinding of the assessor due to visualisation of the implant, measurement of IOP could have been biased by the assessor's knowledge of the treatment. Significant effects on IOP may occur in the first 30 days after treatment and unblinded investigators may have more rigorously reported IOP events during this time.

Adverse events of cataract occurred in 68% of patients with phakic study eye at baseline who were treated with DEX 700, with 59% of the patients requiring cataract surgery during the study, compared to 7% under Sham. Nearly a quarter of cataracts were reported as being of the subcapsular type. The majority of cataract events occurred in Year 2. By means of comparison, the incidence of cataract surgery reported in the pivotal trials for the fluocinolone acetate implant was 80%, though the effect of this implant lasts for up to 3 years and the total steroid exposure may have been higher. In addition, the incidence of cataract surgery in Sham-treated subjects in the fluocinolone acetate pivotal studies was higher with 27% suggesting that the group as a whole may have had a poorer prognosis with regard to cataract. While cataracts were already described as adverse drug reactions in the product information of Ozurdex , the CHMP considered that the current warning should be updated to provide information to health care professionals on the rate of cataract surgeries required in the DME studies for patients treated with dexamethasone.

Other relevant adverse events reported in the Ozurdex studies include vitreous haemorrhage, retinal detachment or tear, endophthalmitis, hypotony, retinitis, and implant misplacement. Except for retinitis, these events had been previously reported either in the context of the clinical development program for the other indications of Ozurdex or post-marketing and were already listed in the SmPC.

Vitreous haemorrhage is a recognised complication of diabetic eye disease, and 4 serious adverse events occurred in the study eye (all in DEX-treated subjects), though none was regarded as related to treatment, and 3 occurred a significant length of time after the last injection. The incidence of events was slightly higher in patients on concomitant anticoagulant/antithrombotic medications. A warning on to this end was already included in section 4.4 of the SmPC and was now updated with data from the DME studies.

Retinal tears and detachments are a potential, though rare, complication of intravitreal injections. Four retinal detachments were reported in the study eye during the studies, with 2 reported in DEX-treated subjects. Furthermore, eleven events of retinal tear were reported, with 8 occurring in the active treatment groups, and 3 of these classified as related to treatment.

Only one event of endophthalmitis occurred that can be obviously related to Ozurdex insertion, out of a total of nearly 3000 injections. This was no higher than the rate reported for other products with an intravitreal injection procedures.

One event of acute retinal necrosis occurred in an Ozurdex-treated subject, which was considered to be related to Ozurdex and to be caused by herpes. It is plausible that latent infections could be reactivated by intraocular steroids. Retinitis secondary to reactivation of latent viral or other ophthalmic infections was therefore reclassified as an important identified risk in the RMP. Furthermore, necrotising retinitis was added to section 4.8 of the SmPC.

Other ocular events of relevance included dry eye, reduced visual acuity, macular fibrosis, and anterior chamber inflammation. With regards to visual acuity reduced, the majority of cases were associated with cataract formation, an adverse reaction to ocular corticosteroids. Therefore the adverse event of impaired visual acuity was considered by the CHMP to be directly related to the use of the product, and has been included as an ADR in section 4.8 of the SmPC. Furthermore, the RMP has been updated to reflect this issue in the context of the identified risk of cataract.

The other three events were reported with a higher frequency in DEX-treated subjects, and there was a reasonable probability that a causal relationship to treatment existed. Therefore, anterior chamber inflammation was included in SmPC section 4.8 as an uncommon adverse drug reaction. However, with regards to events of dry eye, the CHMP considered the exposure-adjusted incidences, the lack of an increase in incidence with cumulative exposure, and, in particular, the high incidence of dry eye in the non-study eye, and concluded that a causal relationship was unlikely. The CHMP furthermore noted that the number of cases of macular fibrosis was relatively small, and that the exposure adjusted incidence and lack of an increase in incidence with cumulative exposure did not support a causal relationship. Furthermore, the underlying disease of DME leads to retinal/macular fibrosis if untreated.

Concerning treatment-related serious adverse events, retinal detachment and endophthalmitis were already listed in section 4.8 of SmPC. Necrotising retinitis was added to the SmPC as previously discussed. Other events such as lens dislocation, macular oedema and vitreous adhesions were reported disproportionately in Ozurdex-treated subjects. However the number of cases was low, and events such as macular oedema and vitreous adhesions were considered to be potentially related to the underlying disease.

Corneal endothelial cell density was measured in a subset of sites in 206 patients. A disproportionate decrease in endothelial cell density was observed for DEX-treated subjects compared to Sham. This appeared to be due to the higher rates of cataract surgery in those subjects.

The incidences of adverse events between DEX 700 and DEX 350 groups were unexpectedly similar. However, this pattern was also seen with Ozurdex for macular oedema due to RVO..

No drug-drug interaction studies have been performed. However due to the low systemic levels of dexamethasone following DEX 700 or DEX 350 treatment, drug-drug interactions were not expected.

With regards to the subgroups of pseudophakic patients and patients with prior DME treatment, the CHMP considered that the safety of Ozurdex was not markedly different to that in the overall population other than for the risk of cataract in pseudophakic patients.

In general, the adverse events reported during the two phase 3 trials for Ozurdex in DME were qualitatively generally consistent with those reported during clinical studies for the other indications approved for Ozurdex. However, the prevalence of adverse events could be expected to be generally higher in DME patients than in RVO and uveitis patients due to the need for longer-term treatment.

Finally, the CHMP considered that a single tabulated list of adverse reactions for all indications should be included in section 4.8 of the SmPC in line with the Guideline on Summary of Product

Characteristics. This was supported by the outcome of an integrated safety analysis across all indications. The CHMP furthermore agreed to an amendment of one of the contraindications to clarify that Ozurdex should also not be used in eyes with iris or transscleral fixated intraocular lens in addition to the existing contraindication in eyes with anterior chamber intraocular lens and ruptured posterior lens capsule due to the risk for device migration as already reflected in the related warning.

2.5.3. Conclusions on clinical safety

In summary, the most frequent adverse drug reactions observed with Ozurdex in clinical trials for DME were raised IOP, cataract, and injection-related events. These were prevalent and not unexpected, and are manageable to an extent. Nevertheless, the high risk of cataract and increased IOP are of concern considering that cataract surgery is not without risk and since increased IOP may result in glaucoma and irreversible loss of vision if left untreated. Furthermore, longer-term treatment could be necessary in patients with DME. Hence the prevalence of adverse events could be expected to be higher in DME patients than in RVO and uveitis patients.

2.5.4. PSUR cycle

The PSUR cycle remains unchanged.

The Annex II related to the PSUR, refers to the EURD list which remains unchanged.

2.6. Risk management plan

2.6.1. PRAC advice

The CHMP received the following PRAC advice on the submitted Risk Management Plan.

PRAC Advice

The PRAC considered that the risk management system version 6.0 was acceptable. The PRAC endorsed PRAC Rapporteur assessment report is attached to this report.

This advice is based on the following content of the Risk Management Plan:

Safety concerns

Important identified risks	Increased intraocular pressure, Glaucoma, Ocular Hypertension Cataract formation and associated Visual acuity reduced Vitreous detachment, haemorrhage Endophthalmitis (infectious/ non-infectious) Retinal tear/detachment Significant vitreous leak or hypotony Device Dislocation Implant misplacement Retinitis secondary to reactivation of latent viral or other ophthalmic infections

Important potential risks	Systemic corticosteroid effects (infections, impaired healing and hypertension)
Missing information	Paediatric Use Pregnancy and lactation Long-term safety, Repeat dosing data Concurrent use of anticoagulants Patients with significant retinal ischaemia

Pharmacovigilance plans

Activity / Study title (type of activity, study title, category 1-3)	**Objectives**	**Safety concerns addressed**	**Status Planned, started,**	**Date for submission of interim or final reports**
206207-025 "**Post-Authorization Safety Study of OZURDEX (Dexamethasone Intravitreal Implant): A Prospective Observational Study to Evaluate Long-Term Safety in Real-World Clinical Practice**" (EU PASS-category 3)	The observational study (N-I PASS) will provide long term outcome and safety data in patients requiring two or more treatments.	Important identified risks and missing information	First patient enrolment occurred in March 2012 as planned. A total of 18 sites have been initiated (9 in DE, 7 in the UK, and 2 in FR). As of 24-January 2014, 783 patients have been enrolled.	Study initiation: 28/03/2012 last patient enrolled: 28/03/2014 Final study report submission: 28/03/2016
Physician Survey "**Evaluation of the Physician Education Component of the Ozurdex Survey for Risk Management Plan**" (category 3)	To determine whether the educational materials are effective in communicating the recommended injection technique and the important risks of OZURDEX to prescribers	Important identified risks:	Study Protocol and Survey were submitted for regulatory review. Assessment Report received on 25/02/2013, the amended survey protocol and form are included in Annex 6.	Final survey report included in Annex 9.

Risk minimisation measures

Safety Concern Important Identified risks	**Routine risk minimization measures**	**Additional risk minimization measures**

Increased IOP, Glaucoma and Ocular Hypertension	Section 4.3 of SmPC listed that "advanced glaucoma which cannot be adequately controlled by medicinal products alone" as a contraindication. Increases in intraocular pressure (IOP) is described in Section 4.4 of the SmPC. Increased IOP is included as "very common" adverse reaction in Section 4. 8 for all indications (Undesirable effects)	Educational material on important risks associated with OZURDEX, including increased intraocular pressure and ocular hypertension. OZURDEX Patient Information brochure (booklet, audio-CD): The Patient Information Brochure includes a description of symptoms following an injection which patients should watch for, which could signify a common adverse event, or a significant adverse event.
Cataract formation and associated Visual acuity reduced	Occurrence of cataract, including observed in clinical studies is described in Section 4.4 of the SmPC Included as a "common" adverse reaction for BRVO/CRVO, "very common" adverse reaction for uveitis and DME in Section 4.8 (Undesirable effects)	Educational material on important risks associated with OZURDEX, including cataracts.
Vitreous Detachment / haemorrhage	Included as "common" adverse reaction for BRVO/CRVO and DME in section 4.8 of the SmPC.	Educational material on important risks associated with OZURDEX, including vitreous detachment/haemorrhage
Endophthalmitis	Section 4.4 of the SmPC warns that any intravitreous injection can be associated with endophthalmitis. Patients must be instructed to report any symptoms suggestive of endophthalmitis or any of the mentioned events without delay. Antimicrobial therapy is recommended in Section 4.2 of the SmPC, as is disinfection of the periocular skin, eyelid and ocular surface with povidone iodine 5%. Endophthalmitis (injection related) is included in Section 4.8 of the SmPC as an uncommon adverse reaction in DME and under post-marketing experience. Endophthalmitis is included in the Sentinel Events List for OZURDEX.	Educational material has been updated to emphasize the use of povidone iodine to disinfect ocular surface and surrounding tissues prior to injection to minimize injection related infection. OZURDEX Patient Information brochure (booklet, audio-CD): The Patient Information Brochure includes a description of symptoms following an injection which patients should watch for, which could signify a common adverse event, or a significant adverse event (e.g. endophthalmitis).

Retinal tear/detachment	Section 4.4 (Special warning and Precautions for Use): Intravitreous injections, including those with OZURDEX, can be associated retinal detachment. Monitoring may consist of a check for perfusion of the optic nerve head immediately after the injection, tonometry within 30 minutes following the injection, and biomicroscopy between two and seven days following the injection. Section 4.8 (Undesirable Effects): Retinal detachment is included as "uncommon" adverse reaction for DME, as "common" adverse reaction for uveitis and is included under post-marketing experience of the SmPC. Retinal tear is listed as common adverse reaction for DME and as an uncommon adverse reaction for BRVO/CRVO, which may be related to the injection procedure rather than the dexamethasone implant.	Educational material on important risks associated with OZURDEX, including retinal tear/detachment.
Significant vitreous leak or hypotony	Section 4.2: Posology and method of administration of the SmPC provides clear instruction on the proper injection procedure. Section 4.8: Undesirable effects of SmPC: Hypotony (associated with vitreous leakage due to injection) is listed as uncommon adverse reaction for DME, and is included under post-marketing experience with OZURDEX. Significant vitreous leak or hypotony are included in the Sentinel Events List for OZURDEX.	Educational material to instruct prescribers on the recommended injection technique and Wet lab training programs (optional for physician)

Device dislocation	Section 4.3 of SmPC (Contraindications) OZURDEX is contraindicated in • Aphakic eyes with ruptured of the posterior lens capsule. • Eyes with Anterior Chamber Intraocular Lens (ACIOL), iris or transscleral fixated Intraocular Lens and ruptured of the posterior lens capsule. Section 4.4 (Special warnings and precautions for use) All patients with posterior capsule tear, such as those with a posterior lens (e.g. due to cataract surgery), and/or those who have an iris opening to the vitreous cavity (e.g. due to iridectomy) with or without a history of vitrectomy, are at risk of implant migration into the anterior chamber. Implant migration to the anterior chamber may lead to corneal oedema. Persistent severe corneal oedema could progress to the need for corneal transplantation. Other than those patients contraindicated (see section 4.3) where OZURDEX should not be used, OZURDEX should be used with caution and only following a careful risk benefit assessment. These patients should be closely monitored to allow for early diagnosis and management of device migration. Section 4.8 (Undesirable Effects): The following adverse reaction has been identified from post-marketing experience with OZURDEX: Device dislocation (migration of implant) with or without corneal oedema. Device dislocation is included in the Sentinel Events List for OZURDEX**.**	Educational material to instruct prescribers on the recommended injection technique and Wet lab training programmes (optional for physician).
Implant misplacement	Section 4.2: Posology and method of administration of the SmPC has clear instruction on the proper injection procedure. Section 4.8 (Undesirable Effects): The following adverse reaction has been identified from post-marketing experience with OZURDEX: Complication of device insertion (implant misplacement) Implant misplacement is included in the Sentinel Events List for OZURDEX.	Educational material to instruct prescribers on the recommended injection technique and Wet lab training programmes (optional for physician).

Retinitis secondary to reactivation of latent viral or other ophthalmic infections	OZURDEX is contraindicated in active or suspected ocular or periocular infection (section 4.3 of the SmPC). Section 4.4 of the SmPC warns that use of corticosteroids may result in secondary ocular infections and that corticosteroids should be used cautiously in patients with a history of ocular herpes simplex and not be used in active ocular herpes simplex. Section 4.8 (Undesirable Effects): Necrotizing retinitis is listed as an uncommon adverse reaction for DME. Retinitis secondary to reactivation of latent viral or other ophthalmic infections is included in the Sentinel Events List for OZURDEX.	None
Important Potential risks	**Routine risk minimization measures**	**Additional risk minimization measures**
Systemic corticosteroid effects	Section 4.4 of the SmPC indicates that the safety and efficacy of OZURDEX administered to both eyes concurrently have not been studied. Therefore administration to both eyes concurrently is not recommended.	None
Missing Information	**Routine risk minimization measures**	**Additional risk minimization measures**
Pediatric Use	Section 4.2 of the SmPC indicates that there is no relevant use of OZURDEX in the paediatric population in • diabetic macular oedema • macular oedema following either BRVO or CRVO. The safety and efficacy of OZURDEX in uveitis in the paediatric population have not been established. No data are available.	None
Pregnancy and lactation	Section 4.6 of the SmPC indicates OZURDEX is not recommended during pregnancy and during breast feeding unless the potential benefit justifies the potential risk to the fetus or clearly necessary.	None

Long-term safety, repeat dosing data	Section 4.2 of the SmPC indicates: For RVO and uveitis Repeat doses should be considered when a patient experiences a response to treatment followed subsequently by a loss in visual acuity and in the physician's opinion may benefit from retreatment without being exposed to significant risk. Patients who experience and retain improved vision should not be retreated. Patients who experience deterioration in vision, which is not slowed by OZURDEX, should not be retreated. There is only very limited information on repeat dosing intervals less than 6 months. There is currently no experience of repeat administrations in posterior segment non-infectious uveitis or beyond 2 implants in RVO. For DME Patients treated with OZURDEX who have experienced an initial response and in the physician's opinion may benefit from retreatment without being exposed to additional risk should be considered for retreatment. Retreatment should be considered if the patient experiences decreased vision and/or an increase in retinal thickness which are secondary to recurrent or worsening diabetic macular oedema. In clinical trials patients received up to 7 treatments. The majority of retreatments were given between 5 and 7 months.	None

Concurrent use of anticoagulants	Section 4.4 of the SmPC describes use of OZURDEX during anticoagulant therapy: In RVO, anti-coagulant therapy was used in 2% of patients receiving OZURDEX; there were no reports of haemorrhagic adverse events in these patients. In DME, anti-coagulant therapy was used in 8% of patients. Among patients who used anti-coagulant therapy, the frequency of haemorrhagic adverse events was similar in the OZURDEX and sham groups (29% vs 32%). Among patients who did not use anti-coagulant therapy, 27% of OZURDEX treated patients reported hemorrhagic adverse events compared to 20% in the sham group. Vitreous haemorrhage was reported in a higher proportion of patients treated with OZURDEX who received anti-coagulant therapy (11%) compared with those not receiving anticoagulant therapy (6%). Anti-platelet medicinal products, such as clopidogrel, were used at some stage during the clinical studies in up to 56% of patients. For patients using concomitant and anti-platelet medication, haemorrhagic adverse events were reported in a slightly higher proportion of patients injected with OZURDEX (up to 29%) compared with the sham group (up to 23%), irrespective of indication or number of treatments. The most common haemorrhagic adverse event reported was conjunctival haemorrhage (up to 24%). OZURDEX should be used with caution in patients taking anti-coagulant or anti-platelet medicinal products.	None
Patients with significant retinal ischaemia	Section 4.4 of the SmPC indicates that OZURDEX has not been studied in patients with macular oedema secondary to RVO with significant retinal ischemia.	None

The PRAC also reviewed the MAH's proposal to omit the HCP leaflet which is provided as tear off section at the end of the package leaflet. The PRAC concluded that the leaflet should be maintained, however, it should be reduced to relevant safety information of the SmPC including all parts of section 4, section 5.3 and section 6.6.

The CHMP endorsed this advice without changes.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.3, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

Changes to SmPC sections 4.1, 4.2, 4.3 and 4.4 are reflected below (additions are underlined, deletions are shown as strike-through text). For all other changes, see annexed product information.

- **SmPC section 4.1**

OZURDEX is indicated for the treatment of adult patients with:

- visual impairment due to diabetic macular oedema (DME) who are pseudophakic or who are considered insufficiently responsive to, or unsuitable for non-corticosteroid therapy
- macular oedema following either Branch Retinal Vein Occlusion (BRVO) or Central Retinal Vein Occlusion (CRVO) (see section 5.1)
- ~~OZURDEX is indicated for the treatment of adult patients with~~ inflammation of the posterior segment of the eye presenting as non-infectious uveitis~~.~~

- **SmPC section 4.2**

Posology

The recommended dose is one OZURDEX implant to be administered intra-vitreally to the affected eye. Administration to both eyes concurrently is not recommended (see section 4.4).

DME

Patients treated with OZURDEX who have experienced an initial response and in the physician's opinion may benefit from retreatment without being exposed to significant risk should be considered for retreatment.

Retreatment may be performed after approximately 6 months if the patient experiences decreased vision and/or an increase in retinal thickness, secondary to recurrent or worsening diabetic macular oedema.

There is currently no experience of the efficacy or safety of repeat administrations in DME beyond 7 implants.

RVO and Uveitis

(...)

Paediatric population

There is no relevant use of OZURDEX in the paediatric population in

- diabetic macular oedema
- macular oedema following either Branch Retinal Vein Occlusion (BRVO) or Central Retinal Vein Occlusion (CRVO)~~.~~

- **SmPC section 4.3**

OZURDEX is contraindicated in

- (...)
- Aphakic eyes with ruptured ~~of the~~ posterior lens capsule.
- Eyes with Anterior Chamber Intraocular Lens (ACIOL), iris or transscleral fixated intraocular lens and ruptured ~~of the~~ posterior lens capsule.

- **SmPC section 4.4**

Patients must be instructed to report any symptoms suggestive of endophthalmitis or any of the above mentioned events without delay e.g. eye pain, blurred vision etc (see section 4.8).

All patients with posterior capsule tear, ~~e.g.~~ such as those with a posterior lens (e.g. due to cataract surgery), and/or those who have an iris opening to the vitreous cavity~~defect~~ (e.g. due to iridectomy) with or without a history of vitrectomy, are at risk of implant migration into the anterior chamber. Implant migration to the anterior chamber may lead to corneal oedema. Persistent severe corneal oedema could progress to the need for corneal transplantation. Other than those patients contraindicated (see section 4.3) where OZURDEX should not be used, OZURDEX should be used with caution and only following a careful risk benefit assessment. These patients should be closely monitored to allow for early diagnosis and management ~~any signs~~ of device~~implant~~ migration.

Use of corticosteroids, including OZURDEX, may ~~produce~~ induce cataracts (including posterior subcapsular cataracts), increased IOP, steroid induced glaucoma and may result in secondary ocular infections.

In the 3 year DME clinical studies, 59% of patients with a phakic study eye treated with OZURDEX underwent cataract surgery in the study eye (see section 4.8).

(…)

The prevalence of conjunctival haemorrhage in patients with non-infectious uveitis of the posterior segment appears to be higher compared with BRVO/CRVO and DME. (…)

As expected with ocular steroid treatment and intravitreal injections, increases in intraocular pressure (IOP) may be seen. The rise in IOP is normally manageable with IOP lowering medication (see section 4.8). Of the patients experiencing an increase of IOP of ≥10 mmHg from baseline, the greatest proportion showed this IOP increase ~~at around~~ between 45 and 60 days following an injection. (…)

Corticosteroids should be used cautiously in patients with a history of *ocular viral (e.g. herpes simplex) infection* and not be used in active ocular herpes simplex.

(…)

A limited number of subjects with Type 1 diabetes were investigated in the Phase 3 studies, and the response to OZURDEX in these subjects was not significantly different to those subjects with Type 2 diabetes.

In RVO, ~~A~~anti-coagulant therapy was used in ~~1.7~~2% of patients receiving OZURDEX; there were no reports of haemorrhagic adverse events in these patients. In DME, anti-coagulant therapy was used in 8% of patients. Among patients who used anti-coagulant therapy, the frequency of haemorrhagic adverse events was similar in the OZURDEX and sham groups (29% vs 32%). Among patients who did not use anti-coagulant therapy, 27% of OZURDEX treated patients reported haemorrhagic adverse events compared to 20% in the sham group. Vitreous haemorrhage was reported in a higher proportion of patients treated with OZURDEX who received anti-coagulant therapy (11%) compared with those not receiving anticoagulant therapy (6%).

Anti-platelet medicinal products, such as clopidogrel, were used at some stage during the clinical studies in ~~over 40%~~up to 56% of patients. ~~In clinical trial patients receiving anti-platelet therapy,~~ For patients using concomitant anti-platelet medication, haemorrhagic adverse events were reported in a slightly higher proportion of patients injected with OZURDEX (up to 2~~7~~9%) compared with the ~~control~~sham group (up to 2~~0~~3%), irrespective of indication or number of

treatments. The most common haemorrhagic adverse ~~reaction~~event reported was conjunctival haemorrhage (up to 24%).

Changes were also made to the PI to bring it in line with the current Agency/QRD template. In line with the SmPC guideline, a single tabulated list of adverse reactions for all indications was included in section 4.8 of the SmPC which was reviewed and accepted by the CHMP. Furthermore, editorial changes as well as amendments to increase the clarify of the safety information were made in several sections of the PI including Annex II.

No user consultation with target patient groups on the package leaflet has been performed. Instead reference to the previous full user testing at the time of the initial marketing authorisation application of Ozurdex as well as the bridging report provided at the time of extension of the indication to non-infectious uveitis. No further testing was considered necessary, which was agreed by the CHMP.

In addition, the list of local representatives in the PL has been revised to amend contact details for the representative of Austria.

3. Benefit-Risk Balance

Benefits

Beneficial effects

The benefits of Ozurdex in the treatment of DME were investigated in 2 multicentre, masked, randomised, controlled phase 3 studies including a total of 1048 patients divided into 3 treatment arms (DEX 700, DEX 350 and Sham). Benefits are summarised for the higher dose of dexamethasone (700 µg) tested in the studies, which is the proposed dose for use in DME.

One of the pivotal studies (study 206207-010) demonstrated a small but statistically significant increase of 2.3 letters in the mean average change in BCVA from baseline (AUC approach) over the 3 year study period for Ozurdex compared to Sham. The other study (206207-011) showed a Sham-correct gain in mean BCVA average change of 0.9 letters, which was not statistically significant. In the pooled analysis, the difference between Ozurdex and Sham was statistically significant with 1.4 letters. Similar results were obtained for the secondary endpoint of mean change in BCVA from baseline.

In both studies, the proportion of Ozurdex subjects who gained at least 15 letters of vision by Year 3 was 22%, which translates into a 9% and 12% increase over Sham in study 206207-010 and 206207-011, respectively. The difference in mean average decrease in macular thickness from baseline to Year 3 between Ozurdex and Sham was 63 µm and 75 µm in Study 206207-010 and -011, respectively.

In both pivotal studies the treatment with dexamethasone had a rapid effect on visual acuity. However, visual acuity was affected by the occurrence of cataract events mainly during the second study year. Post-hoc analyses of the primary endpoint in patients with cataract events and related surgery during the study showed an improved effect after surgery with a mean average BCVA gain of 4.3 letters with Ozurdex treatment compared to 1.7 letters with Sham. The effect size was even greater (5.5 letters difference compared to Sham) in patients who experienced cataract and cataract surgery early on in the study and hence had sufficient time to fully recover.

Subgroup analyses in 275 pseudophakic subjects (pooled analysis), i.e. involving patients whose vision was not biased by the development of cataract, showed that these patients experienced improved outcomes compared to those with a natural lens at baseline both in terms of mean BCVA average gain

(6.5 letters compared to 1.7 letters in the Sham group) and BCVA improvement of ≥15 letters (23.3% versus 10.9% in the Sham group).

Further analyses in patients who had already received DME treatment prior to study start (laser, steroid or anti-VEGF treatment) showed similar results compared to the overall population. This subgroup comprised around three-quarters of subjects, many of whom had received more than one type of treatment previously. Furthermore, the CHMP noted that this population may have had more stubborn disease than treatment naïve patients, hence contributing to the limited treatment benefits observed.

With regards to the tested doses of dexamethasone (350 µg and 700 µg) the efficacy outcomes in both treatment arms were generally comparable. Results related to the responder analyses seemed to be slightly more favourable for the higher dose, with Sham-adjusted differences in the proportion of patients with a gain of ≥15 letters from baseline of 10.2% in patients receiving the 700 µg dose and 6.4% in patient receiving 350 µg dexamethasone.

Uncertainty in the knowledge about the beneficial effects

While one of the two pivotal studies (study 206207-010) achieved statistically significant improvement in the primary endpoint, the other study (206207-011) failed to show superiority of Ozurdex. In this study, the difference in mean BCVA average change from baseline compared to Sham was not significant for either dose of dexamethasone. Furthermore, the clinical relevance of an average increase of 1 to 2 letters over the 3 year study period (1.4 in the pooled analysis compared to Sham) was considered questionable by the CHMP. The CHMP also noted that the sample size calculation was based on an expected 4 letter mean difference between Ozurdex and Sham.

The assessment of the results was furthermore complicated by the high number of discontinuations (more than 50% in the Sham group, mainly due to lack of efficacy), the variability of the effect over the 6-month lifespan of an implant as well as due to the occurrence of cataract in a high percentage of patients, which affected the visual outcome measures (see also discussion below). To address these issues, revised multiple imputation analyses were performed providing a best and worst case estimate of the treatment effect, which ranged from a mean BCVA average gain of 0.5 to 2 letters over the study period, thereby confirming the effect size seen in the primary analysis.

Similar to the primary endpoint, for the main secondary endpoints of mean change in visual acuity at the end of the study, and proportion of patients gaining 15 letters and more, the size of the treatment effect over Sham was limited.

Furthermore, the variability in the effect of Ozurdex over the 6 month treatment window of one implant was seen as a shortcoming in its usefulness in the treatment of visual impairment in DME, as the effect of Ozurdex was largely lost by the 6 month time point after each injection. .Therefore the CHMP recommended that the MAH should conduct a post-approval study to further investigate the optimal posology in terms of the frequency of retreatment.

In both pivotal studies the treatment effect of dexamethasone had a rapid onset, with the effect appearing to wane beyond the second dose. This vision loss has been attributed to the cataract progression in patients with phakic eyes at baseline (see also risk section below). This was partially agreed by the CHMP and supported by the improved outcomes seen in post-hoc analyses for patients after cataract surgery as well as in the subgroup analysis of pseudophakic patients.

A general trend of a greater effect size in study 206207-010 compared with study 206207-011 throughout the different endpoints as well as the overall population and subgroups was seen. The CHMP agreed that at least partially this might have been due to difference in the baseline demographic

and disease characteristics, whereby patients in study 206207-011 may have had more severe diabetic eye disease and less well-controlled diabetes compared to those recruited in study 206207-010. Nevertheless, the differences between the trials make it somewhat questionable as to whether the results can be pooled.

The CHMP furthermore noted that patients discontinuing due to lack of efficacy would be expected to receive escape therapy. Unfortunately, as rescue therapy after discontinuation was not captured in the studies, very little information is available on the outcome of these patients.

Another deficiency of the study design was the lack of an active comparator such as laser.

Finally, with regards to the subgroup analysis in patients with any DME treatment prior to study entry, the MAH suggested that such patients who had persistent oedema despite prior therapy represented a group who may be considered insufficiently responsive to prior therapy. The analysis was therefore proposed to support a restricted indication in DME patients insufficiently responsive to, or unsuitable for non-corticosteroid therapy. Despite the fact that this was a group of which a quarter had previously received an intravitreal steroid injection (triamcinolone) and yet still had DME requiring treatment, the CHMP considered that it would not be unreasonable to propose steroid therapy, since triamcinolone injections are known to be effective for only around 3-4 months. However, the CHMP considered it debatable whether patients in the studies who had previously received any prior treatment for DME accurately represented the proposed restricted target population, since only 10% had previously had an anti-VEGF injection. Yet, this was explained by the fact that such therapies were not licensed when the Ozurdex studies were conducted.

Risks

Unfavourable effects

The risk assessment for Ozurdex in the treatment of DME was mainly based on the pooled analysis of the data of the two pivotal Phase 3 studies. The safety observations from the supportive Phase 2 studies with Ozurdex did not highlight any concerns in addition to what has been seen in the phase 3 trials. The commonest adverse events observed in the Phase 3 studies were expected based on previous knowledge of the effect of intraocular steroids.

Adverse events related to increased intraocular pressure (IOP) were reported in 36% of patients treated with DEX 700 compared to 5% with Sham, and 28% of DEX 700 treated subjects had an IOP increase from baseline of at least 10 mmHg at some point in the trial. A total of 42% of DEX 700 treated subjects required IOP-lowering medication during the study (though 4% were already using medication at baseline). In addition, 7 subjects (1%) required a surgical or laser procedure to control the IOP, including two trabeculectomies. However, IOP increase did not appear to accumulate after repeated treatments and there seemed to be no increase from one year to another.

Increases in IOP may lead to glaucoma if untreated, with progressive and irreversible damage to the retinal nerve fibre layer and a resultant constriction of the visual field. Six (6) patients treated with Ozurdex experienced glaucoma compared to 2 patients in the Sham group and one patient required incisional surgery to manage glaucoma.

Adverse events of cataract occurred in 68% of patients with phakic study eye at baseline that were treated with DEX 700, with 59% of the patients requiring cataract surgery during the study, compared to 7% under Sham. Nearly a quarter of cataracts were reported as being of the subcapsular type. This is not surprising as ocular use of corticosteroids is known to induce cataract formation. Although lens opacities were reported as a baseline finding in the majority of subjects, the degree of opacity was not qualified, but would presumably have been minor in order for patients to qualify for inclusion in the

study. Cataract of some degree is not an unexpected finding in older patients, and diabetes itself is a risk factor for the development of cataract. Although cataract is a manageable and likely occurrence in diabetics, surgery is not without risks, and complications are more common in diabetic patients.

A range of other ocular adverse events were reported, many of which appear to be related specifically to the injection procedure rather than the active substance. Several of these events were known complications of intravitreal injections, and were not reported in a higher than expected frequency in the pivotal DME studies.

Several serious adverse events such as retinal detachment and endophthalmitis were considered treatment-related, but had already been reported either in the context of the clinical development program for the other indications of Ozurdex or post-marketing and were already listed in the SmPC. However, a serious case of necrotising retinitis was reported and this was reflected in SmPC section 4.8.

Finally with regards to the subgroup of patients with prior DME treatment, the CHMP considered that the safety of Ozurdex was not markedly different to that in the overall population. The same applied to pseudophakic patients except for the lack of risk of cataract development.

Uncertainty in the knowledge about the unfavourable effects

There was a concern with the methodology for the measurement of IOP as measurements during the first 30 days after study treatment procedures were conducted by an unblinded investigator. This has the potential to have introduced bias into the IOP results in form of an increased reporting rate in the DEX groups.

Although non-ocular adverse events were not expected with Ozurdex due to the low systemic exposure to dexamethasone, several serious adverse events of infections (cellulitis, pneumonia, gastroenteritis, and urinary tract infection) were reported more frequently in Ozurdex-treated subjects. There remains a degree of uncertainty as to whether infections represent a potential risk of Ozurdex in diabetic patients. Whilst the signal is not currently strong enough to represent an important identified risk or to be mentioned in the SmPC, it was agreed to keep it as an important potential risk in the RMP, and any spontaneous post-marketing reports should be targeted for follow-up.

Benefit-Risk Balance

Importance of favourable and unfavourable effects

Macular oedema represents a leading cause of legal blindness in diabetics, and limited treatment options are available. Once DME has developed, therapeutic interventions aim at halting or slowing the progression of the disease, maintaining and ideally restoring vision.

The effect size of Ozurdex observed in the pivotal phase 3 DME trials in terms of degree of improvement in vision was considered very modest if to be used in the broad DME population, with 1 to 2 letters difference on an ETDRS vision chart compared to Sham. The results for the responder analysis (proportion of patients gaining at least 15 letters) were slightly more relevant, but with 10% difference compared to Sham still represent only a limited benefit. Nevertheless, the results show that at least 10% of the study subjects had a significant improvement in visual acuity of three lines on the vision chart. This suggests that Ozurdex offers a chance of improving vision at least for some patients who have no other treatment options.

Furthermore, the visual outcomes were impacted by the occurrence of cataract events in the majority of patients treated with Ozurdex. Once cataract surgery had been performed and patients had time to

fully recover from surgery, an improved effect on visual acuity was seen. Nevertheless, such analysis discounts the loss of vision experienced during worsening of the cataract and in the early post-operative period, which is misleading, as the majority of patients will experience cataract after treatment with Ozurdex, and will lose vision as a result, albeit temporarily. Furthermore, the lack of consistency of an effect on vision over the lifespan of the implant and the resulting variability in effect size might affect the overall benefit of the treatment

Pseudophakic patients represent a relevant subgroup not at risk of developing steroid induced cataracts (i.e. posterior subcapsular cataract). As could be expected, these patients had improved results compared to the overall study population, gaining 5 letters in visual acuity compared to Sham.

At the same time, the CHMP considered that the risks of treatment were not insignificant. Approximately 40% of Ozurdex-treated patients required medication to lower the IOP, with 1% requiring laser or surgical intervention. Although raised IOP is in itself not detrimental to the vision, if not managed properly it can lead to glaucoma and irreversible blindness. Furthermore, around 60% of the patients with a natural lens and treated with Ozurdex required cataract surgery by the end of the study. During the period of worsening of the cataract, surgery, and post-operative recovery patients experienced loss of vision, and although in most cases vision was recovered after surgery, the surgery itself is not without risk. However, naturally, the risk of steroid-induced cataract is negated in the group of pseudophakic patients.

There were also a range of other ocular adverse reactions that appeared to occur more frequently in patients exposed to Ozurdex, either as a result of the active substance or the injection procedure. Whilst some are not a significant concern, others, such as retinal tear/detachment and endophthalmitis, though known and infrequent, may have a significant detrimental impact on long term vision.

Furthermore, there remained a degree of uncertainty regarding the increased incidence of certain non-ocular adverse events in patients exposed to Ozurdex. Serious adverse events of a range of non-ocular infections were reported more frequently in Ozurdex-exposed subjects. These events were of particular concern in diabetic patients and were considered to require close monitoring.

Benefit-risk balance

The CHMP considered that the benefit-risk balance for Ozurdex in the broad indication of treatment of adult patients with diabetic macular oedema was negative. However, the CHMP was of the opinion that the benefits of Ozurdex in the treatment of adult patients with visual impairment due to diabetic macular oedema who are pseudophakic or who are considered insufficiently responsive to, or unsuitable for non-corticosteroid therapy outweighed its risks and that the benefit-risk balance was favourable in this restricted population.

Discussion on the Benefit-risk balance

The CHMP was of the opinion that the small effect size seen in the pivotal trials, both in terms of visual acuity gain and responders achieving improvements in vision of 15 letters or more, was of questionable clinical relevance for the broad DME population, in particular in light of the variability of the effect over the lifespan of an implant. While it was accepted that the visual study outcomes were affected by the occurrence of cataract in the majority of phakic patients, the loss of vision due to lens opacities and related surgery, even if only temporarily, was considered of relevance. Furthermore, cataract surgery itself is not without risk and long-term intravitreal use of Ozurdex poses additional substantial risks with over a third of Ozurdex treated subjects requiring intervention to manage increased intraocular pressure. There were also a range of other mainly ocular adverse reaction

including serious events such as endophthalmitis and retinal detachment/tear, which add to the overall potential risk of treatment with Ozurdex. Furthermore, uncertainties existed on the reliability of the study results regarding the handling of missing data and the choice of comparator.

In light of the concerns raised by the CHMP, the MAH presented a proposal for a narrower indication with a restricted target population. This proposal included DME patients who already underwent cataract surgery in the affected eye and patients insufficiently responsive to, or unsuitable for non-corticosteroid therapy, for which the MAH claimed an improved benefit-risk balance.

The CHMP agreed that, compared to the overall population, an improved benefit-risk ratio applied to pseudophakic patients as these patients were not at risk of developing steroid-induced cataract and given the improved positive effect on vision weighed against the manageable risk of increased IOP. The CHMP considered that patients with DME were likely to develop cataract at some point during their lifetime requiring lens replacement and therefore this subpopulation was considered to be a reasonable target group. Once scheduled for cataract surgery, Ozurdex could be considered as a future treatment option.

With regard to the proposed restriction to patients unresponsive or unsuitable for non-steroid treatments, the CHMP considered the subgroup analysis in patients receiving any DME treatment prior to study entry. Both the effects and risks in this subgroup were generally similar to the overall study population. However, the CHMP considered that there was an unmet medical need for patients who are not suitable candidates for, or who do not respond adequately to other available DME treatments, including anti-VEGF inhibitors which were the preferred treatment choice at the time of this report. Given the broader anti-inflammatory action of steroids compared with anti-VEGF agents, it was reasonable to assume that steroids would be tried in patients with DME who had not responded to anti-VEGF therapy, or who were unsuitable for monthly anti-VEGF injections, irrespective of lens status. For these patients, the relative risk of cataracts and IOP elevation was considered justifiable compared to the far more serious risk of irreversible vision loss due to persistent DME and considering that both cataract and raised IOP are treatable. Furthermore, the CHMP was of the opinion that there were some benefits in having the choice of a steroid treatment with a shorter duration of effect compared to the longer-acting steroid implant (fluocinolone acetonide) which was available for DME treatment in many EU countries at the time of this report. Such short acting implant would allow physicians to evaluate the safety and efficacy response of patients to steroid treatment and make re-treatment decisions accordingly.

4. Recommendations

Final Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation(s) to the terms of the Marketing Authorisation, concerning the following change(s):

Variation requested		**Type**
C.1.6 a)	Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

Extension of Indication to include in SmPC section 4.1 a new indication for the treatment of adult patients with visual impairment due to diabetic macular oedema who are pseudophakic or who are considered insufficiently responsive to, or unsuitable for non-corticosteroid therapy.

As a consequence, update of section 4.2, 4.3, 4.4, 4.8, 5.1 and 5.2 of the SmPC to provide posology recommendations, update the safety information and provide relevant clinical data on the pharmacodynamic and pharmacokinetic properties. The package leaflet (PL) was updated accordingly. In addition, the HCP leaflet which is provided as tear off section at the end of the PL was reduced to safety information only.

In addition, the MAH took the opportunity to update the list of local representatives for Austria in the Package Leaflet.

Furthermore, the product information (PI) was updated to include information on the reporting of suspected adverse reactions in line with the latest QRD template version 9.0. In addition, editorial changes were made throughout the PI including Annex II. Amendments were also made to increase the clarity of the safety information.

The variation proposed amendments to the Summary of Product Characteristics, Annex II and Package Leaflet.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Extension of Indication to include a new indication for the treatment of adult patients with visual impairment due to diabetic macular oedema who are pseudophakic or who are considered insufficiently responsive to, or unsuitable for non-corticosteroid therapy.

Summary

Please refer to scientific summary.