



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

19 May 2011  
EMA/439447/2011

## ASSESSMENT REPORT

FOR

OZURDEX

International non-proprietary name: dexamethasone

Procedure number: EMEA/H/C/001140/II/0001

Variation Assessment Report as adopted by the CHMP with  
All information of a commercially confidential nature deleted



## Table of contents

<b>1. Executive summary .....</b>	<b>3</b>
1.1. Submission of the dossier.....	3
1.2. Information on Paediatric requirements.....	3
1.3. Marketing Protection.....	3
1.4. Orphan Medicinal Products.....	3
1.5. Scientific Advice.....	3
1.6. Licensing status .....	4
<b>2. Scientific discussion .....</b>	<b>5</b>
2.1. Introduction .....	5
2.2. Quality aspects .....	6
2.3. Non-clinical aspects.....	6
2.4. Clinical aspects .....	6
2.4.1. Introduction .....	6
2.4.2. Pharmacokinetics & Pharmacodynamics .....	6
2.4.3. Clinical efficacy .....	7
2.4.4. Discussion on clinical efficacy .....	19
2.4.5. Clinical safety .....	20
2.4.6. Discussion on clinical safety .....	24
2.4.7. Benefit/Risk balance .....	26
2.5. Pharmacovigilance.....	29
2.5.1. Detailed description of the Pharmacovigilance system.....	29
2.5.2. Risk management plan.....	29
2.6. Product Information.....	32
<b>3. Conclusion .....</b>	<b>33</b>
<b>4. ATTACHMENT.....</b>	<b>34</b>
Assessment report on the novelty of the indication/significant clinical benefit in comparison with existing therapies for Ozurdex 700 micrograms intravitreal implant in applicator.....	34
4.1. Introduction .....	35
4.2. Justification of significant clinical benefit as presented by the MAH .....	40
4.3. CHMP assessment of the MAH's justification of significant clinical benefit.....	42
4.4. CHMP conclusion .....	43
4.5. Outcome.....	43

# **1. Executive summary**

## ***1.1. Submission of the dossier***

With this application for a type II variation the MAH proposed to add the following indication "OZURDEX is indicated for the treatment of adult patients with inflammation of the posterior segment of the eye presenting as non-infectious uveitis" to section 4.1 of the SmPC, with consequential changes to sections 4.2, 4.4, 4.8 and 5.1 of the SmPC.

## ***1.2. Information on Paediatric requirements***

N.A.

## ***1.3. Marketing Protection***

With this variation application the MAH claimed that an additional 1 year of marketing protection should be warranted based on the novelty of the indication/significant clinical benefit in comparison with existing therapies. The CHMP considered that the MAH's justification for one additional year of marketing protection based on the new therapeutic indication for Ozurdex in the treatment of adult patients with inflammation of the posterior segment of the eye presenting as non-infectious uveitis is sufficient and an additional year of marketing protection can be granted.

The full CHMP's assessment on the novelty of the indication/ significant clinical benefit in comparison with existing therapies for Ozurdex 700 micrograms intravitreal implant in applicator is provided in Attachment No. 9 to the CHMP assessment report.

## ***1.4. Orphan Medicinal Products***

On 6 May 2010 the COMP issued a positive opinion on the application for orphan designation for Ozurdex, dexamethasone (intravitreal implant) for the treatment of non-infectious uveitis affecting the posterior segment of the eye (EMA/OD/018/10). The MAH formally requested to be withdrawn from the list of orphan designations based on the fact that it was likely that the indication was going to be filed as a variation to the approved product "Ozurdex" rather than as a new marketing authorisation application.

## ***1.5. Scientific Advice***

The MAH received Scientific Advice from the CHMP in July 2005. The Scientific Advice pertained to the use of the dexamethasone intravitreal implant in an applicator for patients with anterior and intermediate uveitis (EMA/342179/2005). The main points in the Scientific Advice relating to intermediate uveitis were as follow:

- the primary efficacy variable of vitreous haze graded on a standard 5-unit scale (0 to 4+) was the only validated measure to assess disease activity, and that BCVA was an appropriate secondary efficacy variable
- that a comparison to placebo (Sham needle-less DDS applicator without study medication) was acceptable
- that a single injection trial was acceptable to show short-term efficacy of the implant
- that the sample size and 6 month study duration were considered to be sufficient for safety purposes since longer term safety information will be provided from the completed RVO studies and the ongoing, masked, repeat-dose studies in diabetic macular oedema (DME)

The CHMP also:

- confirmed the principle that an application based on 2 single trials, each in a well-defined subpopulation, would be acceptable provided that the results of both trials showed similar effect sizes in the overall population and in both groups of interest
- commented that 6 weeks as an endpoint might be rather long for a placebo group, and therefore a 4-week endpoint was preferred
- outlined clinically relevant target populations as patients with severe non-infectious posterior uveitis (acute or chronic), patients with chronic anterior uveitis resistant to locally applied steroids, and patients with complicated intermediate uveitis

### ***1.6. Licensing status***

Ozurdex was granted positive opinion by the European Medicine Agency (EMA) and approved by the European Commission on 27 July 2010 for the treatment of adults with macular oedema following either BRVO or CRVO; with this application the MAH applied to extend the indications to patients with non-infectious uveitis.

## 2. Scientific discussion

### 2.1. Introduction

This submission is an extension of the current OZURDEX 700 micrograms intravitreal implant in applicator marketing authorisation to include the indication: "*treatment of adult patients with inflammation of the posterior segment of the eye presenting as non-infectious uveitis.*"

#### **Background on the disease:**

Uveitis is a term referring to inflammation affecting structures in the eye including the iris, ciliary body and choroid. The inflammation may affect only one structure or multiple structures. In many cases, both eyes are involved and symptoms may include decreased vision, eye pain, ocular redness, tearing, strabismus and/or leukocoria. Uveitis and complications arising from the disease are the 5th most common cause of visual loss in the developed world, accounting for about 10% of all cases of total blindness. While the cause of the inflammation can sometimes be associated with underlying systemic diseases or reactions to systemic medications, the cause of uveitis is unknown in about 35% to 57% of all cases of uveitis.

The International Uveitis Study Group (IUSG) classified uveitis into 4 major categories based on the anatomic location of the inflammation: anterior (iris and ciliary body), intermediate (peripheral retina and pars plana of the ciliary body), posterior (choroid and retina) and panuveitis. The IUSG anatomic classification scheme was endorsed by the First International Workshop on Standardization of Uveitis Nomenclature (SUN) that was held in 2004 in the USA. In 2008, the IUSG updated this classification system to include aetiological criteria (Deschenes et al, 2008). It includes 3 main categories of uveitis: infectious, noninfectious (including unknown etiology, as well as systemic autoimmune disorders) and masquerade syndromes (neoplastic, drug-induced).

#### Uveitis Affecting the Posterior Segment of the Eye

Inflammation localised to the posterior segment of the eye encompasses the terms intermediate and posterior uveitis described above. The clinical course of posterior uveitis is similar to intermediate uveitis. Uveitis affecting the posterior segment of the eye is not a life threatening disease but is a chronic debilitating condition, with a high risk of permanent visual loss.

Posterior segment uveitis is generally not responsive to topical treatment. Initial management of uveitis posterior to the lens is usually by observation or by periocular and occasionally intraocular glucocorticoid injections. Oral glucocorticoids are frequently recommended for patients with uveitis that is resistant to topical therapy. Other immunomodulatory agents are suggested in patients who have active inflammation that interferes with activities of daily living and have refractory uveitis or drug-related adverse effects from systemic glucocorticoids or persistent requirement for a dose of prednisone greater than 10 mg/day or equivalent.

#### **About the product:**

The Dexamethasone Posterior Segment Drug Delivery System (DEX PS DDS®) contains an extruded dosage form of 700 microgram dexamethasone, in an inactive biodegradable polymer matrix of PLGA.

The DEX PS DDS Applicator System is a sterile, single-use system intended to deliver one biodegradable implant into the vitreous. The DEX PS DDS is injected into the eye via the pars plana using a specially designed applicator. The active ingredient (dexamethasone), is a potent corticosteroid with marked antiinflammatory activity. The mechanism of administration is designed to prolong the duration of the dexamethasone effect in the eye. The dexamethasone is slowly and gradually released

over time to provide a total dose of approximately 700 microgram and the polymer gradually degrades over time so that there is no need to remove the implant.

## **2.2. Quality aspects**

No new quality data were submitted as part of this variation application.

## **2.3. Non-clinical aspects**

No additional non-clinical data have been submitted in support of the new indication. Considering that Ozurdex was initially covered by an orphan designation for uveitis and therefore a limited increase in exposure would not be expected, the CHMP agreed to the MAH's justification that environmental risk assessment (ERA) evaluation does not change for the product in the context of the new indication.

## **2.4. Clinical aspects**

### **2.4.1. Introduction**

The MAH submitted the results of the pivotal phase III study 206207-014 in intermediate or posterior uveitis to support the indication: *"treatment of adult patients with inflammation of the posterior segment of the eye presenting as non-infectious uveitis."*

In addition, data from two supportive clinical studies were provided:

- Phase 2 dose-ranging study with tableted DEX PS DDS in patients with persistent macular oedema associated with diabetic retinopathy, uveitis, retinal vein occlusion or Irvine-Gass syndrome (DC103-06). A subgroup of 14 patients with uveitis was included in this study.
- Phase 3 study with DEX PS DDS applicator system in patients with anterior uveitis (206207-015). This study was terminated due to slow enrolment (only 5 patients).

Due to the small number of patients with uveitis included in the Study DC103-06 (n=14) and the different condition of patients involved in Study 015 (anterior uveitis) neither of the two supportive studies was considered by the CHMP to contribute to the efficacy assessment of the intended indication. Hence, the latter studies are not discussed further in the efficacy part of this report.

The MAH did not perform any systemic PK/PD study in patients because plasma drug concentration of dexamethasone was extremely low following DEX PS DDS 700 microgram administration to the eye. No ocular PK/PD studies in patients were conducted.

### **GCP**

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH 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.

### **2.4.2. Pharmacokinetics & Pharmacodynamics**

No additional PK or PD data have been submitted by the MAH in support of the new indication.

## 2.4.3. Clinical efficacy

### 2.4.3.1. Main study

One main pivotal study supports the efficacy and safety of DEX PS DDS in the treatment of non-infectious inflammation of the posterior segment with intermediate or posterior uveitis: study 206207-014 (Study 014).

It was an 8-week, multicenter, masked, randomized, sham-controlled, parallel-group, safety and efficacy study with an 18-week masked extension. Patients were randomized to receive 700 microgram DEX PS DDS Applicator System (DEX 700), 350 microgram DEX PS DDS Applicator System (DEX 350), or Sham DEX PS DDS Applicator System (needleless applicator, Sham). Patients were stratified at randomization according to their baseline scores for vitreous haze.

Patients underwent the study treatment procedure at the treatment visit. The site (study coordinator or the treating investigator) contacted the patient on day 1 for a post-procedure telephone follow-up. A post-procedure safety visit occurred on day 7; masked outcome assessment visits occurred at weeks 3, 6, 8, 12, 16, 20 and 26.

An overview of the study is provided in the table below.

**Table 2.7.3.2-1 Description of Clinical Efficacy Studies of DEX PS DDS in Uveitis (continued)**

Study ID	Number of Study Centers Location	Study Start Status (Date) Enrollment Total/Goal	Design Control type	Study and Control Drugs Dose, Route and Regimen	Study Objective	# Subjects by Arm Entered/ Completed	Duration	M/F mean age (range) Race	Diagnosis Inclusion Criteria	Primary Endpoint
Module 5.3.5.1 206207-014	16 centers North America 4 centers Latin America 15 centers Europe 5 centers Asia Pacific 6 centers Israel/ South Africa	10 May 2006 completed 28 April 2009 231 planned 229 enrolled	randomized patient and examiner-masked sham control	DEX PS DEX (700 µg dexamethasone) applicator system DEX PS DEX (350 µg dexamethasone) applicator system Sham needleless applicator	evaluate the safety and efficacy in the treatment of non-infectious intermediate or posterior uveitis	DEX 700 77/73 DEX 350 76/73 Sham 76/71	8 weeks with an 18-week masked extension	M 84 (36.7%) F 145 (63.3%) 44.8 years (18 to 32) C 139 (60.7%) B 27 (11.8%) A 45 (19.7%) H 5 (2.2%) O 13 (5.7%)	non-infectious intermediate or posterior uveitis in at least one eye	proportion of patients with vitreous haze score 0 at week 8

M = male, F = female, C = Caucasian, B = black, A = Asian, H = Hispanic, O = other

## Methods

The study was an 8 week multicenter, masked, randomized trial (with an 18-week masked extension) to assess the safety and efficacy of 700 microgram and 350 microgram 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 or posterior uveitis.

Patients were randomized in a 1:1:1 ratio to receive 700 microgram DEX PS DDS Applicator System (DEX 700), 350 microgram DEX PS DDS Applicator System (DEX 350) or Sham DEX PS DDS Applicator System (needleless applicator, Sham). Patients were stratified at randomization according to their baseline scores for vitreous haze into 2 strata: patients with baseline scores of +1.5 or +2 and patients with baseline scores of either +3 or +4. Approximately 231 patients were to be randomized to the 3

treatment groups in order to have 219 patients complete the study at week 8 based on an anticipated dropout rate of 5%.

After the screening visit, the baseline visit occurred within 4 to 14 days. Patients underwent the study treatment procedure at the treatment (day 0) visit. The treatment visit occurred on the same day as the baseline visit or up to 4 days later. A post-procedure safety visit occurred on day 7; masked outcome assessment visits occurred at weeks 3, 6, 8, 12, 16, 20 and 26.

Efficacy variables included vitreous haze, best corrected visual acuity (BCVA), central retinal thickness (optical coherence tomography [OCT] at selected sites only), time to early and late treatment failure and use of escape medications. Safety variables were adverse events, BCVA, IOP, biomicroscopy and ophthalmoscopy.

### ***Study Participants***

The key inclusion criteria were:

- male or female at least 18 years of age;
- vitreous haze (VH)  $\geq +1.5$  at both the screening and baseline visits in the study eye, otherwise media clarity;
- best corrected visual acuity (BCVA) in the study eye of 10 to 75 letters using the Early Treatment of Diabetic Retinopathy Study (ETDRS) method;
- allowable treatments were topical corticosteroids, nonsteroidal anti-inflammatory drugs (NSAIDs), systemic immunosuppression, systemic corticosteroids ( $\leq 20$  mg/day prednisone equivalents), or topical cycloplegia if doses were stable

The key exclusion criteria were:

- uncontrolled systemic disease;
- use of warfarin/heparin/enoxaparin anticoagulant  $\leq 2$  weeks of day 0;
- intraocular pressure (IOP)  $> 21$  mm Hg;
- history of clinically significant IOP elevation in response to corticosteroids, or ocular hypertension/glaucoma;
- use of antiglaucoma medications;
- active ocular infection;
- periocular corticosteroid  $\leq 8$  weeks of day 0 or intravitreal drug injections  $\leq 26$  weeks of day 0 to study eye;
- intravitreal corticosteroid injections except for triamcinolone  $> 26$  weeks prior to Day 0 at doses  $\leq 4$  mg; use of Retisert;
- intraocular surgery or lens in study eye;
- history of pars plana vitrectomy or herpetic infection in study eye;
- BCVA in the non-study eye  $< 34$  letters using the ETDRS method;
- uveitis unresponsive to corticosteroids;
- hypotony

Of note, patients with glaucoma and those with no strict control of ocular hypertension were excluded from participation, as a safety measure. Considering that glaucoma is one of the most important adverse events related to the use of intraocular steroids, this was considered well justified by the CHMP.

### ***Treatments***

Patients received DEX 700, DEX 350, or Sham on the randomisation day 0 visit. The study treatment procedure was performed by the treating investigator in a surgical suite or office setting using a

standard, sterile technique. A combination of topical and subconjunctival anaesthetics was used. Patients randomized to active treatment had the study drug placed into the vitreous through the pars plana using the DEX PS DDS applicator system. Patients randomized to Sham treatment had the needle-less applicator pressed against the conjunctiva.

At the visit preceding the study treatment procedure, the patient was given a bottle of gatifloxacin or ofloxacin ophthalmic solution (where available); otherwise an ophthalmic fluoroquinolone (such as ciprofloxacin) or an ophthalmic aminoglycoside (such as gentamicin or tobramycin) was used. Patients were to administer a drop in the study eye 4 times per day (QID) for 3 days prior to the study treatment procedure, up to QID on the day of the procedure and QID for 3 days post-operatively.

### ***Objectives***

To evaluate the safety and efficacy of the 700 microgram DEX PS DDS Applicator System (700 microgram dexamethasone) and 350 microgram DEX PS DDS Applicator System (350 microgram dexamethasone) compared with Sham DEX PS DDS Applicator System (needleless applicator) in the treatment of non-infectious ocular inflammation of the posterior segment in patients with intermediate or posterior uveitis.

To evaluate the safety and efficacy of the 700 microgram DEX PS DDS Applicator System (700 microgram dexamethasone) compared with the 350 microgram DEX PS DDS Applicator System (350 microgram dexamethasone) in the treatment of non-infectious ocular inflammation of the posterior segment in patients with intermediate or posterior uveitis.

### ***Outcomes/endpoints***

The primary efficacy analysis was the proportion of patients with vitreous haze score of 0 in the ITT population. The primary efficacy assessment was based on ocular inflammation in the study eye as measured by vitreous haze on a standardized 0 to +4 scale (0, +0.5, +1, +1.5, +2, +3, +4).

The primary time point was week 8. In the phase 2 study DC103-06 of patients with persistent macular oedema associated with diabetic retinopathy, uveitis, retinal vein occlusion, and Irvine-Gass syndrome, the greatest gain in visual acuity with DEX was at day 60. Even if a patient was experiencing visual benefit with DEX at day 30, it takes some time for the vitreous cells to clear. Therefore week 8 was selected as the likely time point for maximal clearing of vitreous haze.

#### **Secondary efficacy analyses (performed on the ITT population):**

- time to vitreous haze score 0
- vitreous haze score at least 1-unit improvement from baseline

#### **Other efficacy analyses (performed on the ITT population):**

- the proportion of patients with  $\geq 1$ -unit improvement in vitreous haze
- the proportion of patients with  $\geq 2$ -unit improvement in vitreous haze
- vitreous haze raw score
- the mean change from baseline vitreous haze score
- 1-Unit Deterioration from Baseline in Vitreous Haze Scores
- 2-Unit Deterioration from Baseline in Vitreous Haze Scores
- time to Early or Late Treatment Failure
- use of escape medications

- improvement in BCVA (i.e. the proportion of patients with at least 15 letters improvement from baseline BCVA and the proportion of patients with at least 10 letters improvement from baseline BCVA)
- central macular thickness using OCT
- health outcomes using the National Eye Institute Visual Functioning Questionnaire-25 (NEI-VFQ-25)

The endpoints were in general considered appropriate by the CHMP; improvement in BCVA is a clinical endpoint of major significance to the patient. It is acceptable to demonstrate statistical significance on the primary endpoint, but the results must also be clinically relevant; this prerequisite was met, both the primary endpoint and improvement in BCVA by 15 letters or more were considered clinically relevant.

The main variable of the study initially chosen was the change of vitreous haze score from baseline. During the conduct of the trial it was substituted by a responder rate (the proportion of patients with vitreous haze score of zero) as the main outcome. Several other definitions of responders have been used as secondary endpoints. Complementary information regarding patient's visual acuity, retinal thickness and impact of the change in the quality of life was also assessed through the secondary outcomes. The selected endpoints are validated standard methods for evaluation of uveitis and have been previously used in the clinical development of other medicinal products for the intended indication.

The CHMP did not question the acceptability of VH as cut-off entry criterion for the study and as a primary endpoint, and it was acknowledged that it was in line with the Scientific Advice provided. Nevertheless, it was noted that VH is not necessarily the main criterion guiding therapeutic decisions; it is rather the BCVA and the presence or not of relevant macular oedema, which determine the therapeutic approach.

### ***Sample size***

Based on an anticipated dropout rate of 5%, approximately 231 patients were to be randomised to the 3 treatment groups in a 1:1:1 ratio to have 219 patients complete the study at week 8.

### ***Randomisation***

At the screening visit, each patient who qualified for entry was assigned a study patient number that was used on patient documentation. At randomization on day 0, the site used the IVRS (interactive voice response system) to receive the treatment assignment for each qualified patient.

Patient randomization was stratified according to their baseline vitreous haze scores into 2 groups. Patients with baseline scores of +1.5 or +2 vitreous haze were randomized into one stratum, and patients with baseline scores of either +3 or +4 were randomized into another stratum. Within each stratum, the patient was randomly assigned to 1 of the 3 treatment arms (DEX 700, DEX 350, or Sham) in a 1:1:1 ratio according to the randomization schedule generated by using procedures developed and validated by the MAH.

### ***Blinding (masking)***

Patients remained masked to the study treatment assignment for the duration of the trial.

Study treatment procedures and post procedure safety evaluations (except BCVA) were performed by the treating investigator. The treating investigator had overall responsibility for the safety of the

patient and did not participate in the efficacy procedures. For each patient, the treating investigator was not the same individual as the uveitis specialist assigned as the follow-up investigator.

### ***Statistical methods***

The intent-to-treat (ITT) population consisting of all randomized patients was used for efficacy analyses and data other than safety variables. The per protocol (PP) population consisting of all ITT patients who had no major protocol deviations (determined prior to database lock) was also used for efficacy analyses. The safety population consisting of all randomized and treated patients was used for safety analyses.

The primary efficacy variable was the proportion of patients with vitreous haze score 0. Missing data at weeks 2 through 6, 8, 12, 16, 20, and 26 were imputed using the last observation (scheduled or unscheduled) carried forward (LOCF) method. All available data were used for imputation. For any patients who had received an escape medication, their vitreous haze score was set as missing at visits after the administration of escape medication, and thus imputed by LOCF. The primary analysis was performed using Pearson's chi-square test, with week 8 being the primary time point. A gate-keeping procedure was used to control the overall type I error rate at 5% for the 2 primary between-treatment comparisons (i.e., DEX 700 versus Sham and DEX 350 versus Sham).

The 2 secondary efficacy variables were time to vitreous haze score 0 and at least 1-unit improvement from baseline in vitreous haze score.

All data were summarized with descriptive statistics and/or frequency tables. In general, categorical variables were analysed using Pearson's chi-square test, Fisher's exact test, or the Cochran-Mantel-Haenszel (CMH) method. Continuous variables were analyzed using analysis of variance (ANOVA) for between-group comparisons and paired t-test for within-group analyses of change from baseline. For time to event analyses, treatment group comparisons were analyzed by log-rank test.

The proposed analysis methods were considered acceptable by the CHMP. The method for handling missing data is not conservative. For example, if patients dropped out from the study with a score of 0, they should still be considered as failures, even though the primary analysis would count them as successes. However, as only few patients dropped out, this was not considered to be a concern.

### ***Changes in the Conduct of the Study or Planned Analyses***

Several changes were implemented on the study; the majority of them took place after the study initiation on 10 May 2006 (first patient enrolment).

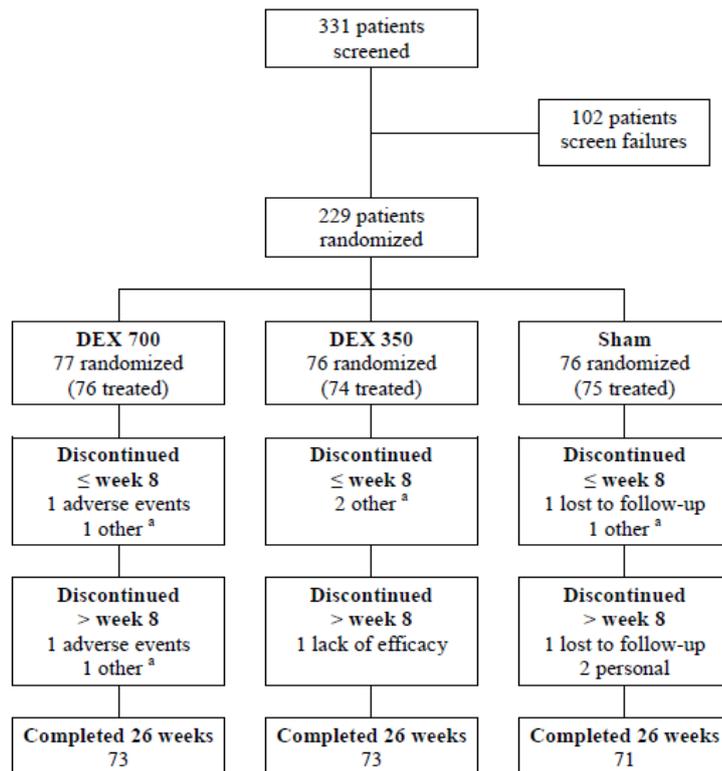
The CHMP considered the following amendments to be the main changes to the protocol:

- a) with respect to the population, posterior uveitis patients were also included and patients of milder affection were allowed.
- b) a secondary measure of efficacy was transformed into the primary measure (and the sample size accordingly increased) and the effect was evaluated later than initially planned
- c) the SAP was modified after study termination

## Results

### Participant flow

Of the 331 patients screened for the study, 102 (30.8%) failed to meet the entry criteria: 21.1% due to inclusion criteria, 6.6% due to exclusion criteria and 4.8% due to Other. A total of 229 patients were randomized and enrolled in the study as shown in the Figure below. Over 97% of patients in each treatment group completed the week 8 visit and nearly 95% of patients completed the 26-week study with the proportion of patients completing the study similar across the treatment groups.



Source: Tables 14.1-1, 14.1-2, and 14.4-1  
a description of "other" reasons for termination in Listing 16.2.1-1

The PP population included 90.4% (207/229) of the ITT population who had no major protocol violations, as determined prior to the 26-week database lock. Twenty-two patients were excluded: 7 patients in the DEX 700 group, 10 patients in the DEX 350 group and 5 patients in the Sham group. Eighteen patients were excluded from the PP population at all visits due to use of prohibited medication. Four patients were randomized but did not receive treatment.

The protocol deviations (a total of 68 patients, including 52 patients receiving prohibited medication) were duly documented and the MAH provided a list of criteria used as a guide in determining the exclusion of patients/ data from the PP analysis.

## Demographics and other Baseline Characteristics

In the ITT population, the mean (range) age was 44.8 (18 to 82) years, 63.3% of patients were female, and 60.7% were Caucasian. The disease diagnosis was intermediate uveitis for 80.8% of patients, and posterior uveitis for 19.2%. There were no statistically significant differences among the treatment groups in the demographic and baseline characteristics in the ITT population, as summarised in the table below:

**Table 10–1 Demographic and Baseline Characteristics (ITT Population)**

Characteristic	DEX 700 N = 77	DEX 350 N = 76	Sham N = 76	P-Value <sup>a</sup>
Age (years)				
mean (range)	44.3 (18 to 75)	45.9 (19 to 82)	44.3 (18 to 82)	0.736
< 45	43 (55.8%)	39 (51.3%)	41 (53.9%)	
45 - 65	28 (36.4%)	32 (42.1%)	27 (35.5%)	
> 65	6 (7.8%)	5 (6.6%)	8 (10.5%)	
Sex				0.639
male	31 (40.3%)	28 (36.8%)	25 (32.9%)	
female	46 (59.7%)	48 (63.2%)	51 (67.1%)	
Race				0.997 <sup>c</sup>
Caucasian	47 (61.0%)	46 (60.5%)	46 (60.5%)	
Black	8 (10.4%)	10 (13.2%)	9 (11.8%)	
Asian	18 (23.4%)	12 (15.8%)	15 (19.7%)	
Hispanic	2 (2.6%)	1 (1.3%)	2 (2.6%)	
Other <sup>b</sup>	2 (2.6%)	7 (9.2%)	4 (5.3%)	
Iris Color				0.597
dark	33 (42.9%)	27 (35.5%)	32 (42.1%)	
light	44 (57.1%)	49 (64.5%)	44 (57.9%)	
Disease Diagnosis				0.448
intermediate uveitis	63 (81.8%)	64 (84.2%)	58 (76.3%)	
posterior uveitis	14 (18.2%)	12 (15.8%)	18 (23.7%)	

Source: Table 14.1-3

a P-value based on 1-way analysis of variance for continuous variables, and Pearson's chi-square or Fisher's exact test for categorical variables

b description of "other" race in Listing 16.2.4-1

c comparison of Caucasian to non-Caucasian

The studied population was considered by the CHMP to be representative of the population suffering from non-infectious posterior segment uveitis.

### Prior Medications and Procedures

Prior to enrolling in study 014, over 40% of patients in each treatment group had received medications for the treatment of ocular inflammation in the study eye.

### Concomitant and Escape Medications

#### Concomitant Medications

Patients were allowed to use the following medications (concomitant medications) under specified conditions:

(1) topical corticosteroid and non-steroidal anti-inflammatory agents if doses were stable for at least 2 weeks prior to screening and remained stable through the treatment on day 0

(2) systemic corticosteroids if doses were 20 mg/day or less for oral prednisone (or equivalent for other corticosteroids), were stable for at least 1 month prior to screening, remained stable through the treatment on day 0, and were expected to remain stable through to week 8

(3) systemic immunosuppressors (eg. cyclosporine and methotrexate) if doses were stable for at least 3 months prior to screening, remained stable through the treatment on day 0, and were expected to remain stable through to week 8

The use of these allowed concomitant medications for uveitis in the study was similar among the 3 treatment groups at each visit. Overall, 75.3% (58/77) of patients in the DEX 700 group, 71.1% (54/76) in the DEX 350 group and 67.1% (51/76) in the Sham group used concomitant medications for uveitis in the study eye during the trial.

### Escape Medications

Escape medications were defined as intravitreal/periorcular injections of corticosteroids in the study eye or systemic medications taken for uveitis or ocular inflammation which were newly started or increased dose from treatment day 0.

Throughout the study, use of escape medications was higher for patients receiving Sham than for those treated with DEX. As shown in the table below, the proportion of patients receiving escape medications from baseline to each visit remained significantly higher in the Sham group compared to DEX 700 (except week 16) and DEX 350 (except week 26).

**Table 6-1 Summary of Escape Medication Use from Baseline to Each Visit (ITT Population, Study 014)**

From Baseline to Visit	DEX 700 N = 77	DEX 350 N = 76	Sham N = 76	P-Value <sup>a</sup>		
				DEX 700 vs Sham	DEX 350 vs Sham	DEX 700 vs DEX 350
Week 3	1.3%	2.6%	14.5%	0.002	0.009	0.620
Week 6	5.2%	3.9%	18.4%	0.011	0.005	>0.999
Week 8	7.8%	5.3%	22.4%	0.012	0.002	0.746
Week 12	14.3%	7.9%	28.9%	0.027	< 0.001	0.209
Week 16	19.5%	13.2%	32.9%	0.059	0.004	0.290
Week 20	19.5%	18.4%	35.5%	0.026	0.018	0.867
Week 26	22.1%	25.0%	38.2%	0.030	0.081	0.670

Source: Day 90 Appendix Table 6-1.3

<sup>a</sup> P-values based on Pearson's chi-square or Fisher's exact test

Overall, use of escape medications was more common in the control group than active treatments: 22.1% (17/77) of patients in the DEX 700 group, 25.0% (19/76) in the DEX 350 group and 38.2% (29/76) in the Sham group.

### **Numbers analysed**

The ITT population included all randomised patients: 77 in the DEX 700 group, 76 in the DEX 350 group and 76 in the Sham group. The PP population included all randomised and treated patients with no major protocol deviations: 70 in the DEX 700 group, 66 in the DEX 350 group, and 71 in the Sham group. The safety population included all randomised patients who received at least one dose of study medication: 76 in the DEX 700 group, 74 in the DEX 350 group and 75 in the Sham group.

The CHMP acknowledged that there were very few missing data, with some occurring between randomisation and treatment. It was acceptable to exclude patients who were randomised but did not receive treatment from the ITT analysis, but the MAH decided to include them, which was acceptable to the CHMP.

With respect to the uveitis subgroups, the study was amended in order for patients with posterior uveitis to be involved. Only 46 out of 229 patients (approximately 20%) suffered from posterior uveitis. Since therapeutic approaches are similar and response to treatment was not expected to be different, this was accepted by the CHMP.

## Outcomes and estimation

### Primary efficacy endpoint (Vitreous Haze Score of Zero)

The proportion of patients whose vitreous haze score decreased to 0 in the study eye at week 8 (primary time point) was statistically significantly higher with DEX 700 compared to Sham ( $p < 0.001$ ). The proportion at week 8 was likewise statistically significantly higher with DEX 350 compared to Sham ( $p < 0.001$ ). Improvements with DEX compared to Sham are clinically relevant, and can be seen from week 6 through the end of the study (table below).

**Table 11–1 Patients with Vitreous Haze Score of Zero (ITT Population)**

Visit	DEX 700 N = 77	DEX 350 N = 76	Sham N = 76	Difference / P-Value <sup>a</sup>		
				DEX 700 vs Sham	DEX 350 vs Sham	DEX 700 vs DEX 350
Week 3	23.4%	14.5%	11.8%	11.5% 0.061	2.6% 0.631	8.9% 0.160
Week 6	42.9%	30.3%	9.2%	33.6% < 0.001	21.1% 0.001	12.6% 0.106
Week 8	46.8%	35.5%	11.8%	34.9% < 0.001	23.7% < 0.001	11.2% 0.158
Week 12	45.5%	42.1%	13.2%	32.3% < 0.001	28.9% < 0.001	3.3% 0.676
Week 16	40.3%	32.9%	21.1%	19.2% 0.010	11.8% 0.100	7.4% 0.344
Week 20	39.0%	42.1%	19.7%	19.2% 0.009	22.4% 0.003	-3.1% 0.692
Week 26	31.2%	28.9%	14.5%	16.7% 0.014	14.5% 0.030	2.2% 0.764

Source: [Table 14.2-1](#)

Note missing values imputed by last observation carried forward at the follow-up visits

<sup>a</sup> P-values based on Pearson's chi-square or Fisher's exact test

Response rates were numerically superior with the 700 microgram dose compared to 350 microgram at each visit (except week 20). At the end of study (week 26), the difference between DEX 700 and Sham was 16.7% ( $p = 0.014$ ) compared to a 14.5% difference between DEX 350 and Sham ( $p = 0.030$ ).

Similar results were observed in the per protocol population.

The CHMP acknowledged that eight weeks after being treated more subjects receiving dexamethasone (700 or 350 microgram) than those treated with sham achieved complete vitreal transparency, i.e. VH scoring of 0 (46% vs. 35.5% vs. 11.8%). This effect was already seen as early as by week 3 and remained stable during the remainder of the study (31.2% vs. 28.9% vs. 14.4% at Week 26).

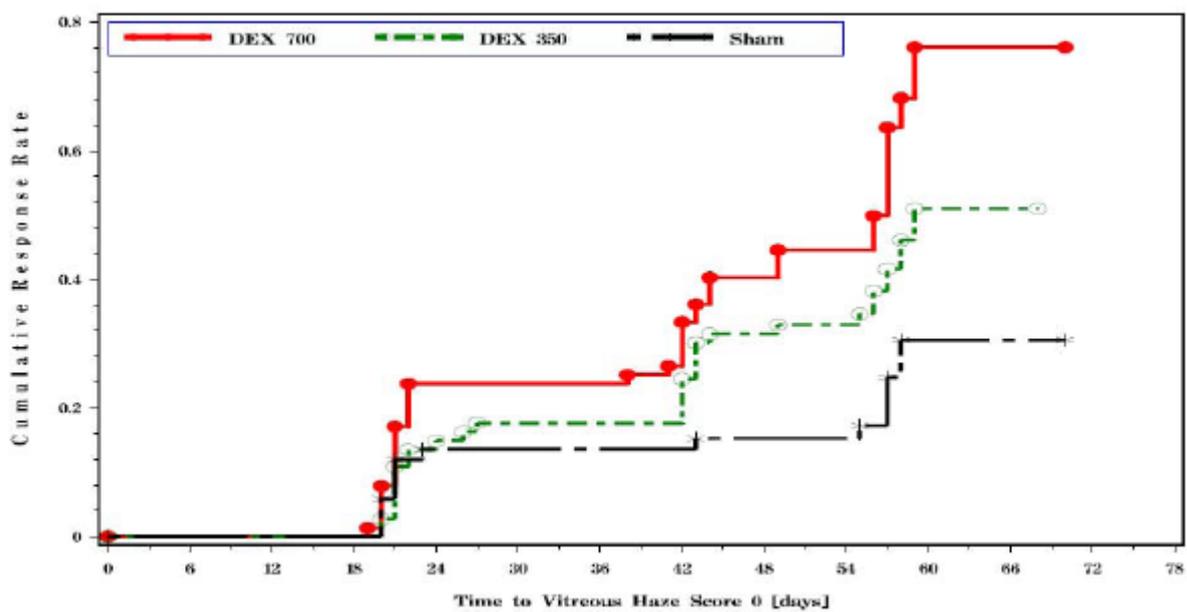
Although a numerically greater proportion of responders was observed with the higher dose, no significant differences were observed between the two dexamethasone doses.

### Secondary Endpoints

#### Time to Vitreous Haze Score of Zero

As a secondary efficacy variable, the time to vitreous haze score of 0 was calculated from day 0 to the first occurrence of vitreous haze score 0 using the 3 common scheduled visits of weeks 3, 6 and 8 or unscheduled or early exit visits occurring before week 8. For patients who did not achieve a score of 0, the time to event was censored at the last exam performed among these visits. Patients receiving DEX demonstrated an earlier onset and greater response as shown in the Kaplan-Meier plot below:

**Figure 11-1 Time to Vitreous Haze Score of 0 up to Week 8 (ITT Population)**



Overall, cumulative response rate curves were significantly different in the DEX 700 group compared to the Sham group ( $p < 0.001$ ) and in the DEX 350 group compared to the Sham group ( $p = 0.026$ ). Cumulative response rates were consistently higher following DEX treatment compared to Sham, with separation of the curves from around week 3 and no crossover during the initial 8 weeks of the study.

The results provided by the MAH on the PP population showed to be consistent with those obtained in the ITT population.

At Least 1-Unit Improvement in Vitreous Haze Score

**Table 11–2 Patients with at Least 1-Unit Improvement from Baseline Vitreous Haze Score (ITT Population)**

Visit	DEX 700 N = 77	DEX 350 N = 76	Sham N = 76	Difference / P-Value <sup>a</sup>		
				DEX 700 vs Sham	DEX 350 vs Sham	DEX 700 vs DEX 350
Week 3	70.1%	75.0%	36.8%	33.3% < 0.001	38.2% < 0.001	-4.9% 0.500
Week 6	90.9%	89.5%	46.1%	44.9% < 0.001	43.4% < 0.001	1.4% 0.765
Week 8	94.8%	86.8%	44.7%	50.1% < 0.001	42.1% < 0.001	8.0% 0.088
Week 12	90.9%	81.6%	52.6%	38.3% < 0.001	28.9% < 0.001	9.3% 0.094
Week 16	87.0%	80.3%	53.9%	33.1% < 0.001	26.3% < 0.001	6.7% 0.259
Week 20	85.7%	80.3%	51.3%	34.4% < 0.001	28.9% < 0.001	5.5% 0.369
Week 26	81.8%	71.1%	51.3%	30.5% < 0.001	19.7% 0.013	10.8% 0.117

Source: [Table 14.2-3](#)

Note missing values imputed by last observation carried forward at the follow-up visits

<sup>a</sup> P-values based on Pearson's chi-square or Fisher's exact test

The effect primarily observed on vitreous haze was considered by the CHMP to be consistently shown in the secondary parameters. In general, both dexamethasone groups were significantly superior to sham treatment. When active groups were compared, the 700 microgram dose was numerically superior to the 350 microgram dose.

The results provided by the MAH on the PP population showed to be consistent with those obtained in the ITT population.

Improvement in BCVA

At each visit, the proportion of patients with at least 15 letters improvement from baseline BCVA was significantly higher with DEX 700 compared to Sham ( $p < 0.001$ ), and with DEX 350 compared to Sham ( $p \leq 0.027$ ).

**Table 11-4 Patients with at Least 15 Letters Improvement from Baseline BCVA (ITT Population)**

Visit	DEX 700 N = 77	DEX 350 N = 76	Sham N = 76	Difference / P-Value <sup>a</sup>		
				DEX 700 vs Sham	DEX 350 vs Sham	DEX 700 vs DEX 350
Week 3	32.5%	25.0%	3.9%	28.5% < 0.001	21.1% < 0.001	7.5% 0.308
Week 6	41.6%	32.9%	7.9%	33.7% < 0.001	25.0% < 0.001	8.7% 0.268
Week 8	42.9%	39.5%	6.6%	36.3% < 0.001	32.9% < 0.001	3.4% 0.671
Week 12	41.6%	39.5%	13.2%	28.4% < 0.001	26.3% < 0.001	2.1% 0.793
Week 16	39.0%	30.3%	13.2%	25.8% < 0.001	17.1% 0.011	8.7% 0.258
Week 20	40.3%	38.2%	13.2%	27.1% < 0.001	25.0% < 0.001	2.1% 0.790
Week 26	37.7%	27.6%	13.2%	24.5% < 0.001	14.5% 0.027	10.0% 0.186

Source: [Table 14.2-10.1](#)

Note missing values imputed by last observation carried forward at the follow-up visits

<sup>a</sup> P-values based on Pearson's chi-square or Fisher's exact test

The CHMP considered that visual acuity is one of the most relevant outcomes in uveitis. Patients with a wide range of impairment were allowed to enter the study (BCVA from 10 to 75 letters), although also patients with higher values (up to 89) were finally recruited. This fact suggested that the indication of intravitreal therapy in a proportion of patients included in the pivotal study may be questionable. However, the data strongly supported a positive effect of Ozurdex in a relevant clinical endpoint, as BCVA is.

#### Central Macular Thickness Using OCT

Central macular thickness using OCT was assessed at selected study sites. At baseline, the mean thickness was 344.0 microns in the DEX 700 group, 338.9 microns in the DEX 350 group, and 324.6 microns in the Sham group. At week 8, there was a significantly greater mean decrease with DEX 700 (-99.4 microns) compared to Sham (-12.4 microns),  $p=0.004$ . Likewise, there was a significantly greater mean decrease with DEX 350 (-91.0 microns) compared to Sham,  $p=0.007$ . At week 26, there were no statistically significant between-group differences.

The central macular thickness changes as measured by OCT were considered by the CHMP to be fully consistent with BCVA findings.

#### Other secondary endpoints

Results were also statistically significant in favour of DEX 700 for the secondary endpoints: proportion of patients with  $\geq 2$ -unit improvement in vitreous haze, mean vitreous haze raw score, mean change from baseline vitreous haze score.

#### **2.4.4. Discussion on clinical efficacy**

The body of evidence supporting the efficacy of Ozurdex in the treatment of non-infectious uveitis is based on a single pivotal study, which was modified during its conduct. The MAH provided a detailed background and chronology of the amendments made to the pivotal study. Considering that the majority of patients (87%) were recruited only after implementation of the most significant modifications, the CHMP agreed that it was unlikely that the changes could have a relevant impact on the study results. In conclusion, although initially raised as an issue, a GCP inspection was not finally considered necessary by the CHMP.

The results of the phase III study demonstrated that the 700 microgram implant was efficacious in the treatment of uveitis of the posterior segment of the eye. Both the 700 microgram and 350 microgram implant groups were statistically significantly superior to the sham group in the ITT and PP populations for the primary and secondary efficacy endpoints. The results for the 700 microgram group were numerically superior to the 350 microgram group on most endpoints, but this comparison was not statistically significant.

The pivotal study included patients suffering from non-infectious inflammation of the posterior segment with intermediate or posterior uveitis in at least one eye. Patients with intermediate uveitis were selected initially. The MAH subsequently expanded the O14 study population to include posterior uveitis, and focused on non-infectious uveitis affecting the posterior segment of the eye. It was noted that the majority of patients included in the study (81%) were diagnosed with intermediate uveitis. Nevertheless, the CHMP agreed that, even though the study was not powered to detect differences between the intermediate and posterior forms of the disease, the results indicated no differences in the efficacy or safety profiles in these subgroups. Both terms "intermediate" and "posterior" refer to ocular structures posterior to the lens and dexamethasone released from the vitreous is equally available to the structures. Furthermore, although the aetiologies may differ, the inflammatory mechanisms in both conditions are the same. Taken together, the proposed indication "inflammation of the posterior segment of the eye" was considered acceptable by the CHMP.

Ozurdex can be regarded as an invasive therapy with the potential risks associated to the intravitreal administration of the drug, in addition to the safety issues related to local corticosteroid action. In this regard, the MAH's approach to include a wide range of patients with VH scoring ranging from 1.5 to 4 and BCVA from 10 to 75 was questioned. The MAH argued that patients with any inflammation posterior to the lens are candidates for this treatment, since systemic steroid, immunosuppressive drugs or peri-ocular injections, which are currently used in clinical practice, do not provide optimal results and can also be considered aggressive therapeutic approaches. The CHMP agreed that an effect of the proposed 700 microgram dose was observed independently of the severity of the disease and, considering the context of current clinical practice, accepted the appropriateness of the invasive nature of the therapeutic approach (intravitreal administration) in the target patient population.

The CHMP considered that an effect on all relevant parameters assessed, and most particularly VH, BCVA and OCT was observed. The results were expectable, since treatment with Ozurdex (dexamethasone) constitutes administration of standard of care, given in a depot intravitreal formulation. In this regard, efficacy results were considered as clinically relevant and not questionable.

The CHMP noted that according to the data in severe patients and the known course of the disease in many instances, repeated use of Ozurdex would be reasonably expected in severe cases of uveitis. It was observed that efficacy appears to diminish around 6 months and therefore, patients may need re-implantation. In terms of efficacy, as Ozurdex is a corticosteroid treatment, it is expected that the efficacy observed with a second implant would be similar as the one observed with the first implant. Although data on re-implantation are not available for Ozurdex in uveitis patients, from the RVO

studies where patients entered a second open label extension after 6 months, patients achieved a similar treatment benefit to that of the first. Given that in both conditions the inflammatory process has a common mechanism, a second injection in uveitis patients is expected to have a similar effect to the one in RVO patients. Furthermore, repeated intravitreal injections of triamcinolone for the treatment of uveitis are well documented in the literature.

The MAH proposed to modify section 4.2 of the SmPC as follows:

#### Current SmPC

There is only very limited information on repeat dosing intervals less than 6 months (see section 5.1). There is currently no experience of repeat administrations beyond 2 implants in Retinal Vein Occlusion.

#### Proposed SmPC

There is only very limited information on repeat dosing intervals less than 6 months (see section 5.1). There is currently no experience of repeat administrations **in posterior segment non-infectious uveitis or** beyond 2 implants in Retinal Vein Occlusion.

This proposal for the SmPC was considered acceptable by the CHMP.

The safety aspects of redosing of Ozurdex are discussed separately in section 4.4.6 and in terms of benefit/ risk in section 4.4.7.

The CHMP discussed the most suitable dose in less severely affected patients, but who would be nonetheless candidates for intravitreal treatment, and asked for a justification of the 700 microgram dose. The MAH concluded that both doses were shown to be safe and effective in patients with baseline VH scores of +1.5 or 2; however, the response to the 700 microgram dose was numerically superior in efficacy across a broad range of endpoints and at almost all timepoints and had an earlier onset and longer duration of action. In this context, the MAH chose to apply only for the higher dose. The CHMP considered that the risk benefit balance was sufficiently substantiated with the current data and that it is positive for the 700 microgram dose in the proposed indication.

The safety aspects of the lower dose of Ozurdex are discussed separately in section 4.4.6 and in terms of benefit/ risk in section 4.4.7.

The use of concomitant and rescue medication during the trial was sufficiently justified by the MAH. More than 70% of patients included in the study were on treatment for uveitis at recruitment and, according to the data provided, the treatment was not modified during the study, which was considered reassuring from the efficacy point of view. Several patients required additional medication as rescue therapy, more patients on sham (38%) than on Ozurdex arms (700 microgram dose – 22%; 350 microgram dose – 25%). The CHMP considered that this data suggested there may be a need for treating some patients again at the end of the treatment period. The SmPC (section 4.2) provides guidance to the health-care professionals (qualified ophthalmologists experienced in intravitreal injections) on repeat administrations according to the response exhibited. Nevertheless, as mentioned above, the CHMP considered that the text in section 4.2 of the SmPC needs to clearly state that currently there is no information on repeat administration in patients with uveitis.

### **2.4.5. Clinical safety**

In this section, only new information from the study in patients with uveitis is discussed.

## Patient exposure

The 77 patients randomised to the DEX 700 group were to receive dexamethasone 700 microgram; 1 patient was randomized but not treated. The 76 patients randomized to the DEX 350 group were to receive dexamethasone 350 microgram; 2 patients were randomized but not treated. The 76 patients randomized to the Sham group were to receive no active treatment; 1 patient was randomised but not treated. The safety analyses are based on a total of 225 patients who received treatment of the 229 patients randomized.

Exposure was similar across the 3 treatment groups. The mean (range) duration was 181.3 (49 to 225) days for patients in the DEX 700 group, 183.1 (140 to 216) days in the DEX 350 group, and 181.0 (22 to 262) days in the Sham group.

## Adverse events

Commonly reported adverse events (greater than 2%) are presented in the tables below:

**Table 2.7.4.2–14 Common Adverse Events Reported by Greater Than 2% of Patients in Any Treatment Group (Study 014)**

System Organ Class Preferred Term <sup>a</sup>	DEX 700 N = 76	DEX 350 N = 74	Sham N = 75
<b>Investigations (includes both study eye and non-study eye)</b>			
intraocular pressure increased	19 (25.0%) <sup>c</sup>	17 (23.0%) <sup>c</sup>	5 (6.7%)
<b>Eye Disorders (includes both study eye and non-study eye)</b>			
conjunctival haemorrhage	23 (30.3%)	13 (17.6%)	16 (21.3%)
eye pain	11 (14.5%)	8 (10.8%)	10 (13.3%)
iridocyclitis	11 (14.5%) <sup>d</sup>	2 (2.7%)	5 (6.7%)
uveitis	10 (13.2%)	7 (9.5%)	10 (13.3%)
ocular discomfort	10 (13.2%)	3 (4.1%)	6 (8.0%)
cataract	9 (11.8%)	6 (8.1%)	7 (9.3%)
myodesopsia	7 (9.2%)	5 (6.8%)	5 (6.7%)
ocular hypertension	6 (7.9%) <sup>b</sup>	7 (9.5%) <sup>c</sup>	0 (0.0%)
conjunctival hyperaemia	5 (6.6%)	7 (9.5%)	7 (9.3%)
vision blurred	5 (6.6%)	4 (5.4%)	3 (4.0%)
eye irritation	4 (5.3%)	2 (2.7%)	3 (4.0%)
intermediate uveitis	4 (5.3%)	0 (0.0%)	1 (1.3%)
visual acuity reduced	3 (3.9%)	7 (9.5%)	6 (8.0%)
macular oedema	3 (3.9%)	4 (5.4%)	6 (8.0%)
eye pruritus	3 (3.9%)	3 (4.1%)	5 (6.7%)
conjunctival oedema	3 (3.9%)	3 (4.1%)	3 (4.0%)
dry eye	3 (3.9%)	2 (2.7%)	1 (1.3%)
vitreous opacities	3 (3.9%)	2 (2.7%)	1 (1.3%)
blepharitis	3 (3.9%)	0 (0.0%)	0 (0.0%)
cataract subcapsular	2 (2.6%)	5 (6.8%)	4 (5.3%)
anterior chamber cell	2 (2.6%)	2 (2.7%)	1 (1.3%)
photopsia	2 (2.6%)	2 (2.7%)	1 (1.3%)
iritis	2 (2.6%)	2 (2.7%)	0 (0.0%)
maculopathy	2 (2.6%)	2 (2.7%)	0 (0.0%)
photophobia	2 (2.6%)	1 (1.4%)	1 (1.3%)
scleral hyperaemia	2 (2.6%)	1 (1.4%)	1 (1.3%)
visual impairment	2 (2.6%)	1 (1.4%)	1 (1.3%)
abnormal sensation in eye	2 (2.6%)	1 (1.4%)	0 (0.0%)
eyelids pruritus	2 (2.6%)	1 (1.4%)	0 (0.0%)
retinal detachment	2 (2.6%)	0 (0.0%)	2 (2.7%)
conjunctivitis	1 (1.3%)	3 (4.1%)	4 (5.3%)
eyelid oedema	1 (1.3%)	3 (4.1%)	3 (4.0%)
choroiditis	1 (1.3%)	2 (2.7%)	2 (2.7%)
hypotony of eye	1 (1.3%)	2 (2.7%)	1 (1.3%)

System Organ Class Preferred Term <sup>a</sup>	DEX 700 N = 76	DEX 350 N = 74	Sham N = 75
conjunctivitis allergic	1 (1.3%)	2 (2.7%)	0 (0.0%)
lacrimation increased	1 (1.3%)	2 (2.7%)	0 (0.0%)
eye swelling	1 (1.3%)	1 (1.4%)	4 (5.3%)
anterior chamber flare	1 (1.3%)	1 (1.4%)	2 (2.7%)
erythema of eyelid	1 (1.3%)	0 (0.0%)	2 (2.7%)
vitreous detachment <sup>e</sup>	0 (0.0%)	3 (4.1%)	0 (0.0%)
foreign sensation in eye	0 (0.0%)	2 (2.7%)	1 (1.3%)
glaucoma	0 (0.0%)	0 (0.0%)	2 (2.7%)
<b>Nervous System Disorders</b>			
headache	5 (6.6%)	6 (8.1%)	5 (6.7%)
migraine	2 (2.6%)	1 (1.4%)	0 (0.0%)
<b>Infections and Infestations</b>			
sinusitis	3 (3.9%)	0 (0.0%)	1 (1.3%)
nasopharyngitis	2 (2.6%)	3 (4.1%)	1 (1.3%)
urinary tract infection	2 (2.6%)	1 (1.4%)	1 (1.3%)
pelvic inflammatory disease <sup>f</sup>	1 (2.2%)	0 (0.0%)	0 (0.0%)
upper respiratory tract infection	1 (1.3%)	2 (2.7%)	1 (1.3%)
<b>Vascular Disorders</b>			
hypertension	2 (2.6%)	0 (0.0%)	3 (4.0%)
<b>Psychiatric Disorders</b>			
depression	1 (1.3%)	0 (0.0%)	2 (2.7%)
insomnia	0 (0.0%)	0 (0.0%)	2 (2.7%)
<b>Reproductive System and Breast Disorders</b>			
dysmenorrhoea <sup>f</sup>	0 (0.0%)	1 (2.1%)	0 (0.0%)
<b>Gastrointestinal Disorders</b>			
vomiting	1 (1.3%)	0 (0.0%)	2 (2.7%)
nausea	0 (0.0%)	2 (2.7%)	4 (5.3%)
<b>Musculoskeletal and Connective Tissue Disorders</b>			
back pain	0 (0.0%)	2 (2.7%)	1 (1.3%)
pain in extremity	0 (0.0%)	2 (2.7%)	0 (0.0%)
arthralgia	0 (0.0%)	1 (1.4%)	2 (2.7%)
<b>Respiratory, Thoracic and Mediastinal Disorders</b>			
cough	0 (0.0%)	2 (2.7%)	1 (1.3%)
<b>General Disorders and Administration Site Conditions</b>			
fatigue	0 (0.0%)	0 (0.0%)	2 (2.7%)
<b>Skin and Subcutaneous Tissue Disorders</b>			
rash	0 (0.0%)	0 (0.0%)	2 (2.7%)

Source: [Module 5.3.5.1 Report 206207-014, Tables 14.3-3 and 14.3-4](#)

Overall, the incidence of adverse events was significantly higher in the DEX groups compared to Sham. Ocular adverse events were also more commonly reported with DEX 700 and DEX 350 than with Sham.

The most frequently reported ocular adverse events were IOP increased, conjunctival haemorrhage, eye pain, iridocyclitis, uveitis, ocular discomfort and cataract. With the exception of eye pain and uveitis, all adverse events were more commonly reported in DEX700 as compared to sham. Although these differences were not significant for any of the adverse events when a formal comparison was made, this trend was consistent for most events.

The incidence of non-ocular systemic adverse events was low and no specific pattern indicating safety risks with the active treatment was revealed.

## Treatment-Related Ocular Adverse Events in the Study Eye

The incidence of treatment-related ocular adverse events in the study eye was significantly higher in the DEX 700 group (59.2%) and DEX 350 group (45.9%) compared to Sham (28.0%),  $p \leq 0.035$ . There was no significant difference between the 700 microgram and 350 microgram doses of DEX. No treatment-related ocular adverse events were reported in the non-study eye. The most frequently reported (> 2% in any treatment group) treatment related ocular events in the study eye are summarised in the following table.

**Table 12-3 Treatment-Related Ocular Adverse Events in the Study Eye Reported by Greater Than 2% of Patients in Any Treatment Group (Safety Population)**

System Organ Class Preferred Term <sup>a</sup>	DEX 700 N = 76	DEX 350 N = 74	Sham N = 75
<b>Investigations (study eye)</b>			
intraocular pressure increased	17 (22.4%) <sup>d</sup>	16 (21.6%) <sup>d</sup>	3 (4.0%)
<b>Eye Disorders (study eye)</b>			
conjunctival haemorrhage	19 (25.0%)	10 (13.5%)	10 (13.3%)
ocular discomfort	9 (11.8%) <sup>e</sup>	1 (1.4%)	3 (4.0%)
cataract	8 (10.5%)	5 (6.8%)	2 (2.7%)
ocular hypertension	5 (6.6%)	5 (6.8%) <sup>c</sup>	0 (0.0%)
eye pain	4 (5.3%)	6 (8.1%)	5 (6.7%)
conjunctival hyperaemia	3 (3.9%)	5 (6.8%)	6 (8.0%)
conjunctival oedema	3 (3.9%)	3 (4.1%)	2 (2.7%)
cataract subcapsular	2 (2.6%)	2 (2.7%)	2 (2.7%)
myodesopsia	2 (2.6%)	1 (1.4%)	0 (0.0%)
floaters <sup>b</sup>	2 (2.6%)	1 (1.4%)	0 (0.0%)
retinal detachment	2 (2.6%)	0 (0.0%)	1 (1.3%)
eyelid oedema	1 (1.3%)	1 (1.4%)	3 (4.0%)
vitreous detachment	0 (0.0%)	2 (2.7%)	0 (0.0%)
eye swelling <sup>f</sup>	0 (0.0%)	0 (0.0%)	4 (5.3%)
erythema of eyelid	0 (0.0%)	0 (0.0%)	2 (2.7%)

Source: Table 14.3-14

a System organ class and preferred terms from MedDRA, version 11.1

b Investigator terms for treatment-related events of myodesopsia were floater, floater in visual field, and floater in vision (Listing 16.2.7-1).

c incidence significantly greater with DEX compared to Sham,  $p \leq 0.05$

d incidence significantly greater with DEX compared to Sham,  $p \leq 0.001$

e incidence significantly greater with DEX 700 compared to DEX 350,  $p = 0.018$

f among-group p-value,  $p = 0.023$

Treatment-related ocular adverse events reported in patients with uveitis were qualitatively similar to those reported in patients with macular oedema following a RVO (as already included in the product information for Ozurdex). Quantitatively, the incidence of treatment-related ocular adverse events for DEX700 are similar in both indications with the following exceptions: conjunctival haemorrhage (25% uveitis vs. 14.7% macular oedema RVO) and cataract (10.5% uveitis vs. 2.1% macular oedema) that occurred with higher incidence in patients with uveitis than in macular oedema.

## Serious adverse events

In the study eye, there were 4 retinal detachments (2 DEX 700 and 2 Sham), 2 cataracts (1 DEX 350 and 1 Sham), 1 necrotizing retinitis (DEX 350) in a patient who was HIV positive, and 1 endophthalmitis (DEX 700) with negative vitreous tap.

**Table 12–4 Patients with Serious Adverse Events (Safety Population)**

Patient	Serious Adverse Event Preferred (Verbatim) Term <sup>a</sup>	Maximum Severity	Treatment Related	Onset Day
<b>DEX 700</b>				
3380-50501	cerebrovascular accident	moderate	no	131
4369-55206	pelvic inflammatory disease	moderate	no	94
5028-60957	retinal detachment in study eye	moderate	yes, applicator/ insertion	50
5282-54303	retinal detachment in study eye	severe	yes, applicator/ insertion	39
6399-56504	cerebellar infarction	moderate	no	110
6405-56609	endophthalmitis in study eye	severe	yes, study drug	81
7410-58613	uveitis (worsening uveitis left eye) in study eye	severe	no	46
<b>DEX 350</b>				
2779-57907	cataract (OD) in study eye	moderate	yes, applicator/ insertion	134
3054-50302	pancreatic carcinoma	severe	no	124
	small bowel obstruction	severe	no	124
5028-60910	ketoacidosis	severe	no	28
5282-54312	pulmonary embolism	moderate	no	88
7410-58605	necrotizing retinitis in study eye	severe	no	85
	HIV test positive	severe	no	86
8295-55608	pupillary disorder (pupillary block) in study eye	severe	no	165
<b>Sham</b>				
4446-51107	retinal detachment in study eye	severe	no	87
5028-60915	retinal detachment in study eye	severe	yes, applicator/ insertion	58
	retinal detachment in study eye	severe	yes, applicator/ insertion	98
	cataract in study eye	severe	yes, study drug	85
5028-60937	pyelonephritis	severe	no	20
5036-52102	ankylosing spondylitis	severe	no	63
6409-56406	hypotony of eye in non-study eye	severe	no	108

Source: Listings 14.3.2 and 16.2.7-3

<sup>a</sup> Preferred terms from MedDRA, version 11.1

## Discontinuation due to adverse events

Three patients in the DEX 700 group discontinued the study due to adverse events (retinal detachment, cerebellar infarction, vitreous opacities), and none in the DEX 350 or Sham groups.

## Post marketing experience

Case reports for Ozurdex in the MAH’s postmarketing database were recorded from 17 June 2009 (IBD; approval by the US FDA). Of note, review of the post-marketing experience revealed there were six cases reported as endophthalmitis, four of which were very well defined and all of which occurred within a short time frame since the Ozurdex implantation. Where information was available, resolution was complete.

### 2.4.6. Discussion on clinical safety

The integrated safety database of study 014 formed the basis for the assessment of the safety of dexamethasone implant in the treatment of the posterior segment uveitis. Safety data from the retinal vein occlusion studies were also presented by the MAH. The latter studies included a very different population in demographics, disease and co-morbidity characteristics as well as in the concomitant

medications used. Thus, the CHMP assessment of the safety data relies on the pivotal phase III trial (Study 014) and data from the macular oedema studies were considered supportive.

A total of 153 patients were treated with dexamethasone implant for intermediate and posterior uveitis and followed-up for 6 months. The studied population was considered representative of the population suffering from non-infectious posterior segment uveitis.

The most frequently reported ocular adverse events were IOP increased, conjunctival haemorrhage, eye pain, iridocyclitis, uveitis, ocular discomfort and cataract. With the exception of eye pain and uveitis, all adverse events were more commonly reported in DEX 700 as compared to sham. In general, comparing the two tested doses, DEX 350 showed a slightly more favourable safety profile, with a lower incidence of the most frequently reported adverse events, than the high dose (DEX 700). On the other hand, a lower incidence of visual acuity reduced and macular oedema AEs, common complications of uveitis, were seen in DEX 700 compared to DEX 350 and Sham.

The overall incidence and profile of treatment related ocular adverse events for DEX 700 were similar in both indications with the following exceptions: conjunctival haemorrhage (25% uveitis vs. 14.7% macular oedema RVO) and cataract (10.5% uveitis vs. 2.1% macular oedema RVO) that appeared with higher incidence in patients with uveitis than in macular oedema. The prevalence of conjunctival haemorrhage was unexpectedly high in the group of patients with uveitis treated with DEX 700. The MAH argued that topical corticosteroids, NSAIDs and systemic corticosteroid allowed during the therapy, together with the intravitreal injection procedure itself, could have increased the incidence of conjunctival haemorrhage. This was considered acceptable by the CHMP. Therefore, the following text was added in the SmPC in Section 4.4: *“The prevalence of conjunctival haemorrhage in patients with non-infectious uveitis of the posterior segment appears to be higher compared with BRVO/CRVO. This could be attributable to the intravitreal injection procedure or to concomitant use of topical and/or systemic corticosteroid or Non-steroidal anti-inflammatory medications. No treatment is required since spontaneous resolution occurs.”*

In the case of cataracts, several factors were considered as contributing to this higher incidence, i.e. the disease itself, previous and concomitant exposure to systemic/local CS. Despite not being unexpected, this high increment in the incidence of cataracts was a matter of concern, particularly in the younger population (< 45 years) for whom the need for additional doses is foreseen. As this issue was considered a key aspect for prescribers when considering this treatment option for a given patient, the CHMP requested that an adequate warning should be reflected in the SPC. Thus, the following text was added in the SmPC in Section 4.4: *“After the first injection the incidence of cataract appears higher in patients with non-infectious uveitis of the posterior segment compared with BRVO/CRVO patients.”*

The CHMP considered the MAH's justification regarding observations on conjunctival haemorrhage and cataracts as acceptable, but was of the opinion that further monitoring of these adverse events in the post-authorisation setting was warranted. Therefore, the CHMP requested that a sub-population of patients with uveitis be included in the long-term PASS study already planned for the RVO population.

Of concern was the one case of endophthalmitis observed in the main study. Endophthalmitis is a very serious adverse event that can lead to vision loss. Even though the case of endophthalmitis reported in the uveitis study was not definitive as bacterial or fungal growth was not revealed, there have been also six reports of endophthalmitis during the post-marketing experience with Ozurdex. In this context, the MAH agreed to include the adverse reaction in the SmPC (in section 4.8), in addition to the current warning in section 4.4. Measures such as emphasis on an aseptic technique and educational materials outlining the symptoms of endophthalmitis are already in place. Endophthalmitis was also re-classified in the RMP from a potential to an identified risk.

Four cases of retinal detachment were also reported (2 in the DEX 700 and 2 in the sham group). The retinal detachments were assessed as causally related to the study treatment in the DEX700 group and in the Sham group to the underlying disease. The MAH agreed with the CHMP to include retinal detachment in the SmPC (in Section 4.8) and re-classify the event in the RMP from a potential to an identified risk.

An important risk related with the local use of corticosteroids is the development of IOP increases/glaucoma. A similar pattern to that seen in macular oedema studies was seen in uveitis. As already observed in macular oedema studies, the younger group (< 45 years) of patients showed a higher incidence of intraocular pressure compared to the mid-age patients and elderly. Considering that young adults are the target population for this new indication, the CHMP requested that the increased risk should be adequately reflected in the SmPC. The MAH agreed to include the new patient population (uveitis patients) in the warning regarding patients of less than 45 years (in Section 4.4).

The CHMP noted that only six month safety data are available in patients with posterior uveitis. The long-term safety data provided were based on the studies presented to support the currently authorised indication, i.e. macular oedema following RVO, and on the ongoing studies in diabetic macular oedema. The CHMP concurred with the MAH that the safety profile of repeated steroid use is likely to be consistent across the uveitis, RVO and DME indications, as each of the conditions contains an element of inflammation. As described above, the safety profile from the six month study in uveitis was, with the exception of cataracts and conjunctival haemorrhage, in line with that of the RVO studies. Taken together, the data presented by the MAH were considered relevant to support safe use of Ozurdex in the uveitis patients.

Overall, as a high percentage of patients may require a second implant (64% of patients with non-infectious intermediate uveitis and 67% with posterior uveitis were classified as quiescent (Nguyen et al, 2011), it was considered relevant to further monitor the long-term safety profile in patients requiring more than 1 implant. In particular, the CHMP considered that the AEs most commonly reported during the first six months (e.g. increased IOP, cataract, conjunctival haemorrhage) should be analysed within repeated administration of Ozurdex in the post-marketing setting. As the MAH is planning a long-term safety/repeat dosing study of Ozurdex in patients with RVO, the CHMP requested that a subgroup of patients with uveitis be included.

#### **2.4.7. Benefit/Risk balance**

##### Benefit

To support the extension of indication for Ozurdex in the treatment of adult patients with inflammation of the posterior segment of the eye presenting as non-infectious uveitis, the MAH submitted a single phase III pivotal trial: An 8-Week, Multicenter, Masked, Randomized Trial (with an 18-Week Masked Extension) to Assess the Safety and Efficacy of 700 microgram and 350 microgram 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 or Posterior Uveitis. Assessment of efficacy and safety of Ozurdex in the treatment of non-infectious uveitis was based on this pivotal study, with safety data from the retinal vein occlusion and macular oedema studies being considered supportive. The initial concerns regarding the number of amendments to the pivotal trial were resolved and the CHMP considered that they did not have a relevant impact on the study results.

The results of the phase III study demonstrated that the 700 microgram implant was efficacious in the treatment of uveitis of the posterior segment of the eye. Both the 700 microgram and 350 microgram implant groups were statistically significantly superior to the sham group in the ITT and PP populations

for the primary and secondary efficacy endpoints. The results for the 700 microgram group were numerically superior to the 350 microgram group on most endpoints, but this comparison was not statistically significant.

#### Uncertainties about the benefit

The CHMP noted that according to the data in severe patients and the known course of the disease in many instances, re-dosing of Ozurdex would be reasonably expected in severe cases of uveitis. It was observed that efficacy appears to decrease after around 6 months and therefore, patients may need re-implantation. In terms of efficacy, as Ozurdex is a corticosteroid treatment, it is expected that the efficacy observed with a second implant would be similar to the one observed with the first implant. Although data on re-implantation are not available for Ozurdex in uveitis patients, in the RVO studies where patients entered a second open label extension after 6 months, patients achieved a similar treatment benefit to that of the first. Given that in both conditions the inflammatory process has a common mechanism, a second injection in uveitis patients was considered to have a similar effect to RVO patients.

#### Risks

The adverse event profile for Ozurdex in the treatment of patients with posterior uveitis was in line with that seen in the RVO studies.

The most frequently reported ocular adverse events were IOP increased, conjunctival haemorrhage, eye pain, iridocyclitis, uveitis, ocular discomfort and cataract, being all except for eye pain and uveitis more commonly reported in DEX 700 as compared to sham. In general, comparing the two tested doses, DEX 350 showed a slightly more favourable safety profile, with a lower incidence of the most frequently reported adverse events, than the high dose (DEX 700). On the other hand, a lower incidence of visual acuity reduced and macular oedema AEs, common complications of uveitis, were seen in DEX 700 compared to DEX 350 and Sham.

#### Uncertainties about the risks

The uncertainty regarding repeated use of Ozurdex was also discussed in terms of limited safety data. The CHMP noted that only six-month safety data are available in patients with posterior uveitis. The long-term safety data provided were based on the studies presented to support the currently authorised indication, i.e. macular oedema following RVO, and on the ongoing studies in diabetic macular oedema. The CHMP considered that the safety profile of repeated steroid use is likely to be consistent across the uveitis, RVO and DME indications, as each condition contains an element of inflammation. As described above in section 4.4.6, the safety profile from the six month study in uveitis was, with the exception of cataracts and conjunctival haemorrhage, in line with that of the RVO studies. Overall, the data presented by the MAH were considered relevant to support a positive benefit risk balance of Ozurdex in the uveitis patients.

As a high percentage of patients may require a second implant (64% of patients with non-infectious intermediate uveitis and 67% with posterior uveitis were classified as quiescent (Nguyen et al, 2011), it was considered relevant to further monitor the long-term safety profile in patients requiring more than 1 implant. In particular, the CHMP considered that the AEs most commonly reported during the first six months (e.g. increased IOP, cataract, conjunctival haemorrhage) should be analysed within repeated administration of Ozurdex in the post-marketing setting. As the MAH is planning a long-term safety/repeat dosing study of Ozurdex in patients with RVO the CHMP requested that at least a subgroup of patients with uveitis be included.

The CHMP also discussed the most suitable dose in less severely affected patients, who would be nonetheless candidates for intravitreal treatment, and asked the MAH for a justification of the 700

microgram dose. The MAH concluded that both doses were shown to be safe and effective in patients with baseline VH scores of +1.5 or 2; nevertheless, the response to the 700 microgram dose was numerically superior in efficacy across a broad range of endpoints and at almost all timepoints, had an earlier onset and longer duration of action and no significant difference in overall safety profile was observed between the two doses. Furthermore the incidence of adverse events such as cataracts and increased IOP which would be expected to increase with increasing corticosteroid dose was not significantly different between the two doses. In this context, the MAH chose to apply only for the higher dose. The CHMP considered that the risk benefit balance was sufficiently substantiated with the current data and that it is positive for the 700 microgram dose in the proposed indication.

#### Conclusion

Overall, the CHMP concluded on a positive benefit-risk balance for the 700 microgram dose in the treatment of adult patients with inflammation of the posterior segment of the eye presenting as non-infectious uveitis.

## ***2.5. Pharmacovigilance***

### **2.5.1. Detailed description of the Pharmacovigilance system**

The CHMP considered that the Pharmacovigilance system as described by the MAH fulfils the legislative requirements.

### **2.5.2. Risk management plan**

With this type II variation of Ozurdex, the MAH has submitted an update of the EU-RMP, version 1.5, dated 14 April 2011.

Ozurdex (dexamethasone intravitreal implant) is currently indicated for the treatment of adult patients with macular oedema following either Branch Retinal Vein Occlusion (BRVO) or Central Retinal Vein Occlusion (CRVO). With this application the MAH proposed to extend the indication of Ozurdex for the treatment of adult patients with inflammation of the posterior segment of the eye presenting as non-infectious uveitis.

The RMP submitted with this extension of indication application for the treatment of patients with non-infectious uveitis presents all the important identified and potential risks for Ozurdex alongside the routine and enhanced pharmacovigilance activities and risk minimisation measures. Besides the previous identified and potential risks associated with Ozurdex therapy, no new significant safety issues were identified, except for endophthalmitis and retinal detachment which were reclassified from potential risks to identified risks. No new areas of missing information were identified. The educational materials were updated accordingly in line with the new indication.

The main areas of concern with the new indication, as with the current indication, are the lack of long term safety data and data on repeat use. The MAH is conducting two phase 3, 3-year studies (206207-010 and 206207-011) in diabetic macular oedema patients that will provide additional long term safety data on the identified and potential risks of Ozurdex. Furthermore, the MAH agreed with the CHMP that the observational study on repeat administration, already planned in the RVO setting to help address the use of multiple implants, will also include a sub-population of uveitis patients. The updated synopsis of the protocol is attached to the RMP and the extended protocol of this observational study will be submitted to the CHMP as a follow-up measure.

The summary of the RMP is provided in the table below:

Important Identified risks	Proposed Pharmacovigilance activities	Proposed risk minimisation activities
Increased IOP, Glaucoma and Ocular Hypertension	<p>Routine pharmacovigilance</p> <p>Enhanced pharmacovigilance:  <b>Studies 206207-010 and 206207-011</b> to provide long-term safety data with repeated dosing (dosing of up to 6 injections in 3 years). Phase 3, multicenter, repeat dose, masked, randomized, sham-controlled trials to assess the safety and efficacy of 700 µg and 350 µg OZURDEX® applicator system in the treatment of patients with diabetic macular edema.</p> <p><b>Observational study</b> conducted in adult patients with macular oedema following either Branch Retinal Vein Occlusion (BRVO) or Central Retinal Vein Occlusion (CRVO) to gain experience with repeat administration. This study will recruit patients requiring a 2nd or subsequent implant due to deteriorating visual acuity with the aim of collecting long term outcome and safety data. The study design will ensure that sufficient patients requiring more than 2 implants are recruited to provide additional useful information on this patient group. The study will include patients with inflammation of the posterior segment of the eye presenting as non-infectious uveitis (as requested by CMHP).</p>	<p>Increases in intraocular pressure (IOP) is described in Section 4.4 of the SmPC</p> <p>Increased IOP is included as "very common" adverse reaction in Section 4.8 (Undesirable effects).</p> <p>Educational material to instruct prescribers on the recommended injection technique and important risks associated with OZURDEX®, including increased intraocular pressure and ocular hypertension.</p> <p>Allergan has created educational materials relating to uveitis (separate from RVO). There is a great deal of overlap in the information between the two indications, but these materials will describe the mechanism of action in uveitis and summarise the efficacy and safety pertinent to this indication. The material/ programmes will be relevant to all licensed indications. Educational materials covering both indications are provided in Annex 8 of the RMP.</p>
Cataracts	<p>Routine pharmacovigilance</p> <p>Enhanced pharmacovigilance:</p> <ul style="list-style-type: none"> <li>• Studies 206207-010 and 206207-011 (see above)</li> <li>• Observational study (see above)</li> </ul>	<p>Occurrence of cataract, including observed in clinical studies is described in Section 4.4 of the SmPC</p> <p>Included as "common" adverse reaction" in Section 4.8 (Undesirable effects).</p> <p>Educational material (see description above)</p>
Vitreous Detachment/haemorrhage	<p>Routine pharmacovigilance</p> <p>Enhanced pharmacovigilance:</p> <ul style="list-style-type: none"> <li>• Studies 206207-010 and 206207-011 (see above)</li> <li>• Observational study (see above)</li> </ul>	<p>Included as "common" adverse reaction" in section 4.8 of the SmPC.</p> <p>Educational material (see description above)</p>
Endophthalmitis	<p>Routine pharmacovigilance</p> <p>Enhanced pharmacovigilance:</p> <ul style="list-style-type: none"> <li>• Studies 206207-010 and 206207-011 (see above)</li> <li>• Observational study (see above)</li> </ul>	<p>Section 4.4 of the SmPC warns that any intravitreal injection can be associated with endophthalmitis</p> <p>Patients must be instructed to report any symptoms suggestive of endophthalmitis or any of the above mentioned events without delay (see section 4.8).</p> <p>Antimicrobial therapy is recommended in Section 4.2 of the SmPC</p> <p>Endophthalmitis (injection related) will be included in Section 4.8 of the proposed SmPC, under Post-Marketing Experience.</p> <p>Educational material (see description above)</p>
Retinal tear/detachment	<p>Routine pharmacovigilance</p> <p>Enhanced pharmacovigilance:</p> <ul style="list-style-type: none"> <li>• Studies 206207-010 and 206207-011 (see above)</li> <li>• Observational study (see above)</li> </ul>	<p>Retinal detachment is described in Section 4.4 and is included as "common" adverse reaction" in section 4.8 of the SmPC.</p>

<b>Important potential risks</b>	<b>Proposed Pharmacovigilance activities</b>	<b>Proposed risk minimisation activities</b>
Retinitis secondary to reactivation of latent viral or other ophthalmic infections	Routine pharmacovigilance  Enhanced pharmacovigilance: <ul style="list-style-type: none"> <li>• Studies 206207-010 and 206207-011 (see above)</li> <li>• Observational study (see above)</li> </ul>	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.
Significant vitreous leak or hypotony	Routine pharmacovigilance  Enhanced pharmacovigilance: <ul style="list-style-type: none"> <li>• Studies 206207-010 and 206207-011 (see above)</li> <li>• Observational study (see above)</li> </ul>	Section 4.2: Posology and method of administration of the SmPC provides clear instruction on the proper injection procedure. Educational material (see description above)
Systemic corticosteroid effects	Routine pharmacovigilance  Enhanced pharmacovigilance: <ul style="list-style-type: none"> <li>• Studies 206207-010 and 206207-011 (see above)</li> <li>• Observational study (see above)</li> </ul>	Section 4.4 of the SmPC indicates that bilateral administration could potentially lead to increased systemic absorption of the steroid
Mechanical failure of device and implant misplacement	Routine pharmacovigilance  Enhanced pharmacovigilance: <ul style="list-style-type: none"> <li>• Studies 206207-010 and 206207-011 (see above)</li> <li>• Observational study (see above)</li> </ul>	Section 4.2: Posology and method of administration of the SmPC has clear instruction on the proper injection procedure. Educational material (see description above)

<b>Missing information</b>	<b>Proposed Pharmacovigilance activities</b>	<b>Proposed risk minimisation activities</b>
Paediatric Use	Routine pharmacovigilance	Section 4.2 of the SmPC indicates that safety and efficacy of OZURDEX in uveitis in the paediatric population has not been established.  There is no relevant use of OZURDEX in the paediatric population in macular oedema following either BRVO or CRVO.
Pregnancy and lactation	Routine pharmacovigilance	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 foetus or clearly necessary.
Long-term safety, repeat dosing data	Routine pharmacovigilance  Enhanced pharmacovigilance: <ul style="list-style-type: none"> <li>• Studies 206207-010 and 206207-011 (see above)</li> <li>• Observational study (see above)</li> </ul>	
Concurrent use of anticoagulants	Routine pharmacovigilance  Enhanced pharmacovigilance: Studies 206207-010 and 206207-011 (see above)	Section 4.4 of the SmPC describes use of OZURDEX® during anticoagulant therapy, including the prevalence of conjunctival haemorrhage in patients with non-infectious uveitis observed in clinical studies
Patients with significant retinal ischaemia	Routine pharmacovigilance  Enhanced pharmacovigilance: Studies 206207-010 and 206207-011 (see above)	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.

## ***2.6. Product Information***

### ***Summary of Product Characteristics (SPC)***

Product Information with changes tracked was attached to the CHMP assessment report.

### ***Labelling***

Not applicable

### ***Annex II***

Product Information with changes tracked was attached to the CHMP assessment report.

### ***Package Leaflet (PL)***

Product Information with changes tracked was attached to the CHMP assessment report.

The MAH included a justification for not submitting a full user testing report together with the variation dossier and submitted a bridging study report for the new indication. The CHMP considered the MAH approach acceptable and concluded that the outcome of the bridging study was sufficient.

### 3. Conclusion

Based on the CHMP review of the data on efficacy and safety, the CHMP considered that the overall benefit-risk balance of Ozurdex in the treatment of adults patients with inflammation of the posterior segment of the eye presenting as non-infectious uveitis is positive and the variation application EMEA/H/C/001140/II/01 for the proposed change to extend the indication to include treatment adults patients with inflammation of the posterior segment of the eye presenting as non-infectious uveitis is approvable.

On 14 April 2011 the CHMP considered this Type II variation to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics, Annex II, Package Leaflet and Annex 127a. In parallel, the CHMP reviewed the data submitted by the applicant taking into account the provisions of Article 14(11) of Regulation (EC) No. 726/2004 and provisions of the "Guidance on elements required to support the significant clinical benefit in comparison with existing therapies of a new therapeutic indication in order to benefit from an extended (11-year) marketing protection period (November 2007)" and considered that the new therapeutic indication brings significant clinical benefit in comparison with existing therapies.

#### Follow-up measures undertaken by the marketing authorisation holder

As requested by the CHMP, the MAH agreed to submit the follow-up measures as listed below and to submit any variation application which would be necessary in the light of compliance with these commitments (Letter of Undertaking attached to the CHMP assessment report):

Area <sup>1</sup>	Description	Due date <sup>2</sup>
Clinical/ Pharmacovigilance	The MAH should commit to submitting a draft protocol of a PASS for Ozurdex: a prospective observational study to evaluate long-term safety in real-world clinical practice (currently under FUM 003), updated to include a sub-group of uveitis patients	The draft updated protocol should be submitted by 30 June 2011.
Pharmacovigilance	The MAH should commit to providing evaluation of the criteria used to verify the success of the educational materials with a review period, in line with the EU-RMP template section 4.	The updated RMP should be submitted with the next PSUR, i.e. by 27 September 2011.

<sup>1</sup> Areas: Quality, Non-clinical, Clinical, Pharmacovigilance.

<sup>2</sup> Due date for the follow-up measure or for the first interim report if a precise date cannot be committed to.

## **4. ATTACHMENT**

*Assessment report on the novelty of the indication/significant clinical benefit in comparison with existing therapies for Ozurdex 700 micrograms intravitreal implant in applicator*

## **4.1. Introduction**

DEX PS DDS applicator system (under the trade name OZURDEX) contains dexamethasone, a corticosteroid that has been shown to suppress inflammation by inhibiting oedema, fibrin deposition, capillary leakage, phagocytic migration of the inflammatory, inhibit the expression of VEGF and additionally, prevent the release of prostaglandins response.

Ozurdex was first granted positive opinion by the European Medicine Agency (EMA) and approved by the European Commission 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).

On 9 September 2010 the Marketing Authorisation Holder (MAH) submitted an application for a Type II variation to include a new indication for Ozurdex, "treatment of adult patients with inflammation of the posterior segment of the eye presenting as non-infectious uveitis" (EMA/H/C/001140/II/0001).

In accordance with the provisions of Article 14(11) of Regulation 726/2004, the MAH also applied for an additional one year marketing protection period for Ozurdex in the context of the current Type II variation (EMA/H/C/799/II/01) to include a new indication for treatment of adult patients with inflammation of the posterior segment of the eye presenting as non-infectious uveitis.

The request was based on the MAH's position that Ozurdex represents a 'significant clinical benefit' in the treatment of adult patients with inflammation of the posterior segment of the eye presenting as non-infectious uveitis based on improved efficacy in comparison with existing therapies.

The evidence supporting an extended marketing protection period based on a new therapeutic indication held to bring a significant clinical benefit in comparison with existing therapies was presented in accordance with the "Guidance on Elements Required to Support the Significant Clinical Benefit in Comparison with Existing Therapies of a New Therapeutic Indication in Order to Benefit from an Extended (11-year) Marketing Protection Period, November 2007" and included a justification for the new therapeutic indication 'uveitis' as well as a justification for significant clinical benefit for the intended population.

The submission was made within the first 8 years of the 10 year marketing protection period granted to OZURDEX following initial approval on 27 July 2010.

### ***Comparison of the proposed indication compared to the therapeutic indications already authorised:***

The additional indication claimed within this application is a *new target disease*:

*"OZURDEX is indicated for the treatment of adult patients with inflammation of the posterior segment of the eye presenting as non-infectious uveitis."*

The therapeutic indication already authorized is:

*"OZURDEX is indicated for the treatment of adult patients with macular oedema following either Branch Retinal Vein Occlusion (BRVO) or Central Retinal Vein Occlusion (CRVO)"*

Uveitis of the posterior segment of the eye is a distinct disease from the indication already approved for OZURDEX (macular oedema following either branch or central vein occlusion).

The distinguishing characteristics of each disease are summarised in the following points and further discussed in the sections below:

- Both diseases might lead to blindness, but their prevalence strongly differs. Intermediate and posterior uveitis may be considered as rare conditions whereas RVO occurs more often in the general population.
- Inflammation is the major pathophysiological component of uveitis whereas systemic vascular factors such as hypertension are important in RVO, in turn leading to inflammation and macular oedema.
- The aetiology of uveitis is often linked to systemic autoimmune disorders. The aetiology of vein occlusions is commonly linked to systemic cardiovascular disease processes.
- Uveitis may occur at any age although the majority of patients are of working age (20 to 60). RVO may occur in younger patients however it occurs predominantly in those over 65 years.
- Uveitis is often bilateral whereas RVO is uncommonly bilateral at any one time.
- Clinical manifestations of uveitis and RVO are easily distinguished.
- The management and treatment for posterior and intermediate uveitis have only a few similarities with RVO

#### Prevalence of non-infectious intermediate and posterior uveitis compared to macular oedema following branch or central vein occlusion

“Non-infectious uveitis affecting the posterior segment of the eye” is listed as a rare disease by Orphanet (<http://www.orpha.net>) and “posterior uveitis” is listed as rare by the National Organisation for Rare Disorders (NORD) (<http://www.rarediseases.org>). The combined prevalence of Intermediate and posterior uveitis is approximately 0.006%. On the other hand the prevalence of retinal vein occlusion is between 0.7 and 1.6% and is the second most common sight-threatening vascular disorder after diabetic retinopathy.

#### Patho-physiology of non infectious intermediate and posterior uveitis compared to macular oedema following branch or central vein occlusion

Uveitis refers to *inflammation* affecting structures in the eye including the iris, ciliary body, and choroid. The inflammation may affect only one or multiple structures. In many cases, both eyes are involved and symptoms may include decreased vision, blurry vision, floaters, and distortion of central vision and/or leukocoria (BenEzra et al, 2005). Pain, redness, or photophobia are not common. The major causes of blindness in patients with uveitis are cystoid macular oedema, secondary cataract, and secondary glaucoma as well as sequelae of a potential combined choroiditis or retinitis (BenEzra et al, 2005; Rothova et al, 1996).

Non-infectious uveitis is a complex set of diseases associated with auto-immune responses of an idiopathic nature, or following auto-immune disease, e.g. sarcoidosis, inflammatory bowel disease, multiple sclerosis, sympathetic ophthalmia, serpiginous choroidopathy, birdshot choroidopathy, Vogt-Koyanagi-Harada or Behçet disease (Whitcup, 2004).

Whereas retinal vein occlusive disease is thought to occur as a consequence of thrombus formation at the lamina cribrosa or by compression of the venous wall by an overlying arteriole leading to macular

oedema at an arteriovenous intersection. Depending on the location of the venous blockage, retinal vein occlusion is classified as branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO). This blockade can be favoured by cardiovascular disorders, ocular hypertension or blood hyperviscosity.

#### Aetiology of non-infectious uveitis compared to macular oedema following branch or central vein occlusion.

Non-infectious intermediate uveitis is usually idiopathic but may occasionally be associated with underlying medical conditions including sarcoidosis, chronic vitritis, retinal phlebitis, or associated with multiple sclerosis (Boyd et al, 2001).

The primary site of inflammation in posterior uveitis is the choroid or the overlying retina, and it may secondarily be associated with a vitritis (Jabs et al, 2005). In many cases the aetiology of non-infectious uveitis is unknown while some cases may either be associated with systemic diseases such as sarcoidosis, Behçet's disease, systemic lupus erythematosus, Vogt-Koyanagi-Harada syndrome (Durrani et al, 2004).

Retinal vein occlusive disease is associated with those factors causing cardiovascular disorders such as hyperlipidaemia, hypertension, diabetes and smoking. (Jackson TL. Moorfields Manual of Ophthalmology, Mosby (2008)). In an Australian study the factors predicting the incidence of RVO included arterial blood pressure, ocular perfusion pressure, obesity and presence of retinal arteriolar wall signs (Cugati, 2006). RVO is also known to occur more often in patient with ocular hypertension and glaucoma (Barnett, 2010) as well as in hypercoagulable states in patients (Lahey, 2002).

#### Age distribution of non-infectious uveitis compared to macular oedema following branch or central vein occlusion.

The incidence of uveitis increases with age and is the highest in the 40-49 years age group. The incidence of uveitis declines significantly after 70 years of age. In contrast, the prevalence and incidence of BRVO and CRVO increases with age and is the highest in those aged 65 years and above (Klein et al., 2000).

#### Bilateral nature of non infectious uveitis compared to macular oedema following branch or central vein occlusion.

In approximately half of the cases uveitis may occur concurrently in both eyes. Bodaghi and al reported that 41.3% of severe cases of chronic uveitis were bilateral in a case series of 927 patients (Bodaghi, 2005). Markomichelakis et al. described the morphologic characteristics of uveitic macular oedema in consecutive patients with uveitis (Markomichelakis, 2004). Twenty-four out of 60 patients presented with a bilateral uveitis. The proportion of patients with bilateral uveitis may affect approximately 80% of patients with intermediate uveitis (Bonfioli, 2005) and about one third of those who present unilaterally eventually develop disease in both eyes (Lai, 2002).

Unlike uveitis, RVO occurrence commonly affects only one eye at a time. The cumulative probability of developing any type of retinal vein occlusion in the fellow eye within 4 years has been estimated to be 11.9% (Christoffersen, 2007).

#### Clinical manifestations of uveitis and RVO are easily distinguished

Inflammation of the posterior segment of the eye presenting as non-infectious uveitis includes:

- Non infectious intermediate uveitis is described as inflammation of the anterior vitreous, although inflammation of the ciliary body and the peripheral retina may also be seen (Jabs, 2005).
- Non infectious posterior uveitis inflammation principally involves the retina or choroid, however it may also involve adjacent structures such as the vitreous or optic nerve head.

Typically clinicians can easily differentiate the above clinical aspects from the signs of RVO such as retina and/or optic nerve oedema, dilated retinal veins, and retinal hemorrhages located on the retinal region drained by the occluded vessels.

In conclusion, the above discussion of a number of parameters shows that non-infectious uveitis of the posterior segment of the eye is a distinct indication from that currently approved for OZURDEX.

#### Details of existing therapies relating to the proposed new indication

- Corticosteroids: highly effective anti-inflammatory agents that inhibit many aspects of the immune response:
- Corticosteroid eye drops are available for uveitis, however the low bioavailability of topical corticosteroids within posterior ocular tissues limits their utility.
- Immunosuppressive drugs: In patients with intolerance to systemic steroids or recalcitrant to therapy, immunosuppressives can be added with/without systemic steroids.
- Periocular and intravitreal injections of triamcinolone acetonide suspensions (Kenalog) have been used to treat uveitis (not an approved indication). Fluocinolone acetonide (Retisert) is approved by the US Food and Drug Administration (FDA), and indicated for the treatment of chronic non-infectious uveitis affecting the posterior segment of the eye (Lim et al, 2005) but is not approved in the European Community.
- OZURDEX has been developed to specifically focus on delivering the required steroid dosage into the inflammation site. OZURDEX, the dexamethasone intravitreal implant in applicator, addresses many of the problems associated with conventional therapies for uveitis of the posterior segment such as fluctuating drug levels, short intraocular half-life, and prolonged systemic exposure to high levels of corticosteroids. The introduction of OZURDEX for the treatment of adult patients with inflammation of the posterior segment of the eye presenting as non-infectious uveitis would offer a longer acting corticosteroid treatment with a well characterised, reassuring safety profile.

**Medicinal products are available in the EU for treatment of non-infectious uveitis:**

**Table 3-1 Medicinal Products Authorised in the European Community for treatment of uveitis**

Tradename, active ingredient/generic	Holder of marketing authorisation	Authorised indication
Calcort® 6 mg tablets, deflazacort	Sanofi-Aventis	A wide range of conditions treated with glucocorticoids, including uveitis, optic neuritis
Deltacortril® 2.5 mg and 5mg gastro-resistant tablets, prednisolone	Alliance Pharmaceuticals	A wide range of conditions including posterior uveitis, scleritis, retinal vasculitis, pseudo-tumours of the orbit, giant cell arteritis, malignant ophthalmic Graves disease
Medrone tablets 2 mg, 4 mg, and 16 mg, methylprednisolone	Pharmacia	A wide range of conditions including anterior uveitis (iritis, iridocyclitis) posterior uveitis, and optic neuritis
Minims Dexamethasone 0.1% w/v Eye Drops, dexamethasone sodium phosphate	Bausch & Lomb	Non-infected, steroid responsive, inflammatory conditions of the eye
Dexsol 2 mg/5 ml oral solution, dexamethasone sodium phosphate	Rosemont Pharmaceuticals	A wide range of conditions including anterior and posterior uveitis, optic neuritis, chorioretinitis, iridocyclitis, temporal arteritis, orbital pseudotumour
Ciclosol® 25 mg, 50 mg, 100 mg capsules, ciclosporin	Ecosol AG	Conditions including uveitis (endogenous)
Sandimmun Neoral® 100 mg capsules, ciclosporin	Novartis	Conditions including uveitis (endogenous)

Although corticosteroid eye drops are available for uveitis, the low bioavailability of topical corticosteroids within posterior ocular tissues limits their utility (Kearns and Williams, 2009; Lee et al, 1989).

A stepwise approach to treatment is undertaken which may include topical corticosteroids, periocular corticosteroid injections, systemic and topical nonsteroidal anti-inflammatory agents, systemic corticosteroids, peripheral cryotherapy, immunosuppressive drugs, and pars plana vitrectomy (Nussenblatt and Whitcup, 2004). The treatment protocol for posterior uveitis is similar to that of intermediate uveitis. Considering that the threat of vision loss is very serious in posterior uveitis, aggressive treatment with corticosteroids is recommended and systemic immunosuppressants may be required (Jabs and Akpek, 2005; Menzo et al, 2005).

Thus, treatment of the underlying inflammatory disease should play a central role in the management of uveitic cystoid macular oedema (CMO), choroidal neovascularization (CNV) and retinal neovascularisation (RNV).

The MAH has developed OZURDEX, the dexamethasone intravitreal implant in applicator, as a novel, applicator drug delivery system that addresses many of the problems associated with conventional therapies for uveitis of the posterior segment such as fluctuating drug levels, short intraocular half-life, and prolonged systemic exposure to high levels of corticosteroids. The introduction of OZURDEX for the treatment of adult patients with inflammation of the posterior segment of the eye presenting as non-infectious uveitis would offer a longer acting corticosteroid treatment with a well characterised, reassuring safety profile (Gulati et al, 2010).

## ***4.2. Justification of significant clinical benefit as presented by the MAH***

### **4.2.1 Justification of significant clinical benefit based on improved efficacy**

In order to demonstrate the effectiveness of OZURDEX in the proposed indication a Phase III study (014) with the relevant primary endpoint for inflammation of vitreous haze was undertaken by the MAH. The 014 study was an appropriately designed clinical trial, and included elements necessary for a valid assessment of the effectiveness of treatment:

The results of this study are summarised below:

- The study demonstrated that OZURDEX can reduce inflammation and substantially improve vision in patients with non-infectious uveitis of the posterior segment. Almost one quarter (23.4%) of patients in the OZURDEX group achieved a vitreous haze score of 0 (no inflammation) as early as 3 weeks after a single treatment. At week 8 (primary time point), 46.8% of patients in the OZURDEX group had a vitreous haze score of 0. This response was maintained, with significantly higher response rates for OZURDEX compared to Sham out to week 26.
- Importantly, improvements in inflammation were accompanied by substantial improvement in vision as measured by the proportion of patients with 15 or more letters gain in BCVA. The improvement from baseline BCVA in the study eye was already apparent at week 3. The statistical superiority compared with sham was seen as early as week 3 and persisted throughout the 26 week study period ( $p < 0.001$ ). At week 8 this difference was more than 6-fold greater with OZURDEX (42.9%) compared to Sham (6.6%).
- Throughout the study, the percentage of Sham patients requiring other additional therapies to treat their uveitis was almost double that in the OZURDEX group (38.2% versus 22.1% at week 26,  $p = 0.030$ ). After 8 weeks the percentage of sham patients requiring additional therapies was almost three times that of the OZURDEX group (22.4% versus 7.8% at week 8,  $p=0.012$ ). Fewer patients in the OZURDEX groups received escape medications, indicating that OZURDEX delivered optimal treatment effects.
- The study shows highly convincing statistical superiority, compared with sham treated patients, for the major efficacy parameters throughout the evaluation period. Furthermore, the study shows strong internal consistency with similar conclusions drawn across the different subgroups and different endpoints. In addition, the prespecified alternative analyses demonstrate consistency of all measures. This further supports the exceptional benefit of OZURDEX.
- Shifts in the severity distributions towards milder ratings for anterior chamber cells, anterior chamber flare, and vitreal cells during the course of the study favoured OZURDEX. This benefit of OZURDEX over Sham was observed despite the substantially greater proportion of patients in the Sham group who had received escape medications. Furthermore, the higher proportion of patients in the Sham group with anterior segment inflammatory signs on biomicroscopy, clearly demonstrates that OZURDEX provides a sound anti-inflammatory effect which, not only offers treatment, but is also instrumental in preventing deterioration of the inflammatory process.
- The phase 3 study 014 demonstrated rapid, marked, sustained, and definitive efficacy of DEX 700 compared to Sham over a broad range of efficacy variables throughout the 26 week study period, with approximately one third of patients still considered to be a responder at study end.

#### ***4.2.2 Justification of significant clinical benefit based on improved safety***

OZURDEX allows for a sustained release of substantially lower daily levels of steroid than are currently used in topical or systemic, or off-label periocular therapies. Furthermore, this mode of administration ensures that treatment is provided directly to the area needed. This minimizes many potential side effects typically observed with steroid administration through other routes of delivery. Moreover, the polymer gradually dissolves over time as it releases its dexamethasone so that there is no need to remove the implant.

In order to evaluate the significance of the role of OZURDEX in the treatment of inflammation of the posterior segment of the eye presenting as non-infectious uveitis, it is important to appreciate the safety concerns which have been described with the alternative modes of steroid administration.

- Topical ocular steroid administration does not allow the delivery of adequate concentrations of steroid to the site of action in the treatment of uveitis of the posterior segment of the eye.
- Periocular steroid administration, which only provides short term effect, poses the risk of local complications including globe perforation, conjunctival or corneoscleral melting, strabismus, proptosis or fat atrophy and fibrosis of the extraocular muscles
- Systemic steroid administration is associated with the risks of systemic hypertension, hyperglycaemia, increased susceptibility to infection and peptic ulcers. Furthermore, ocular side-effects include ocular hypertension, glaucoma, posterior subcapsular cataract formation and secondary ocular infection.

It must be noted that the OZURDEX intravitreal implant is also associated with ocular side effects. However:

- Unlike systemic administration, OZURDEX intravitreal implant guarantees an adequate steroid concentration at the required site of action and only a small proportion of patients experienced increases in IOP which either did not require treatment or were managed with topical IOP-lowering medications and resolved by the end of the study. No patients required incisional surgery for glaucoma.
- Cataracts, a known risk associated with ophthalmic steroid use, were reported at low rates which were similar rates in the uveitis patients and the already approved indication of macular oedema following retinal vein occlusion during the 6-month follow-up. Moreover, the need for cataract surgery is infrequent.

There are no other intravitreal steroids approved in the European Union. However, OZURDEX has advantages when compared to unapproved intravitreal steroid treatments:

- Triamcinolone: Although data from controlled clinical trials are not available, review of the literature suggests that the incidence of both increased intra ocular pressure and cataract formation is significantly in excess of that seen with OZURDEX.
- Fluocinolone acetonide (Retisert): Requires an incision over the pars plana and suturing of the device to the sclera. Although the device delivers fluocinolone acetonide for up to 2.5 years,

It can therefore be concluded that the safety advantage offered by OZURDEX, along with its marked sustained efficacy, have a significant positive impact on the benefit/risk ratio of steroids in the management of non-infectious uveitis. It is considered that OZURDEX represents a breakthrough in patient care and offers clear advantages to the intravitreal steroid implants being currently used off label. The overall benefit risk evaluation is highly beneficial in this condition where currently available therapy is clearly inadequate. Therefore it is the opinion of the applicant that this significant new indication meets the criteria for the granting of one year's additional marketing protection.

#### **4.2.3 Justification of significant clinical benefit based on major contribution to patient care**

Currently available therapies are not always fully effective for uveitis affecting the posterior segment of the eye, and are known to have treatment-limiting adverse effects. In general, topical therapy is ineffective for posterior uveitis and only has limited applicability to treat intermediate uveitis since drug levels achievable by the topical route are below the therapeutic range needed to treat vitreous and posterior segment inflammation.

Compared to topical therapies, patients respond better to periocular injections or systemic therapy. However, periocular injections are not without recognised complications and systemic toxic effects are a significant problem with most existing maintenance therapies. Unlike most therapies that are given daily or intravitreal injections which are usually given monthly, OZURDEX is a sustained-release implant with an extended duration of action, thus avoiding the need for repeated intravitreal injections which is a clear advantage for the patient.

### ***4.3. CHMP assessment of the MAH's justification of significant clinical benefit***

#### Significant clinical benefit based on improved efficacy

The CHMP was of the opinion that the current data provided, generated in a controlled clinical trial with clinically relevant endpoints, have shown that Ozurdex is effective in treatment of adult patients with inflammation of the posterior segment of the eye presenting as non-infectious uveitis. The clinical trial demonstrated sustained efficacy of the proposed product in a group of patients with posterior uveitis throughout the 26-week study period.

The CHMP acknowledged that periocular and intravitreal injections of triamcinolone acetonide suspensions are used to treat uveitis, but not in an approved indication and considered that Ozurdex will be the only available intravitreal corticosteroid implant for patients with inflammation of the posterior segment of the eye presenting as non-infectious uveitis, offering sustained efficacy with evidence based on a well conducted controlled clinical trial.

#### Significant clinical benefit based on improved safety

The safety profile of Ozurdex was as expected from an intravitreal implant with the most commonly observed adverse events being increase in intraocular pressure and cataracts. These adverse events

were easily managed. The CHMP considered that the intravitreal route presents clinical benefit for patients in terms of safety, as it reduces the need for systemic corticosteroids, the use of which is associated with a number of safety concerns including systemic hypertension, hyperglycaemia, increased susceptibility to infection and peptic ulcers. Furthermore, topical ocular corticosteroid administration has limitations, as delivery to the posterior segment of the eye is very limited. Periocular corticosteroid injections are used regularly in clinical practice; this however is an unlicensed indication and the effect is short-term compared to Ozurdex. This leads to the need of more frequent administration and complications associated with that – such as globe perforation, conjunctival or corneo-scleral melting, strabismus, proptosis, fibrosis of extraocular muscles, increased risk of endophthalmitis. Overall, considering the safety concerns of other alternative modes of steroid administration, the CHMP was of the opinion that significant clinical benefit based on improved safety was shown.

#### Significant clinical benefit based on major contribution to patient care

The CHMP considered that unlike most therapies that are given daily or intravitreal injections which are usually given in monthly intervals, OZURDEX is a sustained-release implant with an extended duration of action, thus avoiding the need for repeated intravitreal injections which are associated with a significant number of potentially serious complications. Furthermore, alternative intravitreal injections are not licensed for the treatment of uveitis affecting the posterior segment of the eye. Topical (eye drops) corticosteroids are not effective in posterior uveitis due to the limitations of reaching the target area. The CHMP acknowledged that there are currently no approved intravitreal delivery methods for any drug in Europe for the treatment of uveitis and there remains an unmet medical need to provide a relatively safe and effective sustained-release corticosteroid formulation for treating non-infectious uveitis affecting the posterior segment of the eye. Thus, the CHMP considered that Ozurdex showed significant clinical benefit based on major contribution to patient care.

#### **4.4. CHMP conclusion**

The evaluation of the data submitted allows concluding on a significant clinical benefit.

Following the overall assessment of the efficacy and safety data provided, the CHMP concluded that the benefit/risk ratio of Ozurdex in the treatment of patients with non-infectious posterior uveitis is positive.

Taking into account the significant clinical benefit based on a major contribution to patient care in comparison to existing therapies, the CHMP considered that the justification for one additional year of marketing protection is sufficient and the additional year of marketing protection can be granted.

#### **4.5. Outcome**

The CHMP reviewed the data submitted by the applicant taking into account the provisions of Article 14(11) of Regulation (EC) No. 726/2004 and provisions of the "Guidance on elements required to support the significant clinical benefit in comparison with existing therapies of a new therapeutic

indication in order to benefit from an extended (11-year) marketing protection period (November 2007)” and considered that the new therapeutic indication brings significant clinical benefit in comparison with existing therapies.