15 September 2016
EMA/433651/2016
Committee for Medicinal Products for Human Use (CHMP)

Withdrawal assessment report

Opsiria

International non-proprietary name: sirolimus

Procedure No. EMEA/H/C/003978/0000

Note

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

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List of abbreviations

AE adverse event

AMD age-related macular degeneration

AUC – Area under the curve

BCVA best-corrected visual acuity

CNV choroid neovascularization

CSR clinical study report

DDI – Drug-drug interaction

DE-109 company code for sirolimus injectable solution used during drug development

DME diabetic macular edema

ECG electrocardiogram

EMA European Medicines Agency

ERA – Environmental Risk Assessment

FDA Food and Drug Administration

GCP – Good Clinical Practice

GLP – Good Laboratory Practice

IVT – intravitreal

IOP intraocular pressure

ITT intent-to-treat

LC/MS/MS – Liquid chromatography/Mass spectrometry/Mass spectrometry

MedDRA medical dictionary for regulatory activities

mTOR - mammalian target of rapamycin

NIU(-PS) - non-infectious uveitis (of the posterior segment of the eye)

NOAEL – No-Observed-Adverse-Effect-Level

OCT optical coherence tomography

OL open-label

PEC – Predicted Environmental Concentration

PK pharmacokinetic

PP per-protocol

PT preferred term

SCT - subconjunctival

3Rs –Replacement, Refinement and Reduction

SAE serious adverse event

SAKURA Study Assessing double-masKed Uveitis tReAtment

SCE Summary of clinical efficacy

SCS Summary of Clinical Safety

SCT subconjunctival

SOC System organ class

1. Recommendation

Based on the review of the data on quality, safety and efficacy, the CHMP considers that the application for Opsiria an orphan medicinal product in the treatment of chronic non-infectious uveitis affecting the posterior segment of the eye, **is not approvable** since major objections have been identified which preclude a recommendation for marketing authorisation at the present time.

Proposal for questions to be posed to additional experts

The CHMP was of the view that an ad-hoc expert group should be convened to seek advice on the clinical relevance of the benefits observed with Opsiria in the treatment of non-infectios uveitis of the posterior segment of the eye as well as on regional differences in the disease etiology and their impact on the results of SAKURA 1.

Proposal for inspection

GMP inspection(s)

N/A

GLP inspection(s)

N/A

GCP inspection(s)

The pivotal study was conducted in accordance with the study protocol and protocol amendments, Good Clinical Practice (GCP), International Conference on Harmonization (ICH) of technical requirements for registration of pharmaceuticals for human use guidelines, and Santen's standard operating procedures (SOPs) for clinical investigation. Compliance with these requirements is consistent with the ethical principles that have their origins in the Declaration of Helsinki (Declaration of Helsinki, 2008).

A request for GCP inspection was adopted for the clinical trial with protocol number 32-007. Two investigator sites in India and the sponsor site in the USA were inspected and the final integrated inspection report (IIR) was issued on 10 September 2015. The final IIR stated that the data obtained at the sites inspected are reliable to be accepted as support of the Marketing Authorisation Application.

New active substance status

Not applicable

2. Executive summary

2.1. Problem statement

Non-infectious uveitis (NIU) is a group of diseases characterized by one common finding, ocular inflammation of the ocular tissues. The inflammation is driven by lymphoreticular cells with T-cells playing a pivotal role. A common criterion used to classify NIU is based on the predominant site of inflammation, i.e. anterior segment, intermediate segment, or posterior segment of the eye.

Non-infectious uveitis of the posterior segment of the eye (NIU-PS) is a chronic and progressive immune-mediated inflammatory condition with an early onset, severely affecting vision and overall quality of life. NIU-PS of the eye debilitates patients in their most active and productive years of life. The mean age at disease onset is < 40 years and 70-90% of patients present with NIU-PS between 20-60 years of age. Inflammation associated with this condition involves the middle layer of the eye (uvea, iris, ciliary body, and choroid) and leads to physiological eye changes which impacting vision. The disease is chronic or recurrent in 2/3 of patients and progresses to permanent structural damage when left untreated with up to 70% of patients experiencing structural damage such as retinal detachment, macular holes, and cataract. Up to 70% of NIU-PS patients experience significant visual impairment or legal blindness.

NIU-PS is considered a rare disease due to low prevalence, chronic and debilitating characteristics, as well as need for combined treatment efforts. Prevalence of uveitis has been reported in the United States at 111.1 per 100,000, in France at 38 per 100,000, and in Finland at 68-76.6 per 100,000. This most severe form of uveitis accounts for 6-48% of uveitis cases in Western countries and 2-32% in Eastern countries (Durrani et al., 2004, Wakefield and Chang, 2005).

The primary goal in the management of NIU-PS is to suppress persistent inflammation and achieve remission. In general, corticosteroids are the mainstay of therapy, administered locally or systemically. Co-morbidities associated with systemic corticosteroid therapy use are well known. Locally administered corticosteroids (periocular injection and intraocular implants) have associated side effects including increased intraocular pressure and cataract formation.

In some patients systemic corticosteroids are insufficient to control the disease and immunosuppressive therapy is required (Jabs DA, 2000). Systemic immunosuppression may be started for patients who have poorly controlled ocular inflammation with systemic steroids or for patients in whom ocular inflammation has recurred on reducing the steroid dose. Several agents have reported benefit in the control of ocular inflammation and the preservation or restoration of sight in uveitis (Guly and Forrester, 2010). Immunomodulating drugs may be added to the corticosteroid regimen to eliminate the need for high doses of systemic steroids, or used alone as steroid-sparing agents when steroids are not tolerated. (Nguyen QD, 2007). Similarly, systemic immunomodulatory agents, often used for steroid sparing, are associated with substantial side effects. By systemic route they require several weeks to months to reach peak effectivity, while the reduction in the corticosteroid dose is often delayed significantly taking weeks to months (de Smet MD, 2011).

2.2. About the product

Sirolimus, a macrolide antibiotic also known as rapamycin, is an inhibitor of the mammalian target of rapamycin (mTOR). Sirolimus-induced inhibition of this multifunctional kinase and its downstream signaling molecules results in immunosuppression primarily by interrupting the inflammatory cascade that leads to T-cell activation and proliferation. Emerging evidence suggests that sirolimus also

promotes immune tolerance by inducing CD4+Fox3+ regulatory T-cells (Treg), which may also contribute to the treatment of NIU-PS because of the potential dysfunction of Treg inautoimmune diseases.

Sirolimus is classified as an Immunosuppressant (ATC code: S01XA23). It is the constituent of a product already authorised in the European Union (Rapamune™ by oral route for the prophylaxis of organ rejection in adult patients at low to moderate immunological risk receiving a renal transplant).

The proposed market product (Opsiria) is a non-aqueous, preservative-free, sterile solution containing sirolimus 2% or 44 µg/ml intended for intravitreal injection using a sterile single-use syringe. The formulation used in the pivotal study (SAKURA) is the same as the formulation to be marketed. When the DE-109 formulations (company code for sirolimus injectable solution formulations used during the development program of Opsiria) are injected into the vitreous humor, sirolimus aggregates to form a depot. The depot formation and slow release of sirolimus in the vitreous is proposed as an ideal dosage form for treatment of NIU-PS because it provides high local drug concentrations with very little systemic exposure.

2.3. The development programme/compliance with CHMP guidance/scientific advice

An initial investigator-sponsored trial, known as the Sirolimus as a Therapeutic Approach for Uveitis (SAVE) study was conducted in patients with non-infectious intermediate uveitis, posterior uveitis, or panuveitis. This was a proof-of-concept, open-label, randomized study that assessed the safety, tolerability, and bioactivity of IVT and subconjunctival (SCT) injections of DE-109.

The SAKURA clinical development program consists of two studies being conducted under the same protocol in 17 countries worldwide. Data collected through Month 12 from the first SAKURA Study forms the basis of the Market Authorization Application (MAA) for DE-109 for the chronic treatment of patients with NIU-PS. The second SAKURA Study is currently enrolling subjects and was not part of this MAA.

Two protocol assistances from the Scientific Advice Working Party (SAWP)/CHMP were given:

a) Procedure No. EMEA/H/SA/2340/1/2012/PA/III (July 2012): Nonclinical and clinical program. The CHMP agreed that the proposed nonclinical and clinical program for DE-109 is likely to be sufficient to support a MAA for the chronic treatment of the proposed indication.

b) Procedure No. EMEA/H/SA/2340/2/2013/PA/II (September 2013): Clinical program. The CHMP had no objections to Santen initiating the MAA with one study provided that it provides convincing and robust data to support the indication for the chronic treatment of the proposed indication.

2.4. General comments on compliance with GMP, GLP, GCP

GMP

Drug substance

The activities performed are manufacturing of API, physical and chemical release and stability testing, primary labelling and packaging and storage.

A copy of the GMP certificate for drug substances, issued by Bezirksregierung Köln has been provided. Moreover, the site has been inspected for GMP compliance by the Food and Drug Administration (FDA).

Note that the drug substance Sirolimus is not included in the aforementioned certificate.

As per relevant guidance, a statement issued by the QP has been provided.

Drug Product

Manufacturers

The activities performed are manufacturing of drug product, Sterilization of container closure system, Bioburden testing, Stability testing (Appearance, Identity, Sirolimus and related substance assay, Moisture content, Extractable volume).

The manufacturing site is outside the EEA Community. The site has been inspected for GMP compliance by the FDA. The Company provides summary information as well as a proof of establishment current registration site.

Additional sites

The first manufacturing site is outside the EEA Community. It has provided a letter explaining the Company Regulatory History and it is routinely audited by FDA and the last inspection was with no observations. This manufacturing site is outside the EEA Community.

A second manufacturing site is outside the EEA Community. A letter explaining the Regulatory Inspection at PBL 2010 throught 2013 by FDA has been provided. The site has been inspected for GMP compliance by the FDA and the last inspection was dated in October 2013.

A third manufacturing site is outside the EEA Community. The RMS has accepted a copy of the current manufacturer authorisation as well as a copy of the GMP certificate as certification that acceptable standards of GMP are in place at this site for this product type, issued by MHRA

Batch release in UE

The Applicant has submitted a copy of the manufacturing authorisation. A proof of establishment of the applicant in the EEA has been provided as well as a copy of the GMP certificate issued by the competent authority of Finland (Finnish Medicine Agency)

It was noted that in accordance with EU regulation, the GMP compliance of DP manufacturers should be certified by an EU Authority.

It has been confirmed with the Supervisory Authority that all relevant sites have valid manufacturing authorizations or valid GMP certificates as appropriate.

The QA considers that no inspection is needed at this moment provided that the certificate(s) aforementioned are submitted prior to an opinion on this application.

Moreover, it is recommended that the corresponding protocols and reports of the analytical transference between the drug product manufacturer/developer and the entities proposed as responsible of stability testing (please see above) are revised in the subsequent inspections.

GLP

Safety pharmacology, toxicokinetics and pivotal toxicology studies were conducted in compliance with GLP regulations.

GCP

The pivotal study was conducted in accordance with the study protocol and protocol amendments, Good Clinical Practice (GCP), International Conference on Harmonization (ICH) of technical requirements for registration of pharmaceuticals for human use guidelines, and Santen's standard operating procedures (SOPs) for clinical investigation. Compliance with these requirements is

consistent with the ethical principles that have their origins in the Declaration of Helsinki (Declaration of Helsinki, 2008).

The GCP inspection conducted at 2 sites of the pivotal trial should be reflected in the overview, e.g. as follows: '*A request for GCP inspection was adopted for the clinical trial with protocol number 32-007. Two investigator sites in India and the sponsor site in the USA were inspected and the final integrated inspection report (IIR) was issued on 10 September 2015. The final IIR stated that the data obtained at the sites inspected are reliable to be accepted as support of the Marketing Authorisation Application*.'

2.5. Type of application and other comments on the submitted dossier

- Legal basis

This application concerns a centralised procedure under Mandatory scope "Article 3(1) of Regulation (EC) No 726/2004)" Annex (4) (Orphan designated medicinal product). The application is submitted in accordance with article 8(3) Directive 2001/83/EC.

Orphan drug designation has been granted to Opsiria (sirolimus) on 30 August 2011, for the treatment of chronic NIU-PS (EU/3/11/898).

- Conditional approval/Approval under exceptional circumstances

N/A

- Accelerated procedure

N/A

- Biosimilar application

N/A

- CHMP guidelines/Scientific Advice

See above.

- 1 year data exclusivity

N/A

- Significance of paediatric studies

The Applicant has developed a Paediatric Development Plan (PIP), which was agreed by the PDCO on 2nd April 2014 (PIP Opinion No EMA/PDCO/730889/2013). The PDCO, having assessed the proposed PIP, granted a waiver for the paediatric population from birth to less than 6 years on the grounds that sirolimus does not represent a significant therapeutic benefit as clinical studies are not feasible. The completion of the PIP for sirolimus has been deferred till December 2019.

3. Scientific overview and discussion

3.1. Quality aspects

3.1.1. Introduction

Opsiria is a non-aqueous, preservative-free, sterile solution for intravitreal injection.

It is intended to be administered using a sterile single-use syringe.

Opsiria is provided in a single-use, Type I glass vial containing 0.3mL of formulation comprised of sirolimus (22 mg/mL).

3.1.2. Active Substance

General Information

Rapamycin is a macrolide compound that acts by selectively blocking the transcriptional activation of cytokines thereby inhibiting cytokine production. It is bioactive only when bound to immunophilins. Rapamycin is a potent immunosuppressant.

Moreover, rapamycin possesses both antifungal and antineoplastic properties.

Manufacture, characterisation and process controls

Note that this ASMF has been assessed. The corresponding list of changes between versions has been provided.

The drug substance is adequately characterized and properties are suitably described.

Since it is obtained by fermentation, adherence to Ph. Eur. monograph “Products of fermentation” has been provided.

The manufacturing process has been adequately described**.** Critical steps and corresponding in-process controls have been defined to ensure quality of the final substance. In-process controls performed during the synthesis are suitable to control the reaction progress. Specifications for solvents and reagents have been established however two clarification points are pending in RP.

Specification

To date no official monograph for Rapamycin is available hence its specifications have been set with consideration to ICH Q6A (Specifications) and ICH Q3B (Impurities: Drug Products).

.The finished product release specifications include appropriate tests: appearance, identification (HPLC retention time and IR), and specific rotation, and water content, residue on ignition, heavy metals, chromatographic purity, weight-based assay and residual solvents.

Furthermore two additional tests, Endotoxin and Microbial enumeration test according to USP Chapters <85> and <61>, respectively are also established for customer’s specification.

The parameters and limits are in general acceptable in view of the various European guidelines.

Based on information provided BET limit in DS should be set (and justified) in accordance to endotoxin limits in DP

The analytical procedures used to control the drug substance have been described and validated although some additional information is still requested.

Batch analytical data demonstrating compliance with the drug substance specifications have been provided.

Stability

The company argues that there is no obvious degradation and to assure the quality of Rapamycin and demonstrates with results satisfactory the refrigerated condition (2º-8ºC).

Comparability exercise for Active Substance

N/A

3.1.3. Finished Medicinal Product

Description of the product and Pharmaceutical Development

Opsiria is provided in a single-use Type I glass vial containing 0.3mL of formulation comprised of sirolimus (22 mg/mL)

The company declares that the singles-use components (0.25 mL syringe, 21C x 1½" needle for withdrawal of the vial contents, and 30G x ½" injection needle) are provided separated, for the convenience of the physician.

However, the CHMP consider that they should be included in the package. Note that this is the case of similar drug products registered by centralized procedure, where the difficulties linked to the volume to be administered led to the use of specific medical devices

The excipients are commonly used.

Manufacture of the product and process controls

From a pharmaceutical point of view, the solution dosage form was selected due to its homogeneous nature, and it is relatively easy to manufacture and administer via different routes.

The narrative description of the manufacturing process and the manufacturing process flow diagram, have been provided. The sterility of the drug product is assured by sterilization of the product by sterile filtration through 0.2 µm filters, subsequent aseptic filling into sterile vials and sealing of the container closure system. With the design of a single-use fill configuration, no preservative is needed to maintain the sterility of the drug product after being opened. According to, the decision tree for non-aqueous products in EMA CPMP/QWP/054/098 corr, the company should provide results confirming that dry heat with an alternative combination of time and temperature is not possible either hence. More detailed justification of the choice of sterilisation method is required.

In general, the container closure system has been acceptably studied, although some issues remain to be resolved.

Microbiological attributes have been detailed, although the proposed endotoxin limit should be further discussed and a stricter limit applied if considered necessary. Note that this fact might affect BET limit (as well as analytical procedure and validation) in excipients.

In general, the excipients meet all requirements specified in the respective monograph. For nitrogen some information is missing.

The applicant clarifies that only one batch size is requested. The information for the other size will be deleted.

The DP is designed for a single use, thus preservative is not required in the drug product.

Long-term stability studies of the drug product are referred as support of the compatibility of the excipients with the drug substance.

Product specification

The finished product specifications have been proposed with consideration to ICH Q6A (Specifications) and ICH Q3B (Impurities: Drug Products). They are considered generally acceptable with only minor changes recommended.

The company explains that only one set of impurity specifications for sirolimus applies to both ASMF and DP manufacturer

The presented impurity limits comply with the requirements of EMA/CHMP/CVMP/QWP/199250/2009 corr Guideline on setting specifications for related impurities in antibiotics, except for the limit for impurity A, for which acceptable toxicological data have been presented.

The endotoxin limit should be further discussed and a stricter limit applied, if considered necessary. Note that this might affect BET limit as well as analytical procedure and validation

The analytical procedures are described and validated. However some additional information concerning method descriptions need to be submitted. Several issues concerning method validations remain to be solved.

The analytical results provided up to date for drug product batches support the satisfactory quality of the product.

Stability of the product

Opsiria (DE-109 injectable solution) is filled in a single use container closure system.,

The proposed shelf life was considered acceptable. . However some points for clarification have been raised and should be resolved before concluding on the shelf life and storage conditions.

Comparability exercise for Finished Medicinal Drug Product

N/A

Adventitious agents

N/A

GMO

N/A

3.1.4. Discussion on chemical, pharmaceutical and biological aspects

In general, information on development, manufacture and control of the drug substance have been presented in a satisfactory manner.

The specification for sirolimus set by the DP manufacturer should be amended to avoid the discrepancies with the specification applied by the API manufacturer.

Note that stability information on drug substance allows concluding that temperature does not cause degradation. However it is stored in a cold place (2ºC-8ºC).

In accordance with the DP manufacturing process depicted herein, some IPCs (Ethanol content and viscosity) are proposed to be carried out externally. The CHMP considers that this is not very practical. Note that ethanol content should be adjusted as a result of the measurement aforementioned.

3.1.5. Conclusions on the chemical, pharmaceutical and biological aspects

A recommendation for a marketing authorization can only be made following satisfactory resolution of pending issues

3.2. Non clinical aspects

3.2.1. Pharmacology

The pharmacological profile of sirolimus provided in this application was fully supported by published references. It is known to act via mTOR, exerting a variety of immunoregulatory effects (Sehgal, 1995; Napoli et al., 2001; Sehgal, 2003; Powell et al., 2012).

Focusing on uveitis, the Applicant showed the potential effect of sirolimus for this ocular disorder through some of the available peer-reviewed publications. These studies, both in vitro and in vivo, confirmed the action of rapamycin as therapy for uveitis indication. In the rat experimental autoimmune uveitis (EAU) model (Roberge et al., 1993), sirolimus was delivered to rats via continuous intravenous infusion for 14 days at concentrations ranging from 0.025 to 1 mg/kg/day, and complete inhibition of the disease was noted at 1 mg/kg/day of sirolimus. Other studies have provided additional evidence that sirolimus has a synergistic beneficial effect on uveitis outcomes in animal models of EAU when combined with either cyclosporine A, tacrolimus or steroid (Ikeda et al., 1997; Martin et al., 1995; Roberge et al., 1995). Sirolimus was also evaluated for its anti-inflammatory activities in the rabbit model of endotoxin-induced uveitis (Kulkarni, 1994; Ohia et al., 1992). Intramuscular administration of sirolimus at 10 mg/kg significantly inhibited inflammatory responses at 24 hours following endotoxin injections.

Contrarily, a publication by Zhang et al. (2012) proposes a paradoxical role of rapamycin in experimental autoimmune uveitis, in which low doses of rapamycin (1.5 μg, i.p. in mice) could exacerbate and prolong the disease. The Applicant further discussed this contradictory effect based on the experimental conditions published in the mentioned paper, referring to the differences found in severity of the disease model (histopathological socre) and route of administration (IVT vs. intraperitoneal administration).

Additional studies were performed with the aim to assess the safety pharmacology of sirolimus. No effect on cardiovascular, respiratory and central nervous systems was observed after administration of DE-109.

No secondary pharmacology and pharmacodynamic drug interaction studies were performed with sirolimus. Based on the available data, no toxic effect on safety pharmacology systems is expected after IVT injection of sirolimus at the proposed dose.

3.2.2. Pharmacokinetics

Levels of sirolimus were evaluated by using validated analytical methods (liquid chromatography-tandem mass spectrometry), as stated by the Applicant. No autoradiographic studies were performed, which is considered unusual, since is the most common method to study the local distribution of active substances.

The pharmacokinetic (PK) profile of sirolimus was mainly characterized in rabbits and monkeys after single or repeated doses (IVT injection). The aim of these PK studies was to evaluate the local absorption, distribution and elimination of sirolimus. This approach is reasonable, since the PK profile of sirolimus after oral administration was extensively reported during the development of Rapamune™. In terms of IVT administration and from the PK viewpoint, sirolimus was highly compartmentalised throughout different eye structures. Based on the local administration studies, the Applicant assumed that sirolimus reached the target tissue (choroid/retina). The mechanism provided by the Applicant suggests that after IVT injection, a viscous droplet is formed. Sirolimus precipitates and forms a depot in the vitrous humor. From this depot, it diffuses to the remaining ocular tissues, notably to the retina/choroid. Finally, it is eliminated via incorporation into the systemic circulation from the vasculature in the retina/choroid. The proposed behaviour of sirolimus after IVT injection could be considered as acceptable, although some concerns were voiced regarding to this concept.

Sirolimus has been reported to be a hydrophobic compound and sensitive to temperature, light and pH [Ferron and Jusko. Species differences in sirolimus stability in humans, rabbits and rats. Drug Metab Dispos. 1998 Jan; 26(1):83-4)]. In this sense, the chemical stability of sirolimus during 8 weeks was further discussed from the results of a study performed in rabbit vitreous humor collected after IVT injection with Opsiria. The main compound found after an 8-week period form administration was sirolimus (95%), followed by secosirolimus (4%). This result could support that sirolimus degrades slower in the intravitreal depot than in the aqueous environment.

Another concern arose from the explanation given for the reduced efficacy observed at higher doses (880 μg) than the intended dose for clinical practice (440 μg). The Applicant proposed that larger doses would form a bigger depot, which disperses drug particles in the ocular tissues. Such flowing particles would be responsible for a transient innate immune response resulting in a reduction of efficacy. Given the absence of explanatory studies supporting this rationale, additional data showing a relationship between dose and particle formation were submitted. A representative figure shows the depot occurred after receiving a high dose of sirolimus (880 μg/eye). It was observed that a large drug depot was formed, which could explain the inflammatory response and the loss of efficacy reported at higher dose levels. Furthermore, the relationship between local levels of sirolimus and dose levels administered was shown in a new table. It contained the main pharmacokinetic parameters (C_{max}, AUC, C_{av}, time above the minimally effective dose, mean residence time and elimination half-life) based on the administered dose level (IVT in rabbits). It was observed that sirolimus concentration in the target area (retina/choroid) was above the minimally effective concentration from the dose level of 132 μg/eye.

Additional in vitro studies revealed no binding of sirolimus to melanin. No additional drug-drug-interaction (DDIs) studies were performed with sirolimus, since local and systemic potential DDIs has been considered unlikely. No metabolism of sirolimus is expected in human eye. It is known that

sirolimus is mainly metabolized by cytochrome P450 3A (CYP3A) enzyme, and the expression of its different subtypes is very limited in the human eye.

The Applicant carried out initial studies by using SCT injection. Given the PK profile obtained, this route was thereafter discarded to clinical development.

3.2.3. Toxicology

Sirolimus was evaluated for its toxicological effects in rats, rabbits and monkeys. The toxicology assessment included single and repeated-dose toxicity studies after IVT injection or oral dosing, as well as genotoxicity and reprotoxicity studies after oral treatment with DE-109.

Single dose toxicity of sirolimus after IVT injection was investigated up to a dose of 220 μg/eye in rabbits (minimal and reversible vitreal inflammation and lenticular changes), while systemic lethal dose was established at >500 mg/Kg in rats after oral administration.

With respect to repeated-dose toxicity studies after IVT injection, rabbits and monkeys were used. Although the No-Observed-Adverse-Effect-Level (NOAEL) value was lower in the case of rabbits (minor incipient cataracts were reported at the dose of 66 μg/eye), monkey species was considered the most relevant species in terms of eye structure.

In the repeated-dose toxicity study performed in monkeys (40 weeks), local toxicity findings after IVT injection were reported at the dose level of 880 μg/eye (equivalent to 1760 μg/eye in humans, in accordance with a 2-fold difference in the vitreous volume of monkeys and humans). Such findings consisted in mild ocular inflammation (cellular infiltration and lenticular damage in the ciliary body, conjunctiva and vitrous). After the free dosing period, reversibility of the clinical signs were observed only at this time point. No interim data were reported in this study. Consequently, no comparison with the time course of the human ophtalmological reactions had been provided at the time of this report. Based on the absence of noticeable ophthalmic changes observed in the animals treated with the dose level of 440 μg/eye, the Applicant established a safety margin around 4-6-fold. However, an additional discussion regarding the basis for the calculation of safety margin was still required at the time of this report.

Toxicokinetic analysis revealed that whole blood levels of DE-109 after repeated dose were lower than the systemic immunosuppressive levels in humans. No systemic toxicity was reported after repeated dose of sirolimus. In the case of repeated oral administration, the NOAEL value was established at 0.25 mg/Kg/day for males and 1.0 mg/Kg/day for females.

Genotoxic potential was ruled out after the results of the 3-test standard battery. Carcinogenic potential was also considered as minimal, based on the low systemic exposure obtained after IVT administration. Regarding potential effects on reprotoxicity, the studies were performed after oral administration of DE-109 in rats and rabbits. Higher systemic levels of sirolimus were obtained as compared with IVT injection. The Applicant identified the NOAEL value for fertility at 0.5 mg/Kg/day in rats. NOAEL value for embryofetal toxicity was established at 0.5 mg/Kg/day in rats and 0.1 mg/Kg/day in rabbits (most sensitive species).

Sirolimus was determined to have no phototoxic potential in the neutral red uptake phototoxicity assay.

Alternatively to IVT administration, SCT was also investigated during the preclinical development of DE-109. In the case of SCT route of administration, the NOAEL value was established at < 220 μg/eye.

3.2.4. Ecotoxicity / environmental risk assessment

Regarding the documentation submitted by the Applicant, sirolimus $PEC_{surfacewater}$ value was below the action limit of 0.01 μg/L. The value reported for log K_{ow} was 4.56, although in line with EMA/CHMP/SWP/44609/2010, it should be experimentally determined. At this point, the results of the partition coefficient could not be confirmed. Therefore, estimation of exposure (phase I) is not completed, and no conlusions obtained.

3.2.5. Discussion and conclusions on non-clinical aspects

The Applicant described the mechanism of action and the rationale for using sirolimus in uveitis disease based on published references. The mechanism of action was previously elucidated and reported in a wide variety of *in vitro* systems and animal models.

The PK profile after IVT injection of sirolimus was presented. As such, the formation of a depot after IVT was proposed, which diffuses to the target tissue (choroid/retina). The relationship between ocular sirolimus concentration and dose level (IVT) was shown. A reduction of the efficacy at higher dose levels was also reported. This bell-shaped dose response was attributed to a local reaction caused by the drug depot formed after IVT administration of elevated dose levels (see also discussion on efficacy).

Sirolimus given IVT was generally well tolerated in the non-clinical species, although some findings were reported. In this regard, no data on the progression of the ophthalmological signs during the course of the 40-week repeated dose toxicity study performed in monkeys were reported. Consequently no comparison with human data was possible.

In addition, the ophthalmology safety margin obtained from these studies (4- to 6-fold) needs to be further discussed and justified.

Regarding the Enviromental Risk Assessment of sirolimus, experimental determination of log K_{ow} was missing and no conclusions from the phase I assessment coud be obtained at this point.

3.3. Clinical aspects

3.3.1. Pharmacokinetics

Sirolimus (Rapamune™) is currently available on the market for oral use. It is indicated for the prophylaxis of organ rejection in adult patients at low to moderate immunological risk receiving a renal transplant. Pharmacokinetics (PK) were characterised at doses up to 40mg administered to humans.

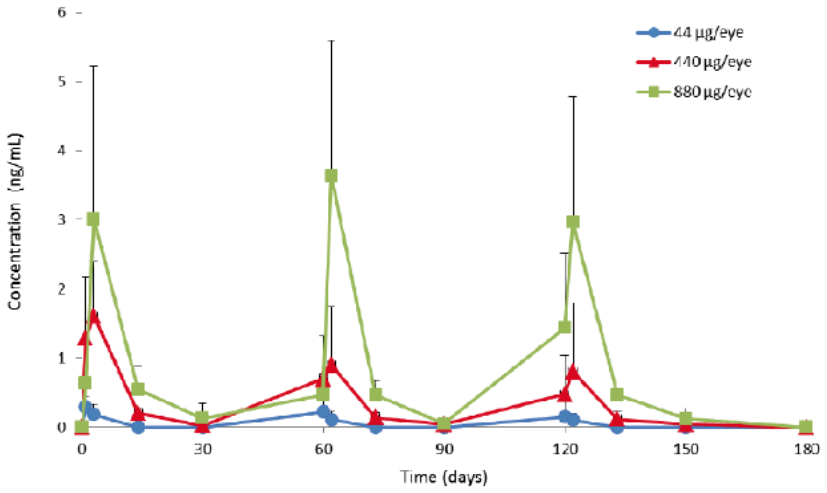
Ocular PK was not conducted in study subjects given limitation of ocular human sample availability. Information on ocular PK and PD data including tissue distribution and related pharmacology and toxicology was extrapolated from several nonclinical models. Tissue (retina/choroid) levels of sirolimus measured after IVT injection suggested that sirolimus reached the target tissue.

Systemic sirolimus levels in whole blood were measured in 6 Phase 1/2 studies conducted by the previous sponsor in subjects with diabetic macular edema (DME) or age-related macular degeneration (AMD), and in the Phase 3 SAKURA Study subjects with NIU-PS who were enrolled at Japan sites.

In the SAKURA 1 study, blood samples were collected before the first administration, at Days 1, 3, 14, 30, 60 (before the second administration), 60 (after the second administration), 62, 73, 90, 120 (after the third administration), 122, 133, 150, and at Month 6 (before the fourth administration).

These data provide indirect information about sirolimus disposition in the eye. In addition to the dose, other factors such as the dissolution rate or the solubility of the formulation may have also a relevant influence in the local distribution and exposure to the product.

Figure 1: Mean Sirolimus Concentrations in Human Blood Following IVT Injection of DE-109 Injectable Solution



Systemic PK profiles following IVT injection of DE-109 were compared with that following oral administration of sirolimus in clinical studies (Kahan et al., 2000). A single oral administration of 2 mg sirolimus yields a Cmax of 16.9 ng/ml with AUC_{0-24} of 209.8 ng·hr/ml. In three clinical studies including the SAKURA study in NIU-PS and two other ocular indications (AMD and DME), a single IVT injection of DE-109 resulted in Cmax lower than 3.06 ng/ml and these sirolimus levels subsequently declined over time.

Systemic sirolimus concentrations remained well below the systemic immunosuppressive trough level throughout the study period. When AUCs were compared between IVT injection in the SAKURA study (estimated from 0 through 60 days) and oral administration (assuming that sirolimus was given orally for 60 days to maintain therapeutic effects with minimal toxicity), systemic exposure following IVT administration of the 440 and 880 µg doses was 3% and 6% of that following 2 mg daily oral sirolimus administration. All measured mean Cmax were below the systemic trough level of 8 ng/mL generally associated with systemic immunosuppression (Saunders et al., 2001).

No specific information is available on relevant aspects such as ocular and non-ocular interactions or PK activity in special population.

DDIs and genetic interactions for oral administration of sirolimus are well characterized so that one can predict potential systemic DDIs between DE-109 and other concomitant drugs based on the evidence for systemic use of sirolimus. However, no or little ocular roles for CYP enzymes and P-glycoprotein (P-gp) and limited systemic exposure of sirolimus following IVT injection reveal that concomitant use of other local and systemic drugs with IVT injection of DE-109 may have a much less impact on ocular and systemic sirolimus concentrations than with oral administration of sirolimus. There was no clinical evidence of systemic DDIs observed in the SAKURA Study.

Similarly, the PK activity of sirolimus has been determined following oral administration in healthy subjects, pediatric patients, hepatically-impaired patients, and kidney transplant patients for Rapamune™. However, taking into account the existing information from the oral form and the limited systemic exposure, no additional risks are expected with the IVT administration of sirolimus.

3.3.2. Pharmacodynamics

No pharmacodynamic studies have been performed. The mechanism of action of sirolimus is well known and described in the scientific literature.

Sirolimus is an inhibitor of the mammalian target of rapamycin (mTOR), which is a multifunctional serine/threonine protein kinase and a downstream target for phosphatidylinositol-3 kinase (PI3K) signaling pathway coupled with cytokine receptors and insulin/insulin-like growth factor receptors. Sirolimus specifically binds to the intracellular immunophilin 12-kDa FK-506 binding protein (FKBP12). This immunophilin FKBP12 is the same target protein for tacrolimus, whereas immunophilin cyclophilin is the target protein for cyclosporine A. The immunophilin-tacrolimus/cyclosporine A complexes suppress T-cell activation through inhibition of calcineurin activity, a protein phosphatase that stimulates cytokine production mediated by nuclear factor of activated T-cells (NFAT). In contrast, the sirolimus-FKBP12 complex inhibits mTOR activity, but not calcineurin activity, resulting in suppression of T-cell, B-cell and dendritic cell functions (Powell et al., 2012).

Although widely regarded as an immunosuppressant, recent findings have clarified that sirolimus is more precisely viewed as an important regulator of immune function (Powell et al., 2012) Emerging evidence suggests that sirolimus promotes immune tolerance by inducing CD4+Fox3+ regulatory T-cells (Treg), which may also contribute to the chronic treatment of NIU-PS with DE-109 because of the potential dysfunction of Treg in autoimmune diseases (Bolon, 2012; Caspi, 2010; Cobbold, 2013; Powell et al., 2012).

3.3.3. Discussion on clinical pharmacology

Sirolimus was readily absorbed and steadily eliminated following IVT administration of 44 µg, 440 µg, and 880 µg doses in SAKURA Study 1 subjects. Exposure to sirolimus, reflected by mean Cmax and area under the curve (AUC) values, generally increased in a dose-proportional manner. Exposure to sirolimus was similar between the first and third administration indicating no accumulation of sirolimus following multiple dosing every 60 days. The systemic exposure when sirolimus is IVT administered is well below (3-6%) the concentrations achieved after oral administration.

No pharmacodynamic studies have been performed. The mechanism of action of sirolimus is well known and described in the scientific literature. The activity in non-infectious uveitis is based on the anti-inflammatory and immunoregulatory effects already claimed when it is used in the prevention of organ rejection in transplanted patients.

Whereas systemic exposure to sirolimus after IVT administration increases in a dose-proportional manner no linear effect has been observed. Several mechanisms have been proposed by the Applicant to explain this pattern (tissular saturation at higher dose, local non-specific immune reaction to remaining drug particles in the ocular tissues, toxic effect masking efficacy). Although some of these hypotheses have certain support from non-clinical studies, further work appears necessary for the arguments to be sufficiently convincing.

3.3.4. Clinical efficacy

The efficacy of sirolimus (DE-109) in the treatment of non-infectious uveitis of the posterior segment of the eye was evaluated in the SAKURA study.

The SAKURA clinical development program consists of two studies being conducted under the same protocol in 17 countries worldwide. Study 1 includes subjects enrolled and randomized through 31 March 2013 (N=347), while Study 2 includes subjects enrolled and randomized on or after 1 April 2013 (enrollment is currently open). The second SAKURA Study was enrolling subjects at the time of this report and was not part of this MAA.

Three doses of DE-109 (44 µg, 440 µg, and 880 µg doses) were tested in the clinical program. The overall duration of the SAKURA Study is 24 months.

Table 1: Description of Clinical Efficacy Study (SAKURA Study)

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Phase 3	32-007 SAKURA STUDY 1	5.3.5.3	Evaluate the safety and efficacy of intravitreal injection of three doses of DE-109 (44 µg, 440 µg, 880 µg) for the treatment of active, non-infectious uveitis of the posterior segment of the eye. Evaluate the long term safety of multiple intravitreal injections of 880 µg dose of DE-109. Evaluate the durability of effect of 880 µg dose(s) of DE-109.	Multi-Center, Randomized, Double-Masked, Clinical Study	Batch number: 0.2% DE-109 injectable solution (used for 44µg dose); batch number 3-FIN-1094 2% DE-109 injectable solution (used for 440µg dose); batch number 3-FIN-1029 4% DE-109 injectable solution (used for 880µg dose); batch number 3-FIN-1031 4% DE-109 injectable solution (used for 880µg dose); batch number 3-FIN-1338 Administered in 20µL IVT injection every 2 months for 6 doses, then prn between Month 12 – 24.	347	Subjects with active non-infectious uveitis affecting the posterior segment of the eye	24 Months	Ongoing. Interim report through Month 12

In addition data from other studies are provided:

- Sirolimus as a Therapeutic Approach for Uveitis (SAVE) study, a proof-of concept, open-label, randomized study that assessed the safety, tolerability, and bioactivity of intravitreal (IVT) and subconjunctival (SCT) injections of DE-109 in 30 patients with non-infectious uveitis.
- Eight legacy studies were conducted by MacuSight (the previous sponsor). Three of 8 legacy studies in subjects with diabetic macular edema and age-related macular degeneration who received IVT DE-109 are presented in the safety analysis of DE-109.

Dose-response studies and main clinical studies

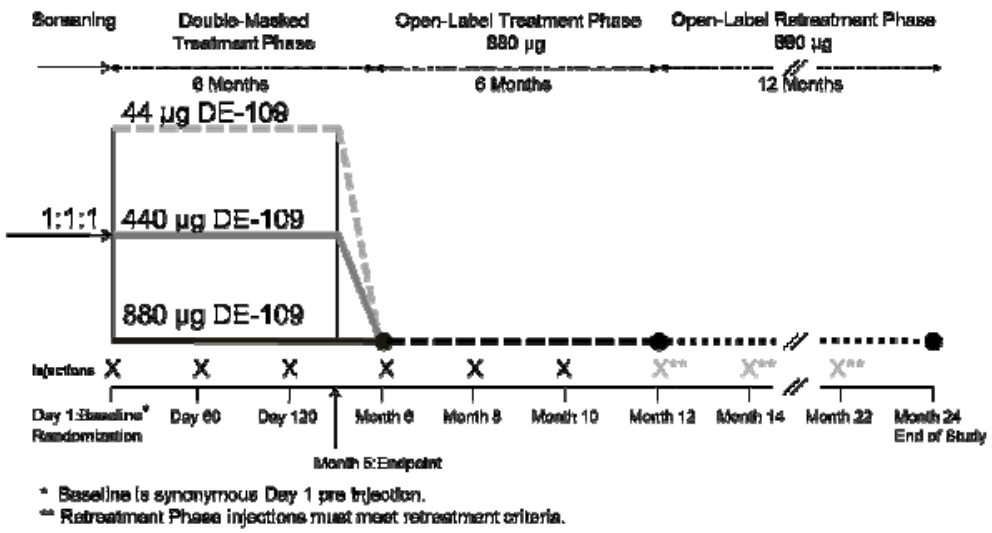
No dose-response studies were conducted. The selection of doses for SAKURA study was based on pK and toxicology data from animal studies, IVT administration of sirolimus for other indications and the results from the "proof-of-concept" SAVE study. Three doses 44 µg, 440 µg and 880 µg were selected to be tested in the SAKURA Studies.

Summary of main efficacy results: SAKURA STUDY 1

SAKURA Study is a Phase 3, multinational, multicenter, randomized, Double-Masked studies assessing the safety and efficacy of the IVT injection of DE-109 administered every 2 months in subjects with active non-infectious uveitis of the posterior segment of the eye.

The study consists of a Screening Period (up to 30 days), a 6-month Double-Masked Treatment Period, a 6-month Open-Label Treatment Period, and a 1-year Open-Label Retreatment Period (Figure 1). Results for the SAKURA Study 1 through Month 12 (up to Study Day 390) form the basis of the Market Authorization Application (MAA) for DE-109 for the chronic treatment of patients with NIU-PS.

Figure 2 ıse 3 SAKURA Study Design Schematic



Study participants

Key Inclusion Criteria were:

- Males or females ≥18 years of age
- Diagnosis of active uveitis of the posterior segment based on the subject's medical history, history of present illness, ocular examination, review of systems, physical examination, and any relevant, pertinent laboratory evaluations. Active uveitis was defined as a > 1+ (excluding 1+) vitreous haze score (Standardized Uveitis Nomenclature [SUN] photographic scale) in the study eye
- Best corrected visual acuity (BCVA) letter score of 19 letters or more (20/400 Snellen equivalent) or better in study eye; vision ≥ 20/200 in the non-study eye

Key Exclusion Criteria were:

Ocular:

- Active infectious uveitis; primary diagnosis of anterior uveitis; ocular or periocular infection in either eye; history of herpetic infection
- Any implantable corticosteroid-eluting device; anticipated use of IVT injections or posterior subtenon steroids or treatment within 90 days prior to Day 1
- Central nervous system or ocular lymphoma; ocular malignancy in the either eye including choroidal melanoma
- Media opacity; pupillary dilation inadequate; any significant ocular disease that could compromise vision in the study eye
- Intraocular surgery within 90 days prior to Day 1 in the study eye; history of vitrectomy

Non-Ocular:

- Treatment with a monoclonal antibody or any other biologic therapy; immunosuppressive therapy other than prednisone or other corticosteroids for the treatment of uveitis within 30 days of the first study drug administration (Day 1)
- Known to be immunocompromised
- Active systemic sarcoidosis within the last 30 months
- History of other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease condition that contraindicates the use of an investigational drug, might affect the interpretation of the results of the study, or renders the subject at high risk for treatment complications
- Malignancy in remission for <5 years prior to study participation (except basal cell or squamous cell skin cancer, or treated melanoma of the skin <24 months since last treatment)

Treatments: Study subjects received one of the 3 doses of DE-109 during the 6-month Double-Masked Treatment Period. All doses were administered via IVT injection (20 µL)

- DE-109 44 µg (0.2% w/w sirolimus, 2.2 µg/µL)
- DE-109 440 µg (2.0% w/w sirolimus, 22 µg/µL)
- DE-109 880 µg (4.0% w/w sirolimus, 44 µg/µL)

Study subjects were treated with 880 µg doses of DE-109 every 2 months (Month 6, Month 8, and Month 10) during the Open-Label Treatment Period.

Study subjects who met clinical benefit criteria and elected to remain on the study for the second year were treated as needed, but no more frequently than a single 20 µL IVT injection every 2 months with DE-109 Open-Label 880 µg.

Systemic corticosteroid therapy at Baseline was only allowed for subjects who were already being treated with systemic corticosteroids. The corticosteroid was rapidly tapered. Patients who were rescued were considered treatment failures.

Outcomes:

Primary endpoint: Vitreous Haze (VH) 0 response, defined as having a VH score of 0 at Month 5 based on the modified Standardized Uveitis Nomenclature (SUN) photographic scale.

Key secondary endpoints:

- VH 0 or 2-unit response: Having a VH score of 0 or a decrease (improvement) of at least 2 units from baseline in VH score at Month 5 (modified SUN scale)
- VH 0 or 0.5+ response: Having a VH score of 0 or 0.5+ at Month 5 (modified SUN scale)
- Corticosteroid tapering success (for the Intent-to-Taper Population): The overall prednisone-equivalent dose being tapered off to ≤ 5 mg/day at Month 5

Other secondary endpoints:

- Month 6: VH 0 response; VH 0 or 2-unit response VH 0 or 0.5+ response.
- Change from baseline in VH score at Month 5 and Month 6
- Change from baseline in ETDRS best corrected visual acuity (BCVA) at Month 5
- Change from baseline in central retinal thickness at Month 5 as measured by optical coherence tomography (OCT)
- Change from baseline in the Visual Functioning Questionnaire-25 (VFQ-25) composite score at Month 5
- Use of rescue therapy before Month 5
- Time to rescue from randomization before Month 5

Sample size: a total of 348 subjects (116 subjects per group) would provide > 80% power to detect a difference of 16% in response rate between 44 µg DE-109 (with a response rate of 8%) and 440 µg or 880 µg DE-109 (with a response rate of 24%) using the Fisher's Exact test (two-sided, Bonferroni corrected $\alpha = 0.025$).

Statistical methods:

The following analysis populations were defined:

- Intent-To-Treat (ITT) Population: The ITT Population is comprised of all randomized subjects. The ITT Population is the analysis population for the primary analysis, performed with subjects as randomized.
- Safety Population: The Safety Population is comprised of the ITT subjects who received at least one injection of study drug. The Safety Population is the analysis population for the safety analyses, performed with subjects as treated.
- Per-Protocol (PP) Population: The PP Population is a subset of ITT population. Any subject who had a significant protocol violation could have altered his/her outcome to treatment will be excluded from the PP population. In addition, any subject with without the Month 5 VH score was excluded from the PP population. The PP Population is the analysis population for some sensitivity analyses performed with subjects as randomized.

- Intent-to-Taper Population: The Intent-to-Taper Population is a subset of the ITT Population and is comprised of all subjects who were taking systemic corticosteroid(s) at Day 1 (Baseline) with the overall prednisone-equivalent dose >5 mg/day. The Intent to-Taper Population is the analysis population for the analysis of corticosteroid tapering success performed with subjects as randomized.
- Pharmacokinetic (PK) Population: The PK Population includes subjects in the Safety Population with at least one post-injection PK assessment. The PK Population is the analysis population for PK analyses performed with subjects as treated.

The primary analysis of the primary endpoint was performed using the Fisher's Exact test, with missing data of subjects not rescued before Month 5 being imputed by the last observation carried forward (LOCF) approach. The Hochberg step-up procedure was followed to control the family-wise Type I error rate at the 0.05 level (two-sided). Subjects rescued before Month 5 were treated as non-responders.

The key secondary endpoint 'time-weighted treatment benefit index' was analyzed using the analysis of variance (ANOVA) with geographic region (Region 1: US and Latin America or Region 2: Rest of the World), baseline VH score of the study eye (1.5+, 2+, or '3+ or 4+'), and treatment as factors.

"Change from baseline in VH score at Month 5 (or Month 6)" and "change from baseline in BCVA at Month 5" was analyzed using the mixed-effects model for repeated measures (MMRM) on observed cases.

For the analysis of change from baseline in central retinal thickness at Month 5, the ANCOVA model included type of OCT machine (Cirrus, Spectralis, or Topcon) and treatment as factors and baseline score as a covariate. For the analysis of change from baseline in the NEI VFQ-25 composite score at Month 5, the ANCOVA model included geographic region (Region 1: US and Latin America or Region 2: Rest of the World), baseline VH score of the study eye (1.5+,2+, or '3+ or 4+'), and treatment as factors and baseline score as a covariate.

For each of these continuous endpoints, the least squares (LS) mean change from baseline in each DE-109 group with its standard error was reported. The LS mean difference for each treatment comparison with the 95% confidence interval (CI) and the unadjusted p-value was reported

To assess the robustness of the primary analysis results, the following sensitivity analyses were performed:

- The primary analysis was repeated on the PP Population
- The primary analysis was repeated on the ITT Population, with the missing data handled using one of the following approaches:
    - The LOCF approach for any ITT subject with missing VH score at Month 5
    - The worst-case scenario approach
- The Cochran-Mantel-Haenszel test stratified by geographic region
- A logistic mixed-effects model for repeated binary data (Lindstrom and Bates, 1990) was fitted on observed cases. The model will include geographic region (Region 1: US and Latin America or Region 2: Rest of the World), baseline VH score of the study eye (1.5+, 2+, '3+ or 4+'), treatment, visit, and treatment-by-visit as fixed effects and subject as a random effect. An unstructured (UN) covariance matrix was be used to model the within-subject errors. For subjects rescued before Month 6, all VH score of the study eye collected after the start date of rescue therapy will be excluded from the analysis. No formal interim analysis was planned.

Examination of Subgroups: To assess the homogeneity of treatment effects among subgroups, descriptive summaries of VH 0 response by age group (< 65 or ≥ 65 years), sex (male or female), race (White or non-White), country (US or non-US), region [US, Latin America, Europe and the Middle East (EMEA), India, or Japan], baseline VH score of the study eye (1.5+, 2+, or '3+ or 4+'), and intent-to-taper status at baseline (Yes or No) were conducted.

Results

A total of 347 subjects (348 study eyes) were randomized between 31 May 2011 and 31 March 2013. A female subject was enrolled twice in Study 1 and randomized to receive the 880 µg dose regimen each time (different eye). The study was conducted at 103 investigational sites in 15 countries. The majority of subjects were randomized in India (33.1%) or the US (31.7%). The remaining subjects were enrolled in 4 countries in Latin America (17.6%), Israel and 7 European countries (13.5%), and Japan (4.0%). Enrollment by region and country was generally balanced between treatment groups.

Table 2 Subject Disposition

	44/880* µg (N=117)	440/880* µg (N=114)	880/880* µg (N=117)	Overall (N=348)
Intent-to-Treat Population	117 (100.0%)	114 (100.0%)	116 (99.1%)	347 (99.7%)
Safety Population	117 (100.0%)	112 (98.2%)	117 (100.0%)	346 (99.4%)
Per-Protocol Population	92 (78.6%)	91 (79.8%)	95 (81.2%)	278 (79.9%)
Pharmacokinetic Population	3 (2.6%)	6 (5.3%)	5 (4.3%)	14 (4.0%)

Baseline data

Table 3 Subject Demographics (ITT Population)

	44 µg (N=117)	440 µg (N=114)	880 µg (N=116)	Overall (N=347)
Age at Randomization (years)				
n	117	114	116	347
Mean (SD)	45.71 (14.970)	46.50 (14.458)	47.39 (14.089)	46.53 (14.486)
Median	46.10	47.10	48.45	47.40
Min, Max	18.4, 83.6	18.1, 78.3	18.9, 74.3	18.1, 83.6
Age Group (years)				
< 65	104 (88.9%)	103 (90.4%)	99 (85.3%)	306 (88.2%)
≥65	13 (11.1%)	11 (9.6%)	17 (14.7%)	41 (11.8%)
Sex				
Male	52 (44.4%)	46 (40.4%)	41 (35.3%)	139 (40.1%)
Female	65 (55.6%)	68 (59.6%)	75 (64.7%)	208 (59.9%)
Females of Childbearing Potential[a]	32 (49.2%)	29 (42.6%)	29 (38.7%)	90 (43.3%)
Race				
White	54 (46.2%)	55 (48.2%)	55 (47.4%)	164 (47.3%)
Asian	44 (37.6%)	43 (37.7%)	45 (38.8%)	132 (38.0%)
Black or African American	8 (6.8%)	8 (7.0%)	8 (6.9%)	24 (6.9%)
American Indian or Alaska Native	0	0	3 (2.6%)	3 (0.9%)
Native Hawaiian or Other Pacific Islander	0	1 (0.9%)	0	1 (0.3%)
Multiple	5 (4.3%)	4 (3.5%)	2 (1.7%)	11 (3.2%)
Unknown	6 (5.1%)	3 (2.6%)	3 (2.6%)	12 (3.5%)
Ethnicity				
Hispanic or Latino	27 (23.1%)	24 (21.1%)	25 (21.6%)	76 (21.9%)
Not Hispanic or Latino	90 (76.9%)	87 (76.3%)	89 (76.7%)	266 (76.7%)
Unknown	0	3 (2.6%)	2 (1.7%)	5 (1.4%)

Refer to Table 14.1.2.1.

[a] 1 For females of childbearing potential in this study, the age at randomization ranged from 18.1 to 65.3 years. Each percentage was calculated with the number of females in the corresponding column as the denominator.

Table 4 Baseline Characteristics (ITT Population)

	44 µg (N=117)	440 µg (N=114)	880 µg (N=116)	Overall (N=347)
Baseline Vitreous Haze Score of Study Eye				
n	117	114	116	347
Mean (SD)	1.94 (0.503)	1.91 (0.442)	1.95 (0.484)	1.94 (0.477)
Median	2	2	2	2
1.5+	43 (36.8%)	44 (38.6%)	41 (35.3%)	128 (36.9%)
2+	61 (52.1%)	58 (50.9%)	61 (52.6%)	180 (51.9%)
3+	11 (9.4%)	12 (10.5%)	13 (11.2%)	36 (10.4%)
4+	2 (1.7%)	0 (0.0%)	1 (0.9%)	3 (0.9%)
Baseline Vitreous Haze Score of Fellow Eye				
n	117	114	114	345
Mean (SD)	0.65 (0.780)	0.64 (0.810)	0.68 (0.714)	0.66 (0.767)
Median	0.5	0.5	0.5	0.5
0	54 (46.2%)	53 (46.5%)	45 (39.5%)	152 (44.1%)
0.5+	20 (17.1%)	19 (16.7%)	20 (17.5%)	59 (17.1%)
1+	17 (14.5%)	23 (20.2%)	27 (23.7%)	67 (19.4%)
1.5+	12 (10.3%)	6 (5.3%)	8 (7.0%)	26 (7.5%)
2+	11 (9.4%)	9 (7.9%)	13 (11.4%)	33 (9.6%)
3+	3 (2.6%)	3 (2.6%)	1 (0.9%)	7 (2.0%)
4+	0	1 (0.9%)	0	1 (0.3%)
Laterality of Uveitis				
Bilateral	75 (64.1%)	78 (68.4%)	78 (67.2%)	231 (66.6%)
Unilateral	42 (35.9%)	36 (31.6%)	38 (32.8%)	116 (33.4%)
Etiology of Uveitis of Study Eye				
Idiopathic	93 (79.5%)	89 (78.1%)	88 (75.9%)	270 (77.8%)
Sarcoidosis	10 (8.5%)	9 (7.9%)	10 (8.6%)	29 (8.4%)
Vogt-Koyanagi-Harada syndrome	6 (5.1%)	5 (4.4%)	7 (6.0%)	18 (5.2%)
Birdshot Chorioretinopathy	1 (0.9%)	4 (3.5%)	4 (3.4%)	9 (2.6%)
Autoimmune	2 (1.7%)	3 (2.6%)	3 (2.6%)	8 (2.3%)
HLA B27+	1 (0.9%)	3 (2.6%)	1 (0.9%)	5 (1.4%)
Multifocal Choroiditis	2 (1.7%)	1 (0.9%)	0	3 (0.9%)
Serpiginous Chorioretinopathy	0	0	1 (0.9%)	1 (0.3%)
Cat Scratch Fever	0	0	1 (0.9%)	1 (0.3%)

	44 µg (N=117)	440 µg (N=114)	880 µg (N=116)	Overall (N=347)
Not Reported	2 (1.7%)	0	1 (0.9%)	3 (0.9%)
Anatomic Location of Uveitis of Study Eye[a]				
Intermediate	43 (36.8%)	37 (32.5%)	38 (32.8%)	118 (34.0%)
Posterior	37 (31.6%)	42 (36.8%)	39 (33.6%)	118 (34.0%)
Panuveitis	37 (31.6%)	35 (30.7%)	39 (33.6%)	111 (32.0%)
Months Since First diagnosis of Uveitis (Study Eye)[b]				
n	117	114	116	347
Mean (SD)	55.77 (74.614)	38.83 (47.278)	48.58 (66.297)	47.80 (64.074)
Median	29.50	21.80	25.75	26.20
Min, Max	0.1, 411.7	0.3, 212.4	0.1, 346.6	0.1, 411.7
Overall Prednisone-Equivalent Dose (Intent-to-Taper Population)[c]				
n	22	26	21	69
Mean (SD)	23.86 (14.469)	22.88 (13.850)	18.93 (10.355)	21.99 (13.079)
Median	20.00	18.75	17.50	20.00
Min, Max	7.5, 60.0	7.5, 50.0	7.5, 40.0	7.5, 60.0
Baseline Best-Corrected Visual Acuity of Study Eye (letters)				
n	117	114	116	347
Mean (SD)	63.6 (16.76)	67.7 (14.24)	64.6 (16.30)	65.3 (15.87)
Median	65	70	68	68
Min, Max	5.0, 92.0	30.0, 95.0	3.0, 90.0	3.0, 95.0

A total of 71.4% received concomitantly corticosteroids (at stable doses), and 69 patients (19.9%) were being treated with systemic corticosteroids with an overall prednisone-equivalent dose >5 mg/day.

Outcomes and estimation

Vitreous Haze Response Endpoints

Table 5: Primary and Key Secondary Efficacy Endpoints; Vitreous Haze Response Endpoints (Study Eye, ITT Population)

		44 µg (N=117)	440 µg (N=114)	880 µg (N=116)
Primary Endpoint				
VH 0 Response	n	117	114	116
	Responders, n (%)	12 (10.3%)	26 (22.8%)	19 (16.4%)
	Odds Ratio (95% CI)		2.6 (1.2, 5.9)	1.7 (0.7, 4.1)
	p-value (vs 44 µg)		0.0126	0.1823
	Adj. *p*-value[a]		0.0252	0.1823
Secondary Endpoints				
VH 0 or 2-Unit Response	n	117	114	116
	Responders, n (%)	19 (16.2%)	32 (28.1%)	22 (19.0%)
	Odds Ratio (95% CI)		2.0 (1.0, 4.0)	1.2 (0.6, 2.5)
	p-value (vs 44 µg)		0.0388	0.6097
VH 0 or 0.5+ Response	n	117	114	116
	Responders, n (%)	41 (35.0%)	60 (52.6%)	50 (43.1%)
	Odds Ratio (95% CI)		2.1 (1.2, 3.6)	1.4 (0.8, 2.5)
	p-value (vs 44 µg)		0.0081	0.2283

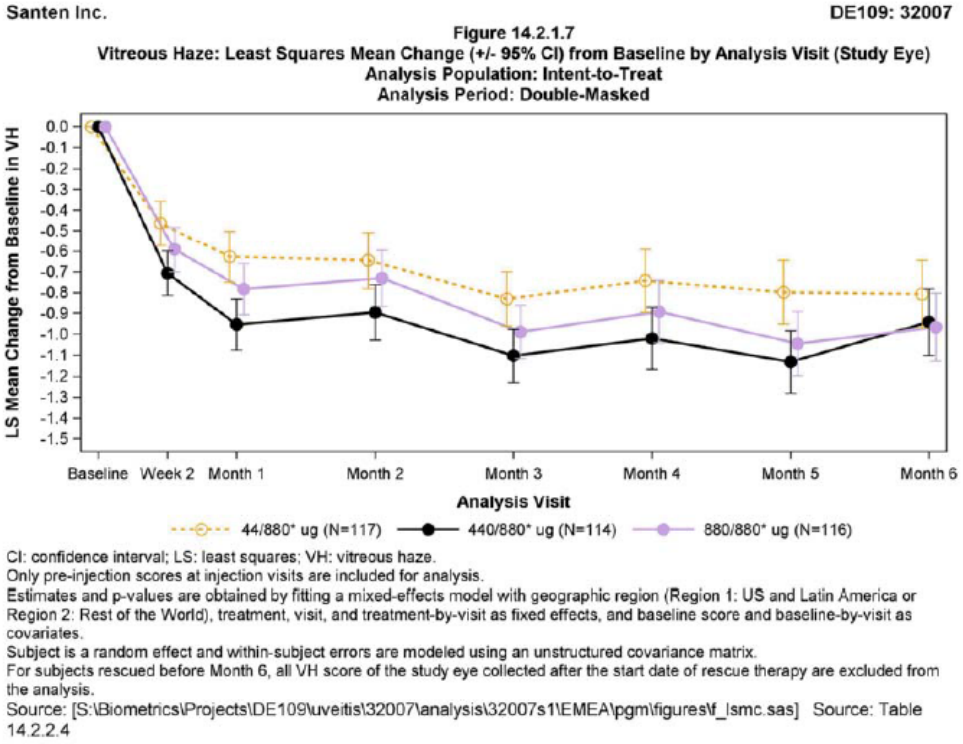
VH: vitreous haze; CI: confidence interval.

Note: For VH response endpoints, subjects rescued before Month 5 were treated as non-responders. For corticosteroid tapering success, subjects tapering rescued before Month 5 were treated as corticosteroid tapering failures. The missing data of subjects not rescued before Month 5 was imputed using the last-observation-carried-forward approach. Each treatment comparison was performed using Fisher's Exact test.

[a] P-values adjusted by Hochberg step-up procedure. An adjusted p-value < 0.05 indicates a statistically significant difference.

Similar results were shown in the PP analysis and in the several sensitivity analyses conducted.

Figure 3: **Vitreous Haze; Least Squares Mean Change (±95% CI) from Baseline by Analysis Visit (Study Eye) (Double-Masked Period till Month 6, ITT Population)**



Corticosteroid Taper Success Endpoints

Table 6 **Key Secondary Endpoint; Corticosteroid Tapering Success (Intent-to-Taper Population)**

	44 µg (N=22)	440 µg (N=26)	880 µg (N=21)
Successes, n (%)	14 (63.6%)	20 (76.9%)	14 (66.7%)
Odds Ratio (95% CI)		1.9 (0.5, 8.2)	1.1 (0.3, 4.8)
p-value (vs 44µg)		0.3551	1.0000

Key Secondary Endpoint: Time Weighted Treatment Benefit

The index was derived as the weighted sum of benefit indicators weighted by study month of visit. The TWTB Index = 0: no treatment benefit observed by Month 5, and the TWTB Index = 1 indicates benefit achieved at all post-baseline visits up to Month 5.

Table 7 Time Weighted Treatment Benefit[1] Index ANOVA (ITT Population)

	44 µg (N=117)	440 µg (N=114)	880 µg (N=116)
N	**117**	**114**	**116**
LS Mean (SE)	0.633 (0.0366)	0.763 (0.0371)	0.714 (0.0365)
LS Mean Diff (95% CI)		0.130 (0.035, 0.225)	0.081 (-0.013, 0.176)
p-value (vs 44 µg)		0.0072	0.0904

Refer to Table 14.2.2.21.
CI: confidence interval; LS: least squares; SE: standard error.
Time-weighted treatment benefit index was analyzed by fitting an ANOVA model with treatment, geographic region (Region 1: US and Latin America or Region 2: Rest of the World), and baseline VH score of the study eye (1.5+, 2+, or '3+ or 4+') as factors.

Best-Corrected Visual Acuity Outcomes

Visual acuity in the ITT Population as assessed with BCVA in the 440 µg dose group was slightly improved during the Double-Masked Treatment Period up to the Month 5 analysis visit.

Table 8 Summary of Subjects with Improved, Worsened, or Maintained Visual Acuity at Month 5 (ITT Population)

Change from Baseline in BCVA at Month 5 (ETDRS letters)	44 µg (N=105)	440 µg (N=107)	880 µg (N=105)
Subjects with Improvement of			
5 letters or more	42 (40.0%)	50 (46.7%)	43 (41.0%)
10 letters or more	20 (19.0%)	25 (23.4%)	28 (26.7%)
15 letters or more	12 (11.4%)	14 (13.1%)	10 (9.5%)
20 letters or more	7 (6.7%)	7 (6.5%)	7 (6.7%)
25 letters or more	6 (5.7%)	7 (6.5%)	4 (3.8%)
30 letters or more	4 (3.8%)	3 (2.8%)	3 (2.9%)
35 letters or more	1 (1.0%)	2 (1.9%)	3 (2.9%)
40 letters or more	1 (1.0%)	1 (0.9%)	2 (1.9%)
Subjects with Worsening of			
5 letters or more	22 (21.0%)	21 (19.6%)	21 (20.0%)
10 letters or more	13 (12.4%)	16 (15.0%)	12 (11.4%)
15 letters or more	8 (7.6%)	9 (8.4%)	8 (7.6%)
20 letters or more	5 (4.8%)	8 (7.5%)	5 (4.8%)
25 letters or more	5 (4.8%)	6 (5.6%)	4 (3.8%)
30 letters or more	2 (1.9%)	5 (4.7%)	2 (1.9%)
35 letters or more	1 (1.0%)	4 (3.7%)	2 (1.9%)
40 letters or more	1 (1.0%)	4 (3.7%)	2 (1.9%)
Subjects with Maintained BCVA			
Absolute Change <5 letters	41 (39.0%)	36 (33.6%)	41 (39.0%)

Refer to Table 14.2.3.9
BCVA: best-corrected visual acuity; ETDRS: Early Treatment Diabetic Retinopathy Study.
Missing data are not imputed for descriptive summaries

Central Retinal Thickness as Measured by Optical Coherence Tomography

Three different OCT machines were used in the study (Cirrus, Spectralis, and Topcon), thus pooling and interpreting the data is somewhat limited.

Subjects in the ITT Population had a mean CRT <300 microns in the study eye at baseline (298.15 microns in the 44 µg dose group, 295.41 microns in the 440 µg dose group and 291.65 microns in the 880 µg dose group). There were no clinically meaningful changes in the mean central retinal thickness in any of the 3 dose groups in the ITT or PP Populations. An analysis of change from baseline at Month 5 using LOCF Analysis of Covariance (ANCOVA) including type of OCT machine and treatment as factors showed no statistical difference between the 440 µg and 44 µg or between the 880 µg and 44 µg dose groups in the ITT or PP Populations.

Administration of Rescue Therapy Before Month 5

There were numerically favorable differences in the use of rescue therapy between the 440 µg and the 44 µg dose groups and between the 880 µg and 44 µg dose.

Table 9 **Analysis of Use of Rescue Therapy before Month 5 using Fisher's Exact Test (ITT Population)**

	44 µg (N=117)	440 µg (N=114)	880 µg (N=116)
n	117	114	116
Rescued, n (%)	26 (22.2%)	16 (14.0%)	21 (18.1%)
Odds Ratio (95% CI)		0.6 (0.3, 1.2)	0.8 (0.4, 1.5)
p-value (vs 44 µg)		0.1257	0.5143

Summary of main efficacy results

The following table summarizes the efficacy of the pivotal study (SAKURA) in the claimed indication.

SAKURA STUDYA Phase III, Multinational, Multicenter, Randomized, Double-Masked, Study Assessing the Safety and Efficacy of Intravitreal Injections of DE-109 (3 doses) for the Treatment of Active, Non-Infectious Uveitis of the Posterior Segment of the Eye		
Study identifier	32-007	
Design	Multinational, Multicenter, Randomized, Double-Masked, Phase 3	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	12 months 30 days screening period 1 year open-label re-treatement period
Hypothesis	Superiority: DE-109 administered via IVT injection at a dose of either 440 µg or 880 µg every 2 months would provide clinically meaningful improvement in the signs and symptoms of active NIU-PS, as compared with 44 µg DE-109	
Treatments groups	group 1	44 µg via IVT every 2 months for 3 doses, then 880 µg open-label every 2 months for 3 doses, number randomized=117
	group 2	440 µg via IVT every 2 months for 3 doses, then 880 µg open-label every 2 months for 3 doses<number randomized=114

	group 3		880 µg via IVT every 2 months for 3 doses, then 880 µg open-label every 2 months for 3 doses<number randomized=117
Endpoints and definitions	Primary endpoint	Vitreous haze (VH) 0 response rate	Having a VH score of 0 at Month 5 (SUN scale), reported as complete resolution of inflammation
	Secondary endpoint	VH0 or 2 unit response	Having a VH score of 0 or a decrease of at least 2 units from VH score at baseline by Month 5 (SUN scale).
	Secondary endpoint	Corticosteroid tapering success	Having successfully tapered corticosteroids from a prednisone-equivalent dose of > 5 mg to ≤ 5 mg/day at Month 5.
Database lock	NA		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to treat			
Descriptive statistics and estimate variability	Treatment group	44µg	440µg	880µg
	Number of subject	n=117	n=114	n=116
	Male/Female (%)	40.1% / 59.9%		
	Median age (ys, range)	46.10 (18.4, 83.6)	47.10 (18.1, 78.3)	48.45 (18.9, 74.3)
	overall subjects enrolled	in India (33.1%), the US (31.7%), Latin America (17.6%), Europe or the Middle East (13.5%), Japan (4.0%).		
	Idiopathic etiology of Uveitis n (%)	93 (79.5)	89 (78.1)	88 (75.9)
	Overall Prednisone−Equivalent Dose (mg/day) Min, max	7.5, 60.0	7.5, 50.0	7.5, 40.0
Effect estimate per comparison		Comparison groups: 440 ug vs 44 ug dose IVT	Comparison groups: 880 µg vs 44 ug dose group	
	Primary endpoint (VH0 Response	VH0 Response Rate: 22.8% vs 10.3 %	VH0 Response Rate: 16.4% vs 10.3%	

	rate)	after multiplicity adjustment	after multiplicity adjustment
		p-value= 0.0252, OR=2.6; 95% CI: 1.2, 5.9	p non significant
	Secondary endpoint Corticosteroid tapering success	Comparison groups:	44 µg (n=22), 440 µg (n=26), and 880 µg dose (n=21) groups
		Success rate:	63.6%, 76.9%, and 66.7%
		P-value:	not significant
	Secondary endpoint VH 0 or 2-unit responders	Comparison groups:	44 µg, 440 µg, and 880 µg dose groups
		Response rate:	16.2%, 28.1%, and 19.0%
		Odds Ratio (95% CI):	440ug vs 44µg : 2.0 (1.0, 4.0) 880ug vs 44µg : 1.2 (0.6, 2.5)
		P-value (adjusted):	440ug vs 44µg: 0.0081 880ug vs 44µg: 0.22830
Notes	Months Since First Diagnosis of Uveitis of Study Eye at Baseline: see separate Table 10 below		

- **Subgroup analyses**

Efficacy Results by Demographic Subgroups

Table 10: Number (%) of Subjects with VH Response of 0 at Month 5 by Treatment Group and Demographic Subgroup (LOCF1, ITT Population)

Demographic Characteristic/ Subgroup	44 µg		440 µg		880 µg	
	N	n (%)	N	n (%)	N	n (%)
Overall						
All Patients	117	12 (10.3)	114	26 (22.8)	116	19 (16.4)
Age at Randomization (years)						
<65	104	12 (11.5)	103	25 (24.3)	99	16 (16.2)
≥18 to <25	9	1 (11.1)	8	4 (50.0)	8	1 (12.5)
≥25 to <45	47	8 (17.0)	39	8 (20.5)	38	6 (15.8)
≥45 to <65	48	3 (6.3)	56	13 (23.2)	53	9 (17.0)
≥65	13	0	11	1 (9.1)	17	3 (17.6)
Gender						
Male	52	5 (9.6)	46	9 (19.6)	41	9 (22.0)
Female	65	7 (10.8)	68	17 (25.0)	75	10 (13.3)
Race						
White	54	7 (13.0)	55	12 (21.8)	55	12 (21.8)
Non-White	63	5 (7.9)	59	14 (23.7)	61	7 (11.5)
Black or African-American	8	0	8	2 (25.0)	8	0
Asian	44	4 (9.1)	43	11 (25.6)	45	6 (13.3)
Other	11	1 (9.1)	8	1 (12.5)	8	1 (12.5)
Geographic Region						
US	37	3 (8.1)	37	11 (29.7)	36	9 (25.0)
Non-US	80	9 (11.3)	77	15 (19.5)	80	10 (12.5)
Latin America	22	3 (13.6)	19	2 (10.5)	20	3 (15.0)
Europe and the Middle East	15	2 (13.3)	17	2 (11.8)	15	1 (6.7)
India	40	4 (10.0)	35	11 (31.4)	40	6 (15.0)
Japan	3	0	6	0	5	0

Efficacy Results by Other Intrinsic Factors

Table 11: Number (%) of Subjects with VH Response of 0 at Month 5 by Treatment Group and Baseline Characteristic Subgroup (LOCF1, ITT Population)

Baseline Characteristic/ Subgroup	44 µg		440 µg		880 µg	
	N	n (%)	N	n (%)	N	n (%)
Overall						
All Patients	117	12 (10.3)	114	26 (22.8)	116	19 (16.4)
Laterality of Uveitis						
Bilateral	75	5 (6.7)	78	16 (20.5)	78	10 (12.8)
Unilateral	42	7 (16.7)	36	10 (27.8)	38	9 (23.7)
Etiology of Uveitis						
Idiopathic	93	10 (10.8)	89	18 (20.2)	88	17 (19.3)
Vogt-Koyanagi-Harada Syndrome	6	1 (16.7)	5	1 (20.0)	7	0
Sarcoidosis	10	1 (10.0)	9	2 (22.2)	10	0
Birdshot chorioretinopathy	1	0	4	2 (50.0)	4	0
Other (excluding not reported)	5	0	7	3 (42.9)	6	2 (33.3)
Months Since First Diagnosis of Uveitis of Study Eye at Baseline						
<3	20	1 (5.0)	21	6 (28.6)	26	4 (15.4)
≥3 to <12	18	2 (11.1)	25	7 (28.0)	14	2 (14.3)
≥12 to <24	13	0	12	1 (8.3)	15	0
≥24	66	9 (13.6)	56	12 (21.4)	61	13 (21.3)
Baseline VH Score						
1.5+	43	6 (14.0)	44	17 (38.6)	41	12 (29.3)
≥2+	74	6 (8.1)	70	9 (12.9)	75	7 (9.3)
2+	61	6 (9.8)	58	8 (13.8)	61	6 (9.8)
3+ or 4+	13	0	12	1 (8.3)	14	1 (7.1)

Baseline BCVA (letters)						
<70	67	5 (7.5)	51	7 (13.7)	69	9 (13.0)
<50	19	1 (5.3)	15	1 (6.7)	17	1 (5.9)
≥50 to <70	48	4 (8.3)	36	6 (16.7)	52	8 (15.4)
≥70	50	7 (14.0)	63	19 (30.2)	47	10 (21.3)
≥70 to <85	45	5 (11.1)	52	14 (26.9)	36	10 (27.8)
≥85	5	2 (40.0)	11	5 (45.5)	11	0
Presence of Macular Edema at Baseline						
Yes (CRT ≥300 microns)	37	4 (10.8)	33	7 (21.2)	39	5 (12.8)
No (CRT <300 microns)	76	8 (10.5)	80	19 (23.8)	71	13 (18.3)
Yes (CRT ≥350 microns)	29	3 (10.3)	27	6 (22.2)	30	4 (13.3)
No (CRT <350 microns)	84	9 (10.7)	86	20 (23.3)	80	14 (17.5)
Use of IOP−Lowering Medication at Baseline						
Yes	17	2 (11.8)	21	3 (14.3)	18	0
No	100	10 (10.0)	93	23 (24.7)	98	19 (19.4)
Presence of Glaucoma at Baseline						
Yes	10	1 (10.0)	14	3 (21.4)	9	1 (11.1)
No	107	11 (10.3)	100	23 (23.0)	107	18 (16.8)
Use of Systemic Corticosteroid at Baseline						
Yes	24	1 (4.2)	32	9 (28.1)	26	4 (15.4)
No	93	11 (11.8)	82	17 (20.7)	90	15 (16.7)
Prior Vitrectomy						
Yes	1	1 (100.0)	3	1 (33.3)	1	0
No	116	11 (9.5)	111	25 (22.5)	115	19 (16.5)

Note: Subjects rescued before Month 5 were treated as nonresponders. In the LOCF1 analysis, missing Month 5 scores were imputed using the last observed score (or the pre-injection score if collected at an injection visit) for subjects not rescued before Month 5. The response status at Month 5 was determined based on the observed or imputed score.
BCVA=best-corrected visual acuity; CRT=central retinal thickness; IOP=intraocular pressure; LOCF=last observation carried forward; VH=vitreous haze

Efficacy Results by Extrinsic Factors

Table 12 **Number (%) of Subjects with VH Response of 0 at Month 5 by Treatment Group and Baseline Extrinsic Factor (LOCF2, ITT Population)**

Baseline Extrinsic Factor/Subgroup	44 µg		440 µg		880 µg	
	N	n (%)	N	n (%)	N	n (%)
Overall						
All Patients	117	16 (13.7)	114	33 (28.9)	116	23 (19.8)
Tapering Status at Month 5						
Success	14	0	20	7 (35.0)	14	4 (28.6)
Failure	8	1 (12.5)	6	3 (50.0)	7	2 (28.6)
Use of Rescue Therapy before Month 5						
Yes	26	4 (15.4)	16	7 (43.8)	21	4 (19.0)
No	91	12 (13.2)	98	26 (26.5)	95	19 (20.0)
Concomitant Medication before Month 5						
Systemic corticosteroid	34	2 (5.9)	37	14 (37.8)	36	7 (19.4)
Nonsystemic corticosteroid	16	3 (18.8)	22	10 (45.5)	24	3 (12.5)
Rescue immunosuppressant	3	1 (33.3)	3	2 (66.7)	1	0
Any of the three types	43	5 (11.6)	49	19 (38.8)	48	7 (14.6)
Use of IOP−Lowering Medication at Month 5						
Yes	26	7 (26.9)	22	5 (22.7)	25	3 (12.0)
No	91	9 (9.9)	92	28 (30.4)	91	20 (22.0)
Presence of Glaucoma at Month 5						
Yes	12	2 (16.7)	14	4 (28.6)	9	2 (22.2)
No	105	14 (13.3)	100	29 (29.0)	107	21 (19.6)

Note: In the LOCF2 analysis, LOCF1 was applied to each ITT subject who did not have a Month 5 score, but regardless of whether the subject was rescued before Month 5 or not.
IOP=intraocular pressure; LOCF=last observation carried forward; VH=vitreous haze

Subjects Without Anterior Uveitis or Panuveitis in the Study Eye at Baseline

A total of 217/347 (62.5%) subjects randomized in the SAKURA study had a diagnosis of intermediate or posterior uveitis, while the remaining 130/347 (37.5%) subjects had a diagnosis including anterior segment involvement, or panuveitis.

Table 13 **VH Response of 0 at Month 5 by Treatment Group (ITT [LOCF1] and PP Populations, Overall and Excluding Subjects with Anterior Uveitis or Panuveitis)**

	All Subjects			Excluding Subjects with Anterior Uveitis or Panuveitis		
Population/Finding	**44 µg**	**440 µg**	**880 µg**	**44 µg**	**440 µg**	**880 µg**
ITT Population						
N	117	114	116	76	70	71
Responders, n (%)	12 (10.3)	26 (22.8)	19 (16.4)	7 (9.2)	21 (30.0)	12 (16.9)
Odds Ratio (95% CI)		2.6 (1.2, 5.9)	1.7 (0.7, 4.1)		4.2 (1.6, 12.6)	2.0 (0.7, 6.4)
p-value[a]		0.0126	0.1823		0.0016	0.2196
PP Population						
N	92	91	95	62	57	58
Responders, n (%)	10 (10.9)	22 (24.2)	18 (18.9)	6 (9.7)	19 (33.3)	12 (20.7)
Odds Ratio (95% CI)		2.6 (1.1, 6.6)	1.9 (0.8, 4.9)		4.7 (1.6, 15.4)	2.4 (0.8, 8.5)
p-value[a]		0.0201	0.1522		0.0029	0.1251

[a] Fisher's Exact test

Note: Subjects rescued before Month 5 were treated as nonresponders. In the LOCF1 analysis, missing Month 5 scores were imputed using the last observed score (or the pre-injection score if collected at an injection visit) for subjects not rescued before Month 5. The response status at Month 5 was determined based on the observed or imputed score.

CI=confidence interval; LOCF=last observation carried forward; PP=per-protocol; VH=vitreous haze

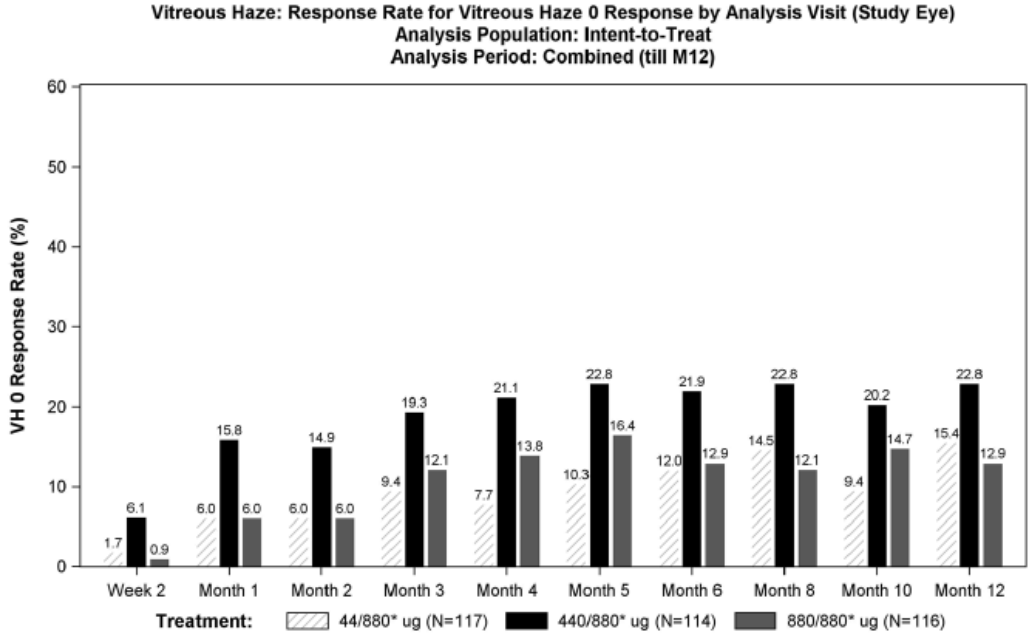
Table 14 **VH 0 or 2-Unit Responders and VH 0 or 0.5+ Responders at Month 5 by Treatment Group (ITT [LOCF1] and Population, Overall and Excluding Subjects with Anterior Uveitis or Panuveitis)**

	All Subjects			Excluding Subjects with Anterior Uveitis or Panuveitis		
Population/Finding	**44 µg**	**440 µg**	**880 µg**	**44 µg**	**440 µg**	**880 µg**
VH 0 or 2-Unit Responders						
N	117	114	116	76	70	71
Responders, n (%)	19 (16.2)	32 (28.1)	22 (19.0)	12 (15.8)	25 (35.7)	14 (19.7)
Odds Ratio (95% CI)		2.0 (1.0, 4.0)	1.2 (0.6, 2.5)		3.0 (1.3, 7.1)	1.3 (0.5, 3.4)
p-value[a]		0.0388	0.6097		0.0075	0.6660
VH 0 or 0.5+ Responders						
N	117	114	116	76	70	71
Responders, n (%)	41 (35.0)	60 (52.6)	50 (43.1)	25 (32.9)	42 (60.0)	33 (46.5)
Odds Ratio (95% CI)		2.1 (1.2, 3.6)	1.4 (0.8, 2.5)		3.1 (1.5, 6.4)	1.8 (0.9, 3.7)
p-value[a]		0.0081	0.2283		0.0015	0.1283

- **Persistence of Efficacy**

Overall, the majority of subjects were in the study at Month 12 (301/348, 86.5% study eyes).

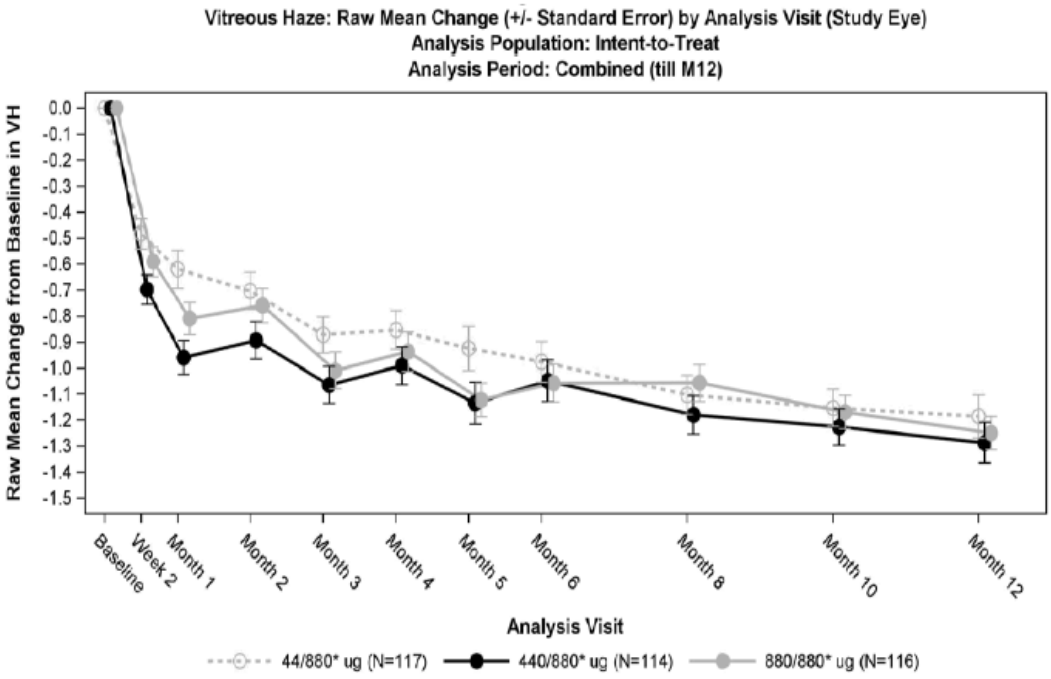
Figure 4 **VH Response of 0 through Month 12 by Treatment Group (ITT [LOCF] Population)**



VH: vitreous haze.
*Treatment group is displayed in the format of 'XXX/YYY µg', where XXX denotes the double-masked dose and YYY denotes the open-label dose.

Note: Subjects rescued before Month 5 were treated as nonresponders.
LOCF=last observation carried forward; VH=vitreous haze

Figure 5 **Mean Change (+/- Standard Error) from Baseline in VH Score through Month 12 by Treatment Group (ITT Population)**



VH: vitreous haze.
Missing data are not imputed for descriptive summaries.
*Treatment group is displayed in the format of 'XXX/YYY µg', where XXX denotes the double-masked dose and YYY denotes the open-label dose.

In response to a question by the CHMP, the Applicant provided additional results from 88 patients receiving Double-Masked treatment for 12 months, which provides long-term data on the use of Opsiria. These patients received one of 3 doses (44 µg, 440 µg or 880 µg) every 2 months for 6 months (Double-Masked Period) and then were treated on an "as needed" PRN basis for an additional 6 months (Double-Masked PRN Period). The number of patients treated per arm is as follows: 44 µg dose: 27 patients; 440 µg dose: 31 patients; 880 µg dose: 30 patients.

In the Month 6 through Month 12 Double-Masked PRN Period, the response rates for the VH 0 and VH 0 or 0.5+ endpoints, without the use of rescue therapy, were fairly well maintained (29.2% and 45.8%, respectively) and demonstrate the long-term ability of Opsiria to control inflammation (Figure 10 and Figure 11). Additionally, patients randomized to Opsiria required the fewest re-treatments (9/31, 29.0%) during the 6 month PRN Period when compared to subjects in the 44 µg and 880 µg dose groups (9/27, 33.3% and 15/30, 50.0%, respectively). The median time to retreatment was similar between the 3 dose groups and was approximately 69 days. Therefore, the suggested posology of Opsiria was bi-monthly administration.

Figure 6 **VH 0 Response Rate by Analyses Visit (Non-Rescued Subjects, Study Eye)**

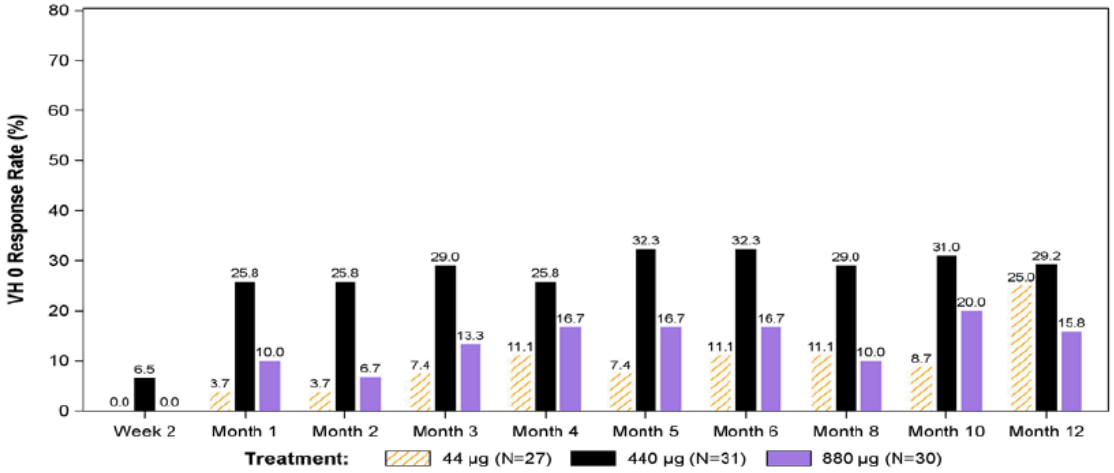
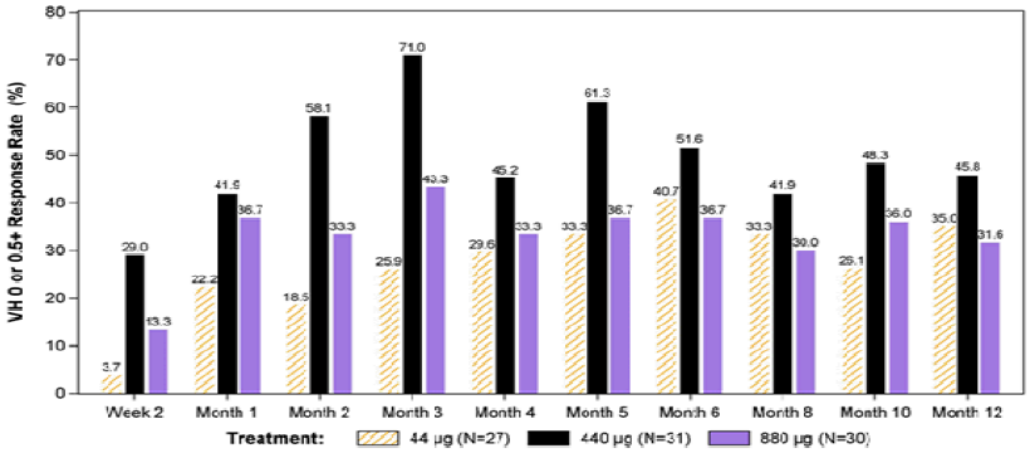


Figure 7 **VH 0 or 0.5+ Response Rate by Analyses Visit (Non-Rescued Subjects, Study Eye)**



Supportive study

- Sirolimus as a Therapeutic Approach for Uveitis (SAVE) study (Nguyen et al., 2013)

This was a proof-ofconcept, open-label, randomized study that assessed the safety, tolerability, and bioactivity of intravitreal (IVT) and subconjunctival (SCT) injections of DE-109 in patients with non-infectious intermediate uveitis, posterior uveitis, or panuveitis.

Patients were stratified at baseline into three categories: (1) active disease and receiving no treatment, (2) active disease and receiving prednisone ≥10 mg/day (or equivalent dose of another corticosteroid) and/or at least one other systemic immunosuppressant, and (3) inactive disease and receiving prednisone <10 mg/day (or equivalent dose of another corticosteroid) and/or at least one other systemic immunosuppressant.

Active disease was defined as having at least 1+ vitreous haze, using the SUN Working Group/ National Eye Institute. Inactive disease was defined as having vitreous haze of 0.5+ or less and vitreous cell count of 0.5+ or less, using the SUN Working Group/National Eye Institute (NEI) scale. All immunomodulatory therapy agents were discontinued at least 30 days prior to the first administration of the study drug at day 0. Patients who were not receiving corticosteroid at screening were not allowed to receive any corticosteroid in the interim 30-day period prior to day 0. Systemic corticosteroid therapy at baseline was allowed to continue for patients who were already receiving corticosteroid therapy. Systemic corticosteroid was tapered immediately upon initiation of the first dose of sirolimus. For patients in category 2, the aim was to reduce the dose of corticosteroid to <10 mg/day. For patients in category 3, the aim was to discontinue corticosteroid or to reduce the dose to less than 5 mg/day.

Patients in each category were randomized in a ratio of 1:1 into one of two treatment groups; group 1 received intravitreal injections of sirolimus in a dose of 352 µg, and group 2 received subconjunctival injections of sirolimus in a dose of 1,320 µg. In this study, 30 patients received either IVT 352 µg or SCT 1,320 µg injections of DE-109 on Days 0, 60, and 120. In patients with bilateral uveitis, the eye with more advanced disease was chosen as the study eye.

The main outcomes were the bioactivity and ocular tolerability of intravitreal and subconjunctival injection of sirolimus in the treatment of non-infectious uveitis. The primary bioactivity analysis was conducted at month 6 and was evaluated by assessing the proportion of patients achieving a complete or partial response in the study eye. Complete response was defined as reduction of vitreous haze by at least two steps when compared to baseline or reduction of a single step to no haze. Partial response was defined as improvement of vitreous haze of no more than one step.

The secondary bioactivity endpoint was defined as the ability of sirolimus to reduce or prevent flare-up of uveitis in the study eye (as expressed by the frequency of ocular attacks during the first 6-month period) as evidenced by increase in vitreous haze and cells and anterior chamber cells when compared to previous visits. Other secondary parameters included change from baseline in best-corrected visual acuity as measured by ETDRS charts and in macular thickness as measured by spectral domain OCT. Changes in quality of life were assessed using the extended VFQ-25.

At month 6, all subjects with active uveitis at baseline showed reduction in vitreous haze of one or more steps. Forty percent of subjects showed reduction of two steps or more of vitreous haze (four in each group), and 60% showed a reduction of one-step vitreous haze (seven in group 1 and five in group 2). Changes in the inflammatory indices were statistically significant ($p < 0.05$) in both study groups. Thirty percent of patients gained one or more lines of visual acuity, 20% lost one or more

lines, and 50% maintained the same visual acuity. There were no statistically significant differences between the two study groups at month 6.

No serious adverse events were found to be related to the study drug.

3.3.5. Discussion on clinical efficacy

Evidence for the efficacy of Opsiria in the treatment of non-infectious uveitis of the posterior segment of the eye is based mainly on data from one of the two initially planned SAKURA Studies. The Applicant submitted the results corresponding to the first 12 months period. At the time of this report the study was ongoing until Month 24.

Design and conduct of clinical studies

SAKURA Study 1 recruited subjects with active non-infectious uveitis of the posterior segment (with vitreal inflammatory activity > 1+) and visual acuity of 20/400 or better (≥ 19 ETDRS letters). Systemic corticosteroids were allowed at stable doses and tapered during the study. No placebo or sham treatment was included as control arm.

Subjects received sirolimus 44 μg, 440 μg or 880 μg via IVT injection every 2 months during the initial 6-month double-masked period. During the following 6-month open label period all patients received 880 μg bi-monthly. Rescue therapy was indicated in case of worsening (defined on the basis of increases of vitreous haze (VH) or deterioration of vision) and subjects who were rescued were considered treatment failures.

A total of 347 patients with non-infectious uveitis were randomized to sirolimus 44 μg IVT dose (n=117), sirolimus 440 μg IVT dose (n=114) and sirolimus 880 μg IVT dose (n=116). Approximately 86.7% of patients remained in the study at Month 12. Although demographic and baseline characteristics were in general comparable across the treatment groups, there were some imbalances at baseline, eg. subjects in the 440 µg dose group had a numerically shorter duration of uveitis in the study eye (mean of 38.8 months) than the other two groups (mean of 55.8 and 48.6 months in 44 µg and 880 µg dose groups, respectively). Similarly, the median duration of uveitis in the study eye differed among dose groups as well (29.50 months, 44 µg; 21.80 months, 440 µg; 25.75 months, 880 µg). None of the patients in the 440 µg dose group had 4+ VH score while there were 2 patients with 4+ VH score in the control group. Although 103 study sites participated from distant and diverse sites, i.e. the study population must be very heterogeneous, such baseline imbalances could have an impact on the clinical outcome.

Patients presented moderate uveitis (mean VH= 1.9) and impaired visual acuity (BCVA 65.3 letters). The majority of patients (67%) had a bilateral uveitis of idiopathic origin (78%). Although highly variable depending on geographical region and anatomical location of uveitis, this figure appears to be higher than that usually reported (Wakefield 2005, Nguyen 2013). It might also be reflecting differences between countries (especially with those with limited diagnostic resources). In this respect, the CHMP noted that only 11.1% of patients were recruited from EU countries. Given the relevance of geographical differences, it may compromise the extrapolation of the results. Therefore, the Applicant was asked to clarify how the results obtained in the Sakura 1 study can be extrapolated to the EU population. In the answer the Applicant stated that only the global perspective is relevant and declined putting the results into European context.

Mean age of patients was around 47 years with about 12% of recruited patients over 65 years. This reasonably represents the spectrum of the target population. A total of 71.4% received concomitantly

corticosteroids, and 69 patients (19.9%) were being treated with systemic corticosteroids with an overall prednisone-equivalent dose >5 mg/day.

The evaluation of efficacy mainly relies on the activity of the vitreous inflammation. The main variable of the study was defined as the proportion of patients with vitreous haze score of zero. Several other definitions of responders have been used as secondary endpoints. Given the role as corticosteroids-sparing agents, the possibility of corticosteroid tapering is also relevant for this population.

Complementary information regarding patient's visual acuity, retinal thickness, use of rescue therapy and impact of the change in the quality of life is also assessed through the secondary outcome variables. 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.

Efficacy data and additional analyses

After five months (three injections) of treatment more subjects receiving sirolimus 880 or 440 µg than those treated with 44 µg dose achieved complete vitreal transparency, i.e. VH scoring of 0 (880 µg 16.4% vs 440 µg 22.8% vs 44 µg 10.3%).

Sirolimus 440 µg dose demonstrated a small but statistically significant increase of 12.5% of difference over the 44 µg group (based on the ITT population). The 880 µg dosing group failed to demonstrate a diference between treatments.

This pattern was consistently observed when VH improvement was measured as secondary outcomes (percentage of patients reaching VH 0 or reduced 2 units; percentage of patients achieving VH 0 or 0.5+). It was also shown in the per protocol (PP) analysis and in the several sensitivity analyses conducted.

In the clinically meaningful improvement category, VH 0 or 2-unit response, the response rate was 28.1%. From indirect comparison, this rate is about one third of the reported success rate of intravitreal dexamethasone (Pleyer U et al.l, Ophthalmologica 2014) or systemic infliximab (Kruh et al., Ophthalmology 2014.).

The clinical relevance of the size of the effect is questionable. The treatment effect observed in vitreous haze was not convincingly translated into clear benefit when other relevant outcomes such as visual acuity, macular edema, corticosteroid tapering or need of rescue therapy were examined. Also, the majority of patients on corticosteroids tapered them and maintained the inflammation controlled regardless the sirolimus dose. In general, the response achieved by the intermediate dose was better than that observed for the high and low dose but the size of the differences between groups was of uncertain relevance. Further justification on the relevance of the main efficacy results was requested by the CHMP. Without submitting new data, the Applicant has pointed towards some groups of patients in which the benefit was more evident (patients with macular oedema without epiretinal membrane, n=7; patients with worst VA at baseline, n=14). However the small size of these subgroups and the fact that they were explored *a posteriori* do not allow to rule out an observation by chance.

Also, the fact that an effect is only observed with the 440 µg dose (and not with the higher active dose) does not help to clarify the efficacy of the product. The response exhibited by patients treated with 880 µg was unexpectedly lower than that of patients treated with the intermediate dose. This inverted U-shaped (or bell-shaped) pattern of response has been explained by the Applicant by the development of a non-specific innate immune response related to the mass of drug particles and contact duration in the vitreous body (Otsuka et al, 2013). The local reaction resulting in exacerbated

inflammation would mask or reduce the anti-inflammatory efficacy of the product. Preservatives, mechanical/rheologic stress due to physical contact, the use of high doses and the pre-existing inflammatory condition have been invoked as relevant factors with potential influence.

It may be admitted that this hypothesis could explain (partly, at least) some of the findings related to the high dose behaviour. Since it is considered an unusual phenomenon, further work appears necessary, in order to better characterise it (especially the dose at which the efficacy is waning) and also for identification of the optimum intravitreal dose of sirolimus before accepting it without reserves.

This dose-dependent inflammatory response has been already described for triamcinolone and correlated with the presence of precipitated particles in ocular tissues. It has been described as sterile endophthalmitis reported in rare instances (< 2%) (Traban et al., 2007; Otsuka et al., 2013). As such, five cases of non-infectious endophtalmitis were described during the double-blind period of SAKURA study. The incidence of this event (1.4%) was within it was expected according literature. Of note, no additional report of sterile endophthalmitis was report during the open label phase (month 6 to month 12) where all patients were treated with the high dose on a bi-monthly basis. In this period no dramatic change in efficacy was observed in the 440 μg group of patients (or in the 44 μg) that could be explained by this dose-response local immune reaction. So, although theoretically possible, the clinical signs supporting this mechanism have not been observed.

Of note, the size of the effect is smaller than that initially estimated (a difference of 16% between groups). For comparison, 60% of patients treated intravitreally with sirolimus 352 μg in SAVE study (Nguyen 2013) showed a reduction of two steps or more of vitreous haze at month 3 and 40% of patients at month 6. In comparison, in the HURON study, where patients with posterior non-infectious uveitis were treated with dexamethasone, 31.2% of patients treated with 700 μg and 28.9% of patients treated with 350 μg achieved vitreous haze score of zero, compared to 14.5% of those treated with sham at Week 26 (Ozurdex EPAR; Lowder et al 2011).

With respect to long-term efficacy data, given that only sirolimus 880 μg dose was tested there is no available data of the intended dose beyond 6 months. This represents one of the drawbacks of the study, mainly when at Month 6 the effect seems to dilute.

The confirmation of these results should be given by the second SAKURA study, still ongoing. As a consequence of the results from SAKURA 1 the Applicant has informed that the following amendments have been implemented in the second SAKURA study protocol: the study has been shortened to 6 month double-blind period (no open label phases are going to be performed) and patients on 880 μg dose have been withdrawn from the study. It means that the population recruited in SAKURA 2 will be composed by patients treated under different regimens according the recruitment date.

Some global results on the second SAKURA study are being submitted in these responses. They only provide a general picture (blinded) on the overall population included. Although consistent with the previous Study these results are of limited supportive value.

A 1-year open-label extension study (SPRING Study) is ongoing and is providing access to the 440 μg dose, as needed, for up to one year, for patients completing the SAKURA study. As there is no efficacy and safety data for this proposed dose beyond 6 months these results will provide supporting information on the safety profile and likely, on the persistence of the effect. The fact that patients are being treated with a dose further discarded due to lack of efficacy is also an issue. It was planned that patients were treated with this high dose for the 2nd year treatment period, currently ongoing. The CHMP asked the Applicant to explain the status of the study and current approach for these patients. Also, the procedure changes (if any) in relation to the doses administered implemented in the Study 2 (also ongoing, but at earlier stage) taking into account the Study 1 results.

In this context, differences have been observed between patients treated during the 12 Month period with 880 µg dose in which the low response observed during the first 6 months is maintained during the whole period (< 19%), and the group treated with 440 µg dose in the initial 6 Month period and 880 µg dose in the last 6 months. Although a lower response would be expected during the high dose treatment, the response remained relatively unchanged. The Applicant has explained this finding suggesting that patients experienced less intraocular inflammation and tolerated the 880 µg dose. However, it is still questionable if the limited effect shown by 440 µg dosage can be considered reliable.

The Applicant conducted a subgroup analysis excluding uveitis with an anterior component. Patients with panuveitis were also excluded. Apparently this analysis was not pre-defined as such in the Statistical Analysis Plan (except for the consideration stated: Other subgroup analyses may be performed as suggested by the data). This subgroup represents 62.5% of the global population. Results in this subgroup were better for the 440 µg (but not for 44 µg and 880 µg doses) than in the global population in terms of reduction of inflammatory activity. The proportion of patients with VH 0 was 30% vs 9.2% in the control group (percentages for the primary analysis in the global population were 22.8% vs 10.3%). Similar response was reported when response was defined as VH improvement (VH 0 or 2-Unit responders; VH 0 or 0.5+ responders). Based on these results, the Applicant indicates that sirolimus is "particularly effective in controlling inflammation in subjects without concurrent anterior segment inflammation". Whereas the rationale for not treating patients with anterior uveitis with intravitreal medicinal products is acknowledged the exclusion of patients with panuveitis as potential candidates to be treated was not understood at the tiem of this report. It was furthermore not entirely clear if this was the Applicant's proposal.

However, patients in real clinical settings are not always restricted to anatomic borders – according to the nature of the disease as well, but one should be aware that involvement of patients with heterogenous clinical picture might challenge the proper diagnosis and the clinical outcome.

Regarding the endpoints it is accepted that VH0 response is the primary, highly preferred outcome in uveitis treatment, but in real clinical setting, especially with long uveitis duration, some debris may be left in the vitreous body even at complete resolution of the active inflammationand these patients will not meet this primary endpoint. Therefore, the endpoint VH0 and 2 unit responders seems to represent those patients who may gain the clinical benefit of this treatment. For this endpoint, responders' rate to IVT DE-109 was 15,8% vs 35,7% among 44 µg vs 440 µg dose group, p=0.0075, i.e. significantly better in the subgroup excluding anterior and pan-uveitis patients. This was not the case with response rate in 880µg group which practically did not differ from that of 44 µg.

Furthermore, taking into account that IVT sirolimus may be much less effective in the anterior segment compared to the posterior segment, the panuveitis or the anterior plus posterior uveitis patients tend to be underdosed with anti-inflammatory drugs during IVT sirolimus injections and corticosteroid tapering in the same time. At the time of this report, the CHMP had sked the Applicant to discuss the robustness of the statistical data and the clinical relevance of the results.

From clinical point of view, it would be useful to have comparative data on the new intravitreal sirolimus treatment with Ozurdex or systemic infliximab treatment. The latter two treatment modalities have proven quite high responder rates with low adverse event rates. Eg. dexamethasone inmplant resulted in 61% vitreous clearance based on a prospective non-comparative study involving 84 patients and infliximab led to 81.8% clinical remission based on a retrospective study involving 88 patients with non-infectious uveitis. The Applicant explained that equal comparisons using non-prospective and non-comparative studies with other therapies and Opsiria are not possible due to

differences in patient population studied, disease characteristics, as well as differences in measurements used to determine disease severity.

3.3.6. Conclusions on clinical efficacy

At the time of this report, the modest efficacy of the product was the main concern. The systemic exposure of sirolimus after the intravitreal administration of the product shows a dose-proportional correlation, but there was no linear dose-effect. The modest effect size of the (intermediate) 440 µg dose has not been sufficiently supported by other clinical relevant outcomes. The limited long-term efficacy data is another drawback of the dossier. Further clarification provided by the Applicant did not resolve the main concerns. At this stage, is the CHMP considered that the results from the single study were not sufficiently convincing to support the clinical benefit of the product.

3.3.7. Clinical safety

The safety analysis of DE-109 for IVT injection is mainly focused on the safety data obtained from the SAKURA Study 1. During the assessment fo this application, the Applicant submitted global results from the SAKURA Study 2 (still ongoing, blinded) where 187 patients has reached the Month 6 endpoint for safety assessment.

In addition, 8 studies utilizing DE-109 formulations administered by IVT or subconjunctival (SCT) injection were performed by the prior owner of this product and by Santen Pharmaceutical Co., Ltd., Japan (Table 16). The 3 studies utilizing IVT injections evaluated DE-109 in other ophthalmic indications (Table 15).

Table 15: Description of Clinical Safety Studies with IVT DE-109

Study ID	Number of Study Centers Location(s)	Study start Enrollment status, Date Total Enrollment / Enrollment goal	Design Control Type	Dose, Route & Regimen	Study Objective	No. Subjs by Arm entered/ compl.	Duration	Gender M/F Median Age (Range)	Diagnosis Inclusion Criteria	Primary Endpoint (s)
SAKURA Study (32-007 Santen Sponsored)	15 Countries Worldwide, 103 Clinical Sites	Enrollment period: 31 May 2011 – 31 March 2013 Enrollment complete Total Enrollment N=347 subjects 348 study eyes Enrollment goal 250	Multi-center, randomized, double-masked and open-label, parallel comparative study.	44µg, 440µg, or 880µg via IVT every 2 months for 3 doses, then 880µg open-label every 2 months for 3 doses	Evaluate safety and efficacy of IVT injection of 3 doses of DE-109 for treatment of active, non-infectious uveitis of the posterior segment	44µg; N=117/102 440µg; N=114/99 880µg; N=117/100	24 Months	Male: 40.1% Female: 59.9% Median age: 47.40 years (18.1, 83.6)	Active, non-infectious uveitis of the posterior segment of the eye	Having a VH score of 0 at Month 5 (modified SUN scale)
Legacy Studies Using IVT DE-109 in Other Ophthalmic Indications										
DR-001/ DME	2 Clinical Sites in USA	Started September, 20, 2006/ Completed June 30, 2008 50/50 subjects	Phase 1, randomized, open-label, dose esc. Safety, Single Dose PK	SCT (220, 440, 880, 1320, or 1760 µg), single dose Or IVT (44, 110, 176, 264, or 352 µg) single dose	Evaluate the safety and tolerability of a single SCT or IVT dose in subjects with DME	50/44 (5 per dose group)	12 months	48% M/52% F Mean Age 63.4 years (37, 82)	DME, BCVA 20/40-20/200, Mean center subfield retinal thickness ≥300 microns	Informal endpoint: Mean change in BCVA
AMD-001/ AMD	3 Clinical Sites, San Lucas Coyoacán, México and Phoenix, AZ, USA	Started October 25, 2006, Completed September 15, 2008 30/30 subjects	Phase 1-2, Randomized, open-label, dose-escalation study, PK	SCT (220, 440, or 880 µg) IVT (44, 110, or 176 µg) single dose	Evaluate the safety and tolerability of a single SCT or IVT dose in subjects with treatment-naïve CNV due to AMD	30/30 (5 per dose group)	12 months	33% M/ 67% F Median Age 77.0 (54, 88)	CNV due to AMD Age≥ 50 years, subfoveal CNV due to AMD, lesion ≤9 disc areas, CNV > 50% of lesion, BCVA 20/40-20/200	Informal endpoint: Mean change in BCVA
AMD-002/AMD	3 Clinical Sites in the USA	Started October 21, 2008, Terminated December 17, 2009 20/20 subjects	Phase 1-2, Randomized, single-masked study	SCT 1320 µg IVT 352 µg	Evaluate safety and efficacy of DE-109 every 60 days for 3 treatments	20/19 completed Month 6 (10 per dose group)	Planned: 12 Months Terminated at 6 months	45% M/ 55% F IVT: 74.1 years (53-93) SCT: 78.9 years (69-91)	CNV due to AMD Subfoveal CNV due to AMD, lesion ≤9 disc areas, 50% active CNV BCVA 34-73 letters	Mean change in BCVA on Day 180

BCVA – best-corrected visual acuity, SUN- Standardized uveitis nomenclature, CNV- Choroidal neovascularization, AMD – age-related macular degeneration, DME – diabetic macular edema, IVT- intravitreal, SCJ – subconjunctival

Table 16: Legacy Studies with Ocular Formulations of DE-109

Study Number	Sponsor	Indication	Route/Doses Studied
AMD-001	MacuSight	AMD	IVT: 44, 110, 176 µg SCT: 220, 440, 880 µg
AMD -002	MacuSight	AMD	IVT: 352 µg SCT: 1320 µg
AMD-003	MacuSight	AMD	SCT: 440 and 1320 µg
DR-001	MacuSight	DME	IVT: 44, 110, 176, 264, 352 µg SCT: 220, 440, 880 1320 and 1760 µg
DR-002	MacuSight	DME	SCT: 220, 440, 880 µg
DES-001	MacuSight	Dry Eye	SCT: 220, 440, 880 µg
AMD-01090806	Santen Pharmaceutical Co., Ltd, Japan	AMD	SCT: 440, 880 µg and 1320 µg (with Lucentis)
DME-01090805	Santen Pharmaceutical Co., Ltd, Japan	DME	SCT: 220, 440, 880 µg

AMD – age-related macular degeneration, DME – diabetic macular edema, DR diabetic retinopathy, DES – dry eye syndrome, IVT-intravitreal, SCJ – subconjunctival

In the SAKURA study the safety of DE-109 is assessed primarily based on comparisons of treatment-emergent AEs among the 3 treatment groups for the Safety Population. The Safety Population as defined in the Statistical Analysis Plan (SAP) of the SAKURA Study includes all subjects who received at least one injection of DE-109. Data from subgroups of the Safety Population are also provided based on data collected during the following 3 analysis periods: Double-Masked Period, Open-Label Period and Combined Period (till M12).

Safety assessments measured during SAKURA study included adverse events, slit-lamp biomicroscopy, endothelial cell count (at selected sites only), indirect ophthalmoscopy, BCVA, intraocular pressure (IOP), fundus photography, fluorescein angiography, laboratory tests (serum chemistry, hematology, and urinalysis), physical examinations and vital signs.

Patient exposure

- **Extent of Exposure in the SAKURA Study (SAKURA Study 1)**

The ITT Population for the SAKURA Study consists of 347 subjects with 348 study eyes (i.e. 348 subject IDs). One subject was mistakenly enrolled and randomized twice at 2 different locations, with 2 different subject IDs, and received study medication in both eyes. The Safety Population is comprised of the 346 subject IDs who received at least one dose of study medication; 2 study subjects who were randomized but discontinued from the study prior to receiving any study medication were not included in the Safety Population. For the safety analyses, subjects are classified by actual treatment received. (Table 17)

Table 17: Summary of Subject Disposition for the SAKURA Study

Category	Treatment Group[a]			Overall
	44/880 µg	440/880 µg	880/880 µg	
Randomized (N)[b]	117	114	117	348
Received Study Drug	117	112	117	346
Discontinued prior to Month 5: n (%)	8 (6.8)	4 (3.5)	5 (4.3)	17 (4.9)
Adverse Event	3 (2.6)	0	2 (1.7)	5 (1.4)
Lost to Follow-Up	1 (0.9)	2 (1.8)	2 (1.7)	5 (1.4)
Withdrawal by Subject	3 (2.6)	1 (0.9)	0	4 (1.1)
Death	1 (0.9)	0	0	1 (0.3)
Other	0	1 (0.9)	1 (0.9)	2 (0.6)
Discontinued prior to Month 6: n (%)	9 (7.7)	6 (5.3)	6 (5.1)	21 (6.0)
Withdrawal by Subject	3 (2.6)	3 (2.6)	0	6 (1.7)
Lost to Follow-Up	2 (1.7)	2 (1.8)	2 (1.7)	6 (1.7)
Adverse Event	3 (2.6)	0	2 (1.7)	5 (1.4)
Death	1 (0.9)	0	0	1 (0.3)
Other	0	1 (0.9)	2 (1.7)	3 (0.9)
Discontinued prior to Month 12: n (%)	15 (12.8)	15 (13.2)	17 (14.5)	47 (13.5)
Withdrawal by Subject	5 (4.3)	5 (4.4)	6 (5.1)	16 (4.6)
Adverse Event	5 (4.3)	3 (2.6)	4 (3.4)	12 (3.4)
Lost to Follow-Up	4 (3.4)	3 (2.6)	4 (3.4)	11 (3.2)
Lack of Efficacy	0	1 (0.9)	0	1 (0.3)
Death	1 (0.9)	0	0	1 (0.3)
Other	0	3 (2.6)	3 (2.6)	6 (1.7)
Received any OL Treatment[c]: n (%)	72 (61.5)	64 (56.1)	75 (64.1)	211 (60.6)
Entered OL Retreatment Period at Month 12: n (%)	49 (41.9)	40 (35.1)	43 (36.8)	132 (37.9)
Completed Study without OL Treatment: n (%)	4 (3.4)	6 (5.3)	3 (2.6)	13 (3.7)
Completed Study without Retreatment: n (%)	4 (3.4)	6 (5.3)	3 (2.6)	13 (3.7)

a Treatment group is displayed in the format of 'XXX/YYY µg', where XXX denotes the double-masked dose and YYY denotes the open-label dose.
b Two screen failure subjects (1, 440/880 µg; 1, 880/880 µg) were randomized but not treated; these subjects were evaluated in the ITT population but not in the Safety Population.
c Three subjects were still under Amendment 2 when they received their Month 10 injection (Double-Masked). Amendments 3 and 4 had been implemented when they returned for their Month 12 visit. The subjects' Month 12 injections fell into the Open-Label Retreatment Period and were not considered part of the Open-Label Treatment Period.
Note: For the Open-Label analysis period (until Month 12), the start date was the date of the first open-label injection and the end date was the date of the last open-label injection date + 120 days, the study exit date, or Day 390, whichever came first. A subject may have entered the Open-Label Retreatment Period during this time interval.
ITT=intent-to-treat; N=number of subject IDs; OL=open-label; VH=vitreous haze

The mean time on study for the Safety Population was 340.8 days, and 88.2% of this Population remained in the study through at least Day 300. There were no notable differences in time on study among dose groups.

Around 70% of patients received 3 IVT injections during the double-masked period and 50% of patients received 3 additional injections during the open label period.

- **Extent of Exposure in the SAKURA Study 2**

As of 12-July-2015, SAKURA Study 2 randomized 207 patients. Among them, 20 patients have not yet reached the Month 6 endpoint for safety assessment. Therefore, the analysis population of Study 2 for safety is comprised 187 randomized patients.

- **Extent of Exposure in the Legacy Studies**

A total of 50 subjects received at least one injection of study medication during the Legacy Studies. The total number of injections administered during the studies was 67, including 10 injections each of 44 µg DE-109, 110 µg DE-109 and 176 µg DE-109, 5 injections of 264 µg DE-109 and 32 injections of 352 µg DE-109. Forty-one subjects received a single dose of DE-109, 1 subject received 2 doses of DE-109 and 8 subjects received 3 doses of DE-109.

All subjects received active study medication in these uncontrolled Phase 1-2 studies. Of these, 1 subject in Study DR-001 (176 µg) was discontinued prior to the end of the study due to subject non-compliance after Day 90. All subjects were followed for at least 6 months and 35 subjects were followed for 12 months in the Legacy Studies.

Adverse events

- **SAKURA STUDY**

Table 18: Adverse Events: Overall Summary -- Analysis Population: Safety – Analysis Period: Double-Masked, Open-Label, and Combined (till Month 12) (Safety Population)

Subject IDs with Any	Double-Masked 44 µg (N=117) n (%)	Double-Masked 440 µg (N=112) n (%)	Double-Masked 880 µg (N=117) n (%)	Double-Masked Overall (N=346) n (%)	Open-Label (N=211) n (%)	Combined till Month 12 (N=346) n (%)
AE(s)	100 (85.5)	97 (86.6)	102 (87.2)	299 (86.4)	152 (72.0)	315 (91.0)
SAR(s)	52 (44.4)	59 (52.7)	64 (54.7)	175 (50.6)	65 (30.8)	193 (55.8)
Study Medication-Related	32 (27.4)	36 (32.1)	49 (41.9)	117 (33.8)	39 (18.5)	136 (39.3)
Serious	27 (23.1)	27 (24.1)	24 (20.5)	78 (22.5)	37 (17.5)	104 (30.1)
Serious SAR(s)	5 (4.3)	14 (12.5)	17 (14.5)	36 (10.4)	17 (8.1)	50 (14.5)
Serious Study Medication-Related	5 (4.3)	12 (10.7)	16 (13.7)	33 (9.5)	12 (5.7)	42 (12.1)
Leading to Discontinuation from Study	10 (8.5)	4 (3.6)	6 (5.1)	20 (5.8)	9 (4.3)	30 (8.7)
Sight Threatening	22 (18.8)	22 (19.6)	23 (19.7)	67 (19.4)	30 (14.2)	88 (25.4)
Death	1 (0.9)	0	0	1 (0.3)	0	1 (0.3)
SAR(s) Leading to Death	0	0	0	0	0	0

AE(s): adverse event(s); SAR(s): suspected adverse reaction(s) SAR(s): AE(s) considered related to the study medication or injection procedure by the Clinical Investigator. Note: Subjects are classified by actual treatment received. Subject AT101-0001 was randomized to the 440 µg group but received 44 µg at Day 1, Month 2, and Month 4, and was placed in the 44 µg group. Subject IT115-0001 was randomized to the 44 µg group but received 880 µg at Month 2, and was placed in the 880 µg group

The main emphasis of discussion of AEs is put on ocular AEs in the study eye because PK studies in animals and humans indicate that there is little or no measurable sirolimus in the systemic circulation following IVT administration.

The most frequently reported PTs for AEs reported during both the Double-Masked and the Combined till Month 12 analysis periods included iridocyclitis, intraocular pressure increased, uveitis, conjunctival haemorrhage, and eye pain, with an incidence greater than 10%. There was a slight dose-dependent trend in proportion of subjects reporting any ocular AE associated with worsened ocular inflammation, which was predominantly panuveitis (Preferred term Uveitis).

In the Double-Masked analysis period, the types and incidences of AEs were similar among the 3 dose groups. In the Open-Label analysis period, the AE reporting incidences substantially decreased compared to the Double-Masked analysis period, with the exception of cataract and subcapsular cataract, which remained unchanged.

The most frequently reported non-ocular AEs were headache (19/346, 5.5%), nasopharyngitis (12/346, 3.5%), and cough (6/346, 1.7%) in the Combined till Month 12 analysis period. There were no dose-related trends noted in non-ocular AEs.

Table 19 Summary of Adverse Events in >3% of Subjects – Double-Masked, Open-Label, and Combined till Month 12 Analysis Periods (Safety Population)

SYSTEM ORGAN CLASS Preferred Term	Double-Masked 44 µg (N=117)	Double Masked 440 µg (N=112)	Double-Masked 880 µg (N=117)	Double-Masked Overall (N=346)	Open-Label (N=211)	Combined Till Month 12 (N=346)
Subject IDs with Any AE(s)	100 (85.5%)	97 (86.6%)	102 (87.2%)	299 (86.4%)	152 (72.0%)	315 (91.0%)
EYE DISORDERS	87 (74.4%)	84 (75.0%)	90 (76.9%)	261 (75.4%)	121 (57.3%)	285 (82.4%)
Iridocyclitis	25 (21.4%)	22 (19.6%)	22 (18.8%)	69 (19.9%)	22 (10.4%)	81 (23.4%)
Uveitis	13 (11.1%)	17 (15.2%)	31 (26.5%)	61 (17.6%)	11 (5.2%)	70 (20.2%)
Conjunctival haemorrhage	18 (15.4%)	17 (15.2%)	21 (17.9%)	56 (16.2%)	15 (7.1%)	63 (18.2%)
Eye pain	9 (7.7%)	15 (13.4%)	14 (12.0%)	38 (11.0%)	9 (4.3%)	42 (12.1%)
Choroiditis	15 (12.8%)	10 (8.9%)	3 (2.6%)	28 (8.1%)	8 (3.8%)	32 (9.2%)
Intermediate uveitis	8 (6.8%)	8 (7.1%)	10 (8.5%)	26 (7.5%)	8 (3.8%)	35 (10.1%)
Conjunctival hyperaemia	10 (8.5%)	8 (7.1%)	6 (5.1%)	24 (6.9%)	9 (4.3%)	28 (8.1%)
Cataract	6 (5.1%)	6 (5.4%)	10 (8.5%)	22 (6.4%)	16 (7.6%)	41 (11.8%)
Cystoid macular oedema	10 (8.5%)	6 (5.4%)	6 (5.1%)	22 (6.4%)	9 (4.3%)	31 (9.0%)
Macular oedema	2 (1.7%)	8 (7.1%)	7 (6.0%)	17 (4.9%)	7 (3.3%)	20 (5.8%)
Dry eye	10 (8.5%)	4 (3.6%)	2 (1.7%)	16 (4.6%)	2 (0.9%)	18 (5.2%)
Iris adhesions	2 (1.7%)	7 (6.3%)	5 (4.3%)	14 (4.0%)	5 (2.4%)	18 (5.2%)
Vitreous floaters	5 (4.3%)	6 (5.4%)	3 (2.6%)	14 (4.0%)	6 (2.8%)	18 (5.2%)
Cataract subcapsular	0	4 (3.6%)	8 (6.8%)	12 (3.5%)	8 (3.8%)	21 (6.1%)
Ocular hyperaemia	5 (4.3%)	4 (3.6%)	3 (2.6%)	12 (3.5%)	1 (0.5%)	13 (3.8%)
Vitreous opacities	4 (3.4%)	1 (0.9%)	6 (5.1%)	11 (3.2%)	4 (1.9%)	13 (3.8%)
Vision blurred	3 (2.6%)	2 (1.8%)	5 (4.3%)	10 (2.9%)	2 (0.9%)	13 (3.8%)
Macular fibrosis	4 (3.4%)	1 (0.9%)	2 (1.7%)	7 (2.0%)	4 (1.9%)	13 (3.8%)
Vitritis	4 (3.4%)	2 (1.8%)	2 (1.7%)	8 (2.3%)	3 (1.4%)	13 (3.8%)
Posterior capsule opacification	4 (3.4%)	3(2.7%)	2 (1.7%)	9 (2.6%)	6 (2.8%)	12 (3.5%)
Visual acuity reduced	2 (1.7%)	4 (3.6%)	0	6 (1.7%)	1 (0.5%)	11 (3.2%)
Conjunctival oedema	4 (3.4%)	3 (2.7%)	1 (0.9%)	8 (2.3%)	3 (1.4%)	11 (3.2%)
Ocular hypertension	2 (1.7%)	0	5 (4.3%)	7 (2.0%)	5 (2.4%)	11 (3.2%)
Glaucoma	4 (3.4%)	2 (1.8%)	2 (1.7%)	8 (2.3%)	2 (0.9%)	10 (2.9%)
Vitreous detachment	5 (4.3%)	1 (0.9%)	2 (1.7%)	8 (2.3%)	1 (0.5%)	9 (2.6%)
Ocular hypertension	2 0(1.7%)	0	5 (4.3%)	7 (2.0%)	5 (2.4%)	11 (3.2%)
Photophobia	4 (3.4%)	3 (2.7%)	0	7 (2.0%)	0	7 (2.0%)

Table 20 Summary of Adverse Events in >3% of Subjects – Double-Masked, Open-Label, and Combined till Month 12 Analysis Periods (Safety Population) (Continued)

SYSTEM ORGAN CLASS Preferred Term	Double-Masked 44 µg (N=117)	Double Masked 440 µg (N=112)	Double-Masked 880 µg (N=117)	Double-Masked Overall (N=346)	Open-Label (N=211)	Combined Till Month 12 (N=346)
Non-infectious endophthalmitis	0	1 (0.9%)	4 (3.4%)	5 (1.4%)	6 (2.8%)	10 (2.9%)
INVESTIGATIONS	26 (22.2%)	29 (25.9%)	34 (29.1%)	89 (25.7%)	34 (16.1%)	114 (32.9%)
Intraocular pressure increased	22 (18.8%)	20 (17.9%)	25 (21.4%)	67 (19.4%)	23 (10.9%)	78 (22.5%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	8 (6.8%)	12 (10.7%)	11 (9.4%)	31 (9.0%)	15 (7.1%)	43 (12.4%)
Medication Residue	1 (0.9%)	7 (6.3%)	6 (5.1%)	14 (4.0%)	10 (4.7%)	21 (6.1%)
INFECTIONS AND INFESTATIONS	18 (15.4%)	16 (14.3%)	28 (23.9%)	62 (17.9%)	19 (9.0%)	77 (22.3%)
Nasopharyngitis	1 (0.9%)	4 (3.6%)	6 (5.1%)	11 (3.2%)	2 (0.9%)	12 (3.5%)
NERVOUS SYSTEM DISORDERS	9 (7.7%)	13 (11.6%)	3 (2.6%)	25 (7.2%)	7 (3.3%)	30 (8.7%)
Headache	5 (4.3%)	8 (7.1%)	3 (2.6%)	16 (4.6%)	5 (2.4%)	19 (5.5%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	14 (12.0%)	11 (9.8%)	5 (4.3%)	30 (8.7%)	10 (4.7%)	39 (11.3%)
Foreign body in eye	4 (3.4%)	3 (2.7%)	1 (0.9%)	8 (2.3%)	4 (1.9%)	14 (4.0%)

Refer to Study CSR Table 14.3.1.3.1, Study CSR Table 14.3.1.3.2, Study CSR Table 14.3.1.3.3.
AE(s): adverse event(s).
Note: Any subject who experienced multiple AEs within a system organ class or preferred term was counted only once for that system organ class or preferred term. Subjects were classified by actual treatment received. Subject AT101-0001 was randomized to the 440 µg group, but received 44 µg at Day 1, Month 2, and Month 4 and was put in the 44 µg group. Subject IT115-0001 was randomized to the 44 µg group, but received 880 µg at Month 2 and was put in the 880 µg group. AEs were coded using MedDRA Version 16.0.

The majority of AEs reported were mild or moderate in severity. In the Double-Masked analysis period, the incidences of severe AEs were similar among the 3 dose groups. In the Open-Label analysis period, the overall incidences of severe AEs decreased compared to the Double-Masked analysis period, with the exception of non-infectious endophthalmitis and medication residue, both of which increased slightly.

Study Medication-Related Adverse Events

In the Double-Masked analysis period, the incidences of study medication-related AEs were lower in the 44 and 440 µg dose groups compared to the 880 µg dose group with the exception of medication residue and IOP increase. In the Open-Label analysis period, the incidences of study medication-related AEs decreased overall compared to the Double-Masked analysis period, with the exception of non-infectious endophthalmitis, which increased slightly.

Table 21: Summary of Study Medication-Related Adverse Events in >3% of Subjects – Double-Masked, Open-Label, and Combined till Month 12 Analysis Periods

System Organ Class/Preferred Term	Double-Masked 44 µg (N=117) n (%)	Double Masked 440 µg (N=112) n (%)	Double-Masked 880 µg (N=117) n (%)	Double-Masked Overall (N=346) n (%)	Open-Label (N=211) n (%)	Combined till Month 12 (N=346) n (%)
Subjects with Any Study Medication-Related AE(s)	32 (27.4)	36 (32.1)	49 (41.9)	117 (33.8)	39 (18.5))	136 (39.3)

System Organ Class/Preferred Term	Double-Masked 44 µg (N=117) n (%)	Double Masked 440 µg (N=112) n (%)	Double-Masked 880 µg (N=117) n (%)	Double-Masked Overall (N=346) n (%)	Open-Label (N=211) n (%)	Combined till Month 12 (N=346) n (%)
Eye Disorders	23 (19.7)	18 (16.1)	40 (34.2)	81 (23.4)	25 (11.8)	100 (28.9)
Iridocyclitis	4 (3.4)	6 (5.4)	8 (6.8)	18 (5.2)	1 (0.5)	19 (5.5)
Uveitis	1 (0.9)	4 (3.6)	9 (7.7)	14 (4.0)	2 (0.9)	15 (4.3)
Conjunctival hyperaemia	4 (3.4)	0	1 (0.9)	5 (1.4)	1 (0.5)	5 (1.4)
Non-infectious endophthalmitis	0	1 (0.9)	4 (3.4)	5 (1.4)	4 (1.9)	8 (2.3)
General Disorders and Administration Site Conditions	2 (1.7)	6 (5.4)	6 (5.1)	14 (4.0)	9 (4.3)	19 (5.5)
Medication Residue	1 (0.9)	6 (5.4)	6 (5.1)	13 (3.8)	9 (4.3)	19 (5.5)
Investigations	8 (6.8)	13 (11.6)	10 (8.5)	31 (9.0)	12 (5.7)	35 (10.1)
Intraocular pressure increased	7 (6.0)	12 (10.7)	10 (8.5)	29 (8.4)	12 (5.7)	33 (9.5)

Injection Procedure-Related Adverse Events

The most common AE was conjunctival haemorrhage. In general, no dose-dependent relationship was observed.

Table 22 **Summary of Injection Procedure-Related Adverse Events in >3% of Subjects – Double-Masked, Open-Label, and Combined till Month 12 Analysis Periods**

System Organ Class/Preferred Term	Double-Masked 44 µg (N=117) n (%)	Double Masked 440 µg (N=112) n (%)	Double-Masked 880 µg (N=117) n (%)	Double-Masked Overall (N=346) n (%)	Open-Label (N=211) n (%)	Combined till Month 12 (N=346) n (%)
Subjects with Any Injection Procedure-Related AE(s)	36 (30.8)	36 (32.1)	33 (28.2)	105 (30.3)	37 (17.5)	117 (33.8)
Eye Disorders	29 (24.8)	29 (25.9)	26 (22.2)	84 (24.3)	24 (11.4)	94 (27.2)
Conjunctival haemorrhage	17 (14.5)	15 (13.4)	18 (15.4)	50 (14.5)	11 (5.2)	53 (15.3)
Eye pain	4 (3.4)	7 (6.3)	8 (6.8)	19 (5.5)	0	19 (5.5)
Conjunctival hyperaemia	8 (6.8)	4 (3.6)	1 (0.9)	13 (3.8)	4 (1.9)	15 (4.3)
Investigations	8 (6.8)	5 (4.5)	4 (3.4)	17 (4.9)	6 (2.8)	19 (5.5)
Intraocular pressure increased	7 (6.0)	5 (4.5)	4 (3.4)	16 (4.6)	6 (2.8)	18 (5.2)

Refer to 32-007, Study CSR, Table 14.3.1.9.1, Study CSR Table 14.3.1.9.2, Study CSR Table 14.3.1.9.3.
AE(s): adverse event(s).
Any subject who experienced multiple injection-procedure related AEs within a system organ class or preferred term is counted only once for that system organ class or preferred term. Subjects are classified by actual treatment received. Subject AT101-0001 was randomized to 440 µg group but received 44 µg at Day 1, Month 2, and Month 4, and is put in the 44/880 µg group. Subject IT115-0001 was randomized to 44 µg group but received 880 µg at Month 2, and is put in the 880/880 µg group. AEs are coded using MedDRA Version 16.0.

Immediate Adverse Events (AEs occurring within 14 days of injection)

Table 23 **Summary of Immediate Adverse Events in >3% of Subjects – Double-Masked, Open-Label, and Combined till Month 12 Analysis Periods**

System Organ Class/Preferred Term	Double-Masked 44 µg (N=117) n (%)	Double Masked 440 µg (N=112) n (%)	Double-Masked 880 µg (N=117) n (%)	Double-Masked Overall (N=346) n (%)	Open-Label (N=211) n (%)	Combined till Month 12 (N=346) n (%)
Subjects with Any Injection Procedure-Related AE(s)	70 (59.8)	72 (64.3)	86 (73.5)	228 (65.9)	109 (51.7)	255 (73.7)
Eye Disorders	56 (47.9)	57 (50.9)	74 (63.2)	187 (54.0)	83 (39.3)	212 (61.3)
Conjunctival haemorrhage	16 (13.7)	16 (14.3)	20 (17.1)	52 (15.0)	13 (6.2)	56 (16.2)
Iridocyclitis	9 (7.7)	10 (8.9)	13 (11.1)	32 (9.2)	11 (5.2)	41 (11.8)
Uveitis	3 (2.6)	8 (7.1)	19 (16.2)	30 (8.7)	3 (1.4)	32 (9.2)
Eye pain	5 (4.3)	10 (8.9)	13 (11.1)	28 (8.1)	2 (0.9)	29 (8.4)
Conjunctival hyperaemia	10 (8.5)	8 (7.1)	4 (3.4)	22 (6.4)	7 (3.3)	24 (6.9)
Cataract	1 (0.9)	4 (3.6)	3 (2.6)	8 (2.3)	10 (4.7)	18 (5.2)
Cystoid macular oedema	6 (5.1)	2 (1.8)	2 (1.7)	10 (2.9)	4 (1.9)	13 (3.8)
Choroiditis	7 (6.0)	3 (2.7)	1 (0.9)	11 (3.2)	5 (2.4)	12 (3.5)
Iris adhesions	2 (1.7)	4 (3.6)	4 (3.4)	10 (2.9)	2 (0.9)	12 (3.5)
Vitreous floaters	3 (2.6)	4 (3.6)	2 (1.7)	9 (2.6)	5 (2.4)	12 (3.5)
Intermediate uveitis	5 (4.3)	2 (1.8)	3 (2.6)	10 (2.9)	2 (0.9)	11 (3.2)
Conjunctival oedema	4 (3.4)	3 (2.7)	1 (0.9)	8 (2.3)	2 (0.9)	10 (2.9)
Dry eye	5 (4.3)	1 (0.9)	1 (0.9)	7 (2.0)	1 (0.5)	8 (2.3)
Photophobia	4 (3.4)	2 (1.8)	0	2 (0.9)	0	6 (1.7)
Non-infectious endophthalmitis	0	1 (0.9)	4 (3.4)	5 (1.4)	6 (2.8)	10 (2.9)
Investigations	16 (13.7)	19 (17.0)	22 (18.8)	57 (16.5)	21 (10.0)	67 (19.4)
Intraocular pressure increased	15 (12.8)	17 (15.2)	18 (15.4)	50 (14.5)	17 (8.1)	57 (16.5)
General Disorders And Administration Site Conditions	7 (6.0)	10 (8.9)	9 (7.7)	26 (7.5)	10 (4.7)	31 (9.0)
Medication residue	1 (0.9)	7 (6.3)	6 (5.1)	14 (4.0)	10 (4.7)	21 (6.1)
Nervous System Disorders	4 (3.4)	8 (7.1)	2 (1.7)	14 (4.0)	2 (0.9)	15 (4.3)
Headache	3 (2.6)	5 (4.5)	2 (1.7)	10 (2.9)	2(0.9)	11 (3.2)

Refer to Table S2.1.14.1, Table S2.1.14.2 and Table S2.1.14.3
AE(s): adverse event(s).
Any subject who experienced multiple injection-procedure related AEs within a system organ class or preferred term is counted only once for that system organ class or preferred term. Subjects are classified by actual treatment received. Subject AT101-0001 was randomized to 440 µg group but received 44 µg at Day 1, Month 2, and Month 4, and is put in the 44/880 µg group. Subject IT115-0001 was randomized to 44 µg group but received 880 µg at Month 2, and is put in the 880/880 µg group. AEs are coded using MedDRA Version 16.0.

SAKURA Study; 44 µg Dose Group Compared to Historical Sham from the HURON Study

A clinical study was conducted by Allergan, Inc., investigating the use of the dexamethasone implant device (350 and 700 µg doses) versus sham for the treatment of non-infectious intermediate or posterior uveitis (HURON study; Ozurdex EPAR). A retrospective analysis has been submitted to support this application comparing the 44 µg DE-109 dose to the sham arm of the HURON study to provide perspective on the relative bioactivity of the 44 µg DE-109 dose.

Table 24 Most Frequent AEs (>2%; Ocular and Non-ocular)[a]

	SAKURA Study (Safety Population Excluding Panuveitis)			HURON Study (Randomized, Treated Subjects)
Preferred Term	**44 µg (N=80)**	**440 µg (N=78)**	**880 µg (N=78)**	**Sham (N=75)**
Iridocyclitis	**16 (20.0%)**	13 (16.7%)	18 (23.1%)	5 (6.7%)
Intraocular pressure increased	**11 (13.8%)**	11 (14.1%)	16 (20.5%)	5 (6.7%)
Choroiditis	**9 (11.3%)**	7 (9.0%)	2 (2.6%)	2 (2.7%)
Conjunctival haemorrhage	**8 (10.0%)**	12 (15.4%)	14 (17.9%)	**16 (21.3%)**
Conjunctival hyperaemia	8 (10.0%)	4 (5.1%)	4 (5.1%)	7 (9.3%)
Intermediate uveitis	**7 (8.8%)**	6 (7.7%)	9 (11.5%)	1 (1.3%)
Dry eye	**7 (8.8%)**	3 (3.8%)	0	1 (1.3%)
Uveitis	5 (6.3%)	8 (10.3%)	15 (19.2%)	**10 (13.3%)**
Eye pain	5 (6.3%)	10 (12.8%)	9 (11.5%)	**10 (13.3%)**
Headache	4 (5.0%)	6 (7.7%)	1 (1.3%)	5 (6.7%)
Conjunctival oedema	4 (5.0%)	1 (1.3%)	1 (1.3%)	3 (4.0%)
Vitreous detachment	**4 (5.0%)**	0	0	0
Vitreous opacities	3 (3.8%)	1 (1.3%)	4 (5.1%)	1 (1.3%)
Foreign body/sensation in eye	3 (3.8%)	3 (3.8%)	1 (1.3%)	1 (1.3%)
Glaucoma	3 (3.8%)	1 (1.3%)	0	2 (2.7%)
Cataract	2 (2.5%)	3 (3.8%)	6 (7.7%)	**7 (9.3%)**
Vision blurred	2 (2.5%)	2 (2.6%)	3 (3.8%)	3 (4.0%)
Lacrimation increased	2 (2.5%)	0	1 (1.3%)	0
Cough	2 (2.5%)	0	0	1 (1.3%)
Macular oedema	1 (1.3%)	7 (9.0%)	3 (3.8%)	**6 (8.0%)**
Ocular hypertension	1 (1.3%)	0	3 (3.8%)	0
Visual acuity reduced	1 (1.3%)	3 (3.8%)	0	**6 (8.0%)**
Photophobia	1 (1.3%)	2 (2.6%)	0	1 (1.3%)
Conjunctivitis	1 (1.3%)	0	1 (1.3%)	**4 (5.3%)**
Eyelid oedema	1 (1.3%)	0	1 (1.3%)	3 (4.0%)
Arthralgia	1 (1.3%)	1 (1.3%)	0	2 (2.7%)
Vomiting	1 (1.3%)	0	1 (1.3%)	2 (2.7%)
Cataract subcapsular	0	1 (1.3%)	8 (10.3%)	**4 (5.3%)**
Nasopharyngitis	0	2 (2.6%)	3 (3.8%)	1 (1.3%)
Visual impairment	0	1 (1.3%)	3 (3.8%)	1 (1.3%)

Table 25 Most Frequent AEs (>2%; Ocular and Non-ocular)[a] (Continued)

	SAKURA Study (Safety Population Excluding Panuveitis)			HURON Study (Randomized, Treated Subjects)
Preferred Term	**44 µg (N=80)**	**440 µg (N=78)**	**880 µg (N=78)**	**Sham (N=75)**
Retinal detachment	0	3 (3.8%)	0	2 (2.7%)
Nausea	0	2 (2.6%)	1 (1.3%)	**4 (5.3%)**
Sinusitis	0	0	2 (2.6%)	1 (1.3%)
Eye pruritus	0	1 (1.3%)	1 (1.3%)	**5 (6.7%)**
Hypertension	0	1 (1.3%)	1 (1.3%)	**3 (4.0%)**

[a] Bolded data highlight key differences between the SAKURA 44 µg dose group and the SURON sham group
Refer to (Valentine et al., 2014)

During the course of the assessment of this application, the Applicant has submitted safety data for 88 patients that received Double-Masked treatment for 12 months (44 µg dose: 27 patients, 440 µg dose: 31 patients and 880 µg dose: 30 patients). These patients received intravitreal sirolimus during the first 6 months every 2 months and as needed (PRN) from month 6 to month 12. Among patients included in the double-masked PRN period, 9/27, 15/30 and 9/31 patients required retreatment with 44 µg, 440 µg and 880 µg, respectively.

Adverse events reported are summarized in tables 26, 27 and 28.

Table 26 Key Ocular Adverse Events by SOC and PT (Study Eye), Double-Masked Treatment Period; Day 1 - Month 6

SYSTEM ORGAN CLASS Preferred Term	44 µg (N=27)	440 µg (N=31)	880 µg (N=30)	Overall (N=88)
Subject IDs with Any Ocular AE(s) in Study Eye	19 (70.4%)	25 (80.6%)	23 (76.7%)	67 (76.1%)
Endophthalmitis	0	0	1 (3.3%)	1 (1.1%)
Non-infectious endophthalmitis	0	0	4 (13.3%)	4 (4.5%)
Iridocyclitis	7 (25.9%)	7 (22.6%)	6 (20.0%)	20 (22.7%)
Uveitis	4 (14.8%)	2 (6.5%)	4 (13.3%)	10 (11.4%)
Intermediate uveitis	3 (11.1%)	2 (6.5%)	1 (3.3%)	6 (6.8%)
Choroiditis	3 (11.1%)	2 (6.5%)	2 (6.7%)	7 (8.0%)
Cataract	2 (7.4%)	2 (6.5%)	1 (3.3%)	5 (5.7%)
Cataract subcapsular	0	2 (6.5%)	1 (3.3%)	3 (3.4%)
Intraocular pressure increased	3 (11.1%)	4 (12.9%)	3 (10.0%)	10 (11.4%)
Ocular hypertension	0	0	3 (10.0%)	3 (3.4%)
Glaucoma	1 (3.7%)	2 (6.5%)	1 (3.3%)	4 (4.5%)
Medication residue	0	1 (3.2%)	1 (3.3%)	2 (2.3%)

Table 27 **Key Ocular Adverse Events by SOC and PT (Study Eye), Double-Masked Re-Treatment Period; Month 6 - Month 12**

SYSTEM ORGAN CLASS Preferred Term	44 µg (N=27)	440 µg (N=31)	880 µg (N=30)	Overall (N=88)
Subject IDs with Any Ocular AE(s) in Study Eye	14 (51.9%)	17 (54.8%)	20 (66.7%)	51 (58.0%)
Endophthalmitis	0	0	1 (3.3%)	1 (1.1%)
Non-infectious endophthalmitis	0	0	0	0 (0.0%)
Iridocyclitis	5 (18.5%)	2 (6.5%)	1 (3.3%)	8 (9.1%)
Uveitis	3 (11.1%)	0	4 (13.3%)	7 (8.0%)
Intermediate uveitis	3 (11.1%)	4 (12.9%)	1 (3.3%)	8 (9.1%)
Choroiditis	0	3 (9.7%)	1 (3.3%)	4 (4.5%)
Cataract	2 (7.4%)	2 (6.5%)	0	4 (4.5%)
Cataract subcapsular	0	1 (3.2%)	0	1 (1.1%)
Intraocular pressure increased	2 (7.4%)	0	3 (10.0%)	5 (5.7%)
Ocular hypertension	0	0	1 (3.3%)	1 (1.1%)
Glaucoma	0	0	1 (3.3%)	1 (1.1%)
Medication residue	0	0	0	0 (0.0%)

Table 28 **Ocular AEs in Subjects Receiving Retreatment between Months 6 and 12**

AEs Between Months 6 and 12	No Retreatment		With Retreatment	
SYSTEM ORGAN CLASS Preferred Term	440 µg (N=22)	880 µg (N=15)	440 µg (N=9)	880 µg (N=15)
EYE DISORDERS				
Endophthalmitis	0	0	0	1 (6.7%)
Uveitis	0	2 (13.3%)	0	2 (13.3%)
Choroiditis	2 (9.1%)	0	1 (11.1%)	1 (6.7%)
Intermediate uveitis	3 (13.6%)	0	1 (11.1%)	1 (6.7%)
Iridocyclitis	2 (9.1%)	0	0	1 (6.7%)
Intraocular Pressure Increased	0	1 (6.7%)	0	2 (13.3%)
Ocular hypertension	0	1 (6.7%)	0	0
Glaucoma	0	1 (6.7%)	0	0
Uveitic glaucoma	0	0	0	1 (6.7%)

- **SAKURA Study 2**

Table 29 **Adverse Events: Overall Summary - Analysis Periods: Double-Masked, Open-Label, and Entire Study (Safety Population, Study 1 and Study 2)**

Subjects with Any Adverse Events	Double Masked		Open-Label		Entire Study	
	Overall Study 1 (N=346)	Overall Study 2 (N=187)	Overall Study 1 (N=211)	Overall Study 2 (N=106)	Overall Study 1 (N=346)	Overall Study 2 (N=187)
AE(s)	301 (87.0%)	152 (81.3%)	161 (76.3%)	58 (54.7%)	319 (92.2%)	162 (86.6%)
Serious	79 (22.8%)	34 (18.2%)	46 (21.8%)	13 (12.3%)	116 (33.5%)	46 (24.6%)
Death	1 (0.3%)	0	0	0	1 (0.3%)	0
Ocular AE(s) in Study Eye	260 (75.1%)	136 (72.7%)	134 (63.5%)	50 (47.2%)	294 (85.0%)	148 (79.1%)
Serious	64 (18.5%)	28 (15.0%)	34 (16.1%)	12 (11.3%)	93 (26.9%)	39 (20.9%)
Death	0	0	0	0	0	0
Non-Ocular AE(s)	139 (40.2%)	62 (33.2%)	65 (30.8%)	16 (15.1%)	185 (53.5%)	79 (42.2%)
Serious	10 (2.9%)	4 (2.1%)	9 (4.3%)	0	21 (6.1%)	4 (2.1%)
Death	1 (0.3%)	0	0	0	1 (0.3%)	0

Table 30 **Key Ocular Adverse Events - Analysis Periods: Double-Masked, Open-Label, and Entire Study (Safety Population, Study 1 and Study 2) (Continued)**

SYSTEM ORGAN CLASS Preferred Term	Double Masked		Open-Label		Entire Study	
	Overall Study 1 (N=346)	Overall Study 2 (N=187)	Overall Study 1 (N=211)	Overall Study 2 (N=106)	Overall Study 1 (N=346)	Overall Study 2 (N=187)
Endophthalmitis	1 (0.3%)	1 (0.5%)	4 (1.9%)	0	5 (1.4%)	1 (0.5%)
Non-infectious endophthalmitis	5 (1.4%)	3 (1.6%)	7 (3.3%)	4 (3.8%)	11 (3.2%)	7 (3.7%)
Iridocyclitis	70 (20.2%)	26 (13.9%)	23 (10.9%)	7 (6.6%)	85 (24.6%)	32 (17.1%)
Uveitis	61 (17.6%)	23 (12.3%)	14 (6.6%)	5 (4.7%)	73 (21.1%)	28 (15.0%)
Intermediate uveitis	26 (7.5%)	17 (9.1%)	7 (3.3%)	2 (1.9%)	35 (10.1%)	22 (11.8%)
Choroiditis	30 (8.7%)	8 (4.3%)	11 (5.2%)	1 (0.9%)	38 (11.0%)	8 (4.3%)
Cataract	22 (6.4%)	11 (5.9%)	22 (10.4%)	11 (10.4%)	49 (14.2%)	26 (13.9%)
Cataract subcapsular	11 (3.2%)	13 (7.0%)	12 (5.7%)	8 (7.5%)	26 (7.5%)	21 (11.2%)
Intraocular pressure increased	67 (19.4%)	42 (22.5%)	35 (16.6%)	11 (10.4%)	90 (26.0%)	49 (26.2%)
Ocular hypertension	7 (2.0%)	0	7 (2.0%)	0	7 (2.0%)	0
Glaucoma	8 (2.3%)	1 (0.5%)	4 (1.9%)	0	12 (3.5%)	1 (0.5%)
Medication residue	15 (4.3%)	9 (4.8%)	11 (5.2%)	4 (3.8%)	24 (6.9%)	11 (5.9%)

The overall safety profiles between Study 1 and Study 2 are similar in all 3 phases of the study (Double-Masked, Open-Label and the Entire Study combined). There is a slightly lower rate of AEs, including ocular AEs, in Study 2 compared to Study 1. The rates of non-ocular AEs are also lower in Study 2 compared to Study 1.

Key ocular AEs in both studies are listed above. There is a slightly lower rate of the following AEs in Study 2 compared to Study 1: Iridocyclitis, worsening Uveitis (worsening panuveitis, pars planitis,

uveitis), worsening Choroiditis, and Glaucoma (a rise in intraocular pressure in a subject with glaucoma at baseline).

- **LEGACY STUDIES**

Ocular Adverse Events Reported

At least 1 ocular AE was reported for all 50 subjects who received IVT DE-109 in the Legacy Studies. The most common ocular AE was conjunctival haemorrhage (40/50 subjects, 80%), followed by eye pain (12/50 subjects, 24%) and visual acuity reduced (14/50 subjects, 28%).

Several AEs appeared to be related to the underlying disease: worsening diabetic retinal edema (9/25 subjects with DME, all reported after Day 90), macular degeneration (9/25 subjects with AMD), retinal haemorrhage (10/25 subjects with AMD), retinal disorder (5/25 subjects with AMD, 1/25 with DME) and retinal exudates (3 subjects each with AMD and DME) and retinal scar (3 subjects with AMD). Adverse events that occurred in more than 2 subjects include cataract (6 subjects), myodesopsia/ vitreous floaters (6 subjects), and vitreous detachment (6 subjects). These AEs may be related to the administration procedure.

In Studies DR-001 and AMD-002, all ocular AEs were considered mild or moderate in nature. In Study AMD-001, 2 AEs were considered severe in nature: retinal haemorrhage and retina scar.

In Study AMD-001, 5 AEs (1 case each) were considered related to the study medication: visual acuity reduced (110 µg), retinal haemorrhage (110 µg), vitreous degeneration (44 µg), visual disturbance (176 µg), and vitreous floater (176 µg). In Study DR-001, 3 AEs occurring in the same subject were considered related to study medication: anterior chamber cell, flare, and iritis (352 ug). In Study AMD-002 several ocular AEs were considered related to the injection procedure: subconjunctival haemorrhage, ocular pain, eye irritation, ocular itching, foreign body sensation, ciliary muscle spasm, and lacrimation increased. No AEs were considered related to the study medication in Study AMD-002 (Valentine, 2014).

Serious Ocular Adverse Events

In Study AMD-001, 3 subjects experienced 5 ocular SAEs during the study period (3 cases of retinal scar, 1 case of retinal haemorrhage, and 1 case of subretinal fibrosis). Only 1 SAE was considered related to study medication (retinal haemorrhage which resolved without sequelae). In Study AMD-002, 2 subjects in the IVT group (352 µg) experienced ocular SAEs in the study eye: macular degeneration retinal haemorrhage; none were considered related to study.

No serious ocular AEs were reported in Study DR-001 (Valentine, 2014).

Non-Ocular Adverse Events

Four non-ocular AEs reported in the Legacy Studies occurred in more than 2 subjects: diabetes mellitus inadequate control (20%, 5 subjects/25 diabetic subjects), diarrhea (6%, 3/50 subjects), hypertension (12%, 6/50 subjects), and triglycerides increased (8%, 4/50 subjects).

Three of the non-ocular AEs were considered possibly related to the study medication: 1 case each of increased triglycerides, decreased cholesterol, and increased gamma glutamyl transferase (GGT). All 3 of these events were mild and resolved without treatment.

There were no deaths among subjects treated with IVT DE-109 in any of the studies.

Adverse Events Related to Ocular Inflammation or Endophthalmitis Reported

The incidence of possible AEs related to any form of uveitis, ocular inflammation or endophthalmitis was determined in each of the Legacy studies. There were few AEs related to ocular inflammation reported during the studies: 2 cases of anterior chamber cells (44 µg in AMD-001 and 352 µg in DR-001), 1 case of anterior chamber flare (352 µg in DR-001) and 1 case of iritis (352 µg in DR-001). The 3 AEs in DR-001 occurred in the same subject who was reported to have iritis on Study Days 13-86 and anterior chamber cell and flare on Study Days 47-86.

The case of iritis was considered possibly related to study medication. Finally, there were no cases of endophthalmitis or sterile endophthalmitis reported during these studies.

Based on these data, there does not appear to be a significant safety concern for endophthalmitis or ocular inflammation with IVT doses of DE-109 of ≤352 µg in subjects without uveitis, with consideration for the disease states investigated in the Legacy studies.

Serious adverse events and deaths

- **Deaths**

There were two deaths during SAKURA study (one in 44 µg dose group and one in 880 µg dose group). Both of them were unrelated to study drug.

- **Serious adverse events**

In the Double-Masked analysis period, the incidences of SAEs were similar among the 3 dose groups. There was an increased incidence of choroiditis in the 44 µg dose group and a higher incidence of non-infectious endophthalmitis in the 880 µg dose group as compared to the 440 µg dose group. In the Open-Label analysis period, the overall incidences of SAEs decreased compared to the Double-Masked analysis period, with the exception of non-infectious endophthalmitis, endophthalmitis, and medication residue, which increased slightly.

Table 31: Summary of Serious Adverse Events in >1% of Subjects – Double-Masked, Open-Label, and Combined till Month 12 Analysis Periods

System Organ Class/Preferred Term	Double-Masked 44 µg (N=117) n (%)	Double Masked 440 µg (N=112) n (%)	Double-Masked 880 µg (N=117) n (%)	Double-Masked Overall (N=346) n (%)	Open-Label (N=211) n (%)	Combined till Month 12 (N=346) n (%)
Subjects with Any Serious AE(s)	27 (23.1)	27 (24.1)	24 (20.5)	78 (22.5)	37 (17.5)	104 (30.1)
Eye Disorders	23 (19.7)	17 (15.2)	20 (17.1)	60 (17.3)	23 (10.9)	77 (22.3)
Uveitis	5 (4.3)	8 (7.1)	8 (6.8)	21 (6.1)	3 (1.4)	25 (7.2)
Choroiditis	8 (6.8)	3 (2.7)	2 (1.7)	13 (3.8)	3 (1.4)	14 (4.0)
Cataract	3 (2.6)	3 (2.7)	3 (2.6)	9 (2.6)	3 (1.4)	14 (4.0)
Non-infectious endophthalmitis	0	1 (0.9)	4 (3.4)	5 (1.4)	6 (2.8)	10 (2.9)
Iridocyclitis	2 (1.7)	0	2 (1.7)	4 (1.2)	0	4 (1.2)
Vitritis	2 (1.7)	1 (0.9)	0	3 (0.9)	2 (0.9)	5 (1.4)
Glaucoma	1 (0.9)	1 (0.9)	0	2 (0.6)	2 (0.9)	4 (1.2)
Visual acuity reduced	0	3 (2.7)	0	3 (0.9)	0	3 (0.9)
Investigations	2 (1.7)	2 (1.8)	3 (2.6)	7 (2.0)	2 (0.9)	9 (2.6)
Intraocular Pressure Increased	2 (1.7)	1 (0.9)	2 (1.7)	5 (1.4)	2 (0.9)	7 (2.0)
Infections and Infestations	1 (0.9)	1 (0.9)	1 (0.9)	3 (0.9)	4 (1.9)	7 (2.0)
Endophthalmitis	0	0	1 (0.9)	1 (0.3)	3 (1.4)	4 (1.2)
General Disorders and Administration Site Conditions	1 (0.9)	2 (1.8)	3 (2.6)	6 (1.7)	5 (2.4)	9 (2.6)
Medication Residue	1 (0.9)	2 (1.8)	2 (1.7)	5 (1.4)	5 (2.4)	8 (2.3)

AE(s): adverse event(s). Note: Any subject who experienced multiple serious AEs within a system organ class or preferred term is countedonly once for that system organ class or preferred term. Subjects are classified by actual treatment received. Subject AT101-0001 was randomized to 440 µg group but received 44 µg at Day 1, Month 2, and Month 4, and is put in the 44 µg group. Subject IT115-0001 was randomized to 44 µg group but received 880 µg at Month 2, and is put in the 880 µg group. AEs are coded using MedDRA Version 16.0.

Other Significant Adverse Events in the SAKURA Study

Identified Risks

- Endophthalmitis: There were a total of 4 (1.2%) subjects with SAEs of endophthalmitis reported during the Combined till Month 12 analysis period, 1 subject in the 880 µg dose group during the Double- Masked analysis period and 3 subjects during the Open-Label analysis period. Of these, 3 subjects had endophthalmitis in the study eye (related to the injection procedure, but not related to the study medication). Of these 3 events, 2 events were culture negative and 1 was culture positive. One report of endophthalmitis in the fellow eye was assessed by the Investigator as not related to study medication or to the injection procedure. All 4 subjects were reported to have recovered from endophthalmitis.

- Traumatic Cataract: There have been no reports of traumatic cataract during the 12-month study period reported through the clinical database. Two reports of possible traumatic cataract have been reported through the drug safety monitoring.
- Sterile Endophthalmitis: Over the Combined till M12 analysis period, a total of 10 subjects experienced at least 1 SAE of non-infectious endophthalmitis. These AEs occurred in 1 subject while being treated with the Double-Masked 440 µg dose and 9 subjects while being treated with the 880 µg dose (either Double-Masked or Open-Label). Among these 10 subjects, 2 subjects had sterile endophthalmitis determined to be related to the injection procedure but not related to the study medication, 1 subject had sterile endophthalmitis determined to be related to both the injection procedure and the study medication, and 7 subjects had sterile endophthalmitis determined to be related to the study medication but not the injection procedure.
- Drug Depot in the Visual Axis: A total of 8 subjects had SAEs of medication residue during the Combined till M12 analysis period. All these SAEs were assessed by the Investigator as related to study medication and all resolved.
- Hypersensitivity, systemic: Seven subjects were identified. Three of the 7 subjects experienced a drug allergy attributed in the verbatim term to a concomitant medication (Bactrim, Alphagan P and Ofloxacin). Of the remaining four reports, two reports of urticaria occurred at >28 days after the last study drug injection and two reports of face swelling occurred 13 days and 79 days after the last study drug injection. Only one event occurred within 7 days of study drug injection and resolved within 20 days with treatment.

Potential Risks

- Retinal detachment: Over the Combined till Month 12 analysis period, 6 AEs of retinal detachment in 5 subjects were reported. A total of 5 events (two related to study medication) occurred in the study eyes of 4 subjects and 1 retinal detachment event occurred in the fellow eye of 1 subject. Three of the subjects with retinal detachment permanently discontinued study medication. All retinal detachment events were reported as resolved, except for 1 subject who experienced retinal detachment in both the study eye and the fellow eye.
- Increased intraocular pressure**:** A total of 70 (20.2%) subjects experienced any AE(s) of IOP increased in the study eye during the Combined till Month 12 analysis period.
    - A total of 58 subjects had AEs of IOP increased during the Double-Masked analysis period; 20 (17.1%) subjects in the 44 µg dose group, 18 (16.1%) subjects in the 440 µg dose group, and 20 (17.1%) subjects in the 880 µg dose group, respectively.
    - A total of 21 (10.0%) subjects experienced IOP increased as an AE during the Open-Label analysis period.

In total, 44 (12.7%) subjects experienced IOP increased AEs that were considered related to the study medication or the injection procedure with no apparent dose dependency.

- During the Double-Masked analysis period 3 subjects had SARs of IOP increased in the study eye (1 in each dose group).
- One serious suspected adverse reaction of IOP increased considered related to study medication occurred in the study eye during the Open-Label analysis period.

A total of 8 (2.3%) subjects experienced an AE of ocular hypertension in the study eye during the Combined till Month 12 analysis period.

- Ocular hypertension was reported as an AE for 5 subjects during the Double-Masked analysis period: 1 (0.9%) subject in the 44 µg dose group and 4 (3.4%) subjects in the 880 µg dose group.
- A total of 4 (1.9%) subjects had AEs of ocular hypertension during the Open-Label analysis period.

A total of 3 subjects had AEs that were considered related to the study medication or injection procedure: 2 (1.7%) subjects from the 880 µg dose group during the Double-Masked analysis period and 1 (0.9%) subject in the Open-Label analysis period. Only one subject had a SAE of ocular hypertension, which occurred during the Double-Masked analysis period in the 880 µg dose group. Although the amount of study medication injected is small (ie, 20 µL), the effect of IVT injections of DE-109 continues to be monitored.

- Cataract: Over the Combined till Month 12 analysis period, 9 (2.6%) subjects experienced any SAE of cataract in the study eye and 7 (2.0%) subjects experienced any SAE of cataract in the fellow eye. Four (4/346, 1.2%) subjects experienced a SAE of cataract in the study eye that was considered related to study medication or injection procedure.
- Vitreoretinal hemorrhage: No SAEs for vitreous or retinal hemorrhage were reported in the study eye.

Events of Special Interest

- Pregnancy: Two pregnancies and one spontaneous abortion were reported in this study.
- Medication Errors: A total of 13 (3.8%) subjects experienced a medication error during the Combined till Month 12 analysis period:
  - 4 subjects were injected with an incorrect dose (no AEs reported)
  - 3 subjects were injected with a non-protocol needle (1 AE of Air Bubble, and 1 AE of subconjunctival haemorrhage reported)
  - 3 subjects were injected with a non-protocol syringe (no AEs reported)
  - 2 subjects were injected with study medication that was incorrectly prepared prior to injection (protocol required study medication to be drawn into the syringe 60 minutes after removing from freezer and after 5 minutes of hand rotation; 1 AE of conjunctival hyperaemia reported)
  - 1 subject was injected at an incorrect injection site (1 AE of subconjunctival haemorrhage reported).

Systemic adverse events

The non-ocular AEs with an incidence ≥3% were nasopharyngitis and headache. The majority of AEs which were considered related to study medication or injection procedure were ocular AEs and the only suspected non-ocular AE with an incidence ≥1% was nausea.

The incidences of the potential AEs of sirolimus were very low and did not exhibit a dose dependent relationship. These AEs are considered extremely unlikely due to the low systemic exposure with DE-109.

There is also a potential for AEs related to delayed wound healing or activation of latent viral infections in the eye. The incidences of AEs which may be due to delayed wound healing or viral infections were minimal.

Laboratory findings

There were no clinically significant changes in the mean laboratory results, vital signs, physical examinations, and electrocardiograms. The intraocular pressure significantly increased in the study eye with respect to the fellow eye, treated with standard treatment. Therefore, this AE seems to be more linked to the IVT drug administration rather than to the uveitis condition.

Ophthalmic Examinations such as lid hyperemia, lid edema, conjunctival hyperemia, corneal oedema, etc. clinically assessed with slit-lamp biomicroscopy do not experienced significant changes from baseline. A slight increasing trend in the severity of cataract is observed.

Safety in special populations

The Applicant has submitted the safety profile of DE-109 by dose and by different subgroups covering age, gender, race and ethnicity, location of uveitis, duration of uveitis, etiology of uveitis, vitreous haze score at baseline, baseline BCVA, lens status at baseline, presence or absence of glaucoma at baseline and present and absence of macular oedema at baseline.

Safety profile by age

The incidences of common ocular AEs in the youngest age subgroup (18-24 years) were lower than those in the older age subgroups; however, the subgroup may be too small to draw inferences.

In the age subgroup 25-44 years (440 um dose group) iridocyclitis rose up to 35.9%, compared to 13 % in the 45-64 years age group. Again in the 440 ug dose group, the incidence of choroiditis fell with aging (12.8% vs 3.7% in the 25-44 vs 45-64 years group). In the same dose group the composite incidence of cataract and cataract subcapsular in the 25-44 years age group was 2.6%, and 14% in the age group 45-64 ys age group. Again, the incidence of raised intraocular pressure rose with age 12,8 vs 22.2% in these 2 age groups.

There were 3 common ocular SAEs in the study eye with incidences ≥3% in any dose group of the overall Safety Population: uveitis, choroiditis, and non-infectious endophthalmitis. There were no common ocular SAEs in the youngest subgroup (18-24 years). Serious AEs of choroiditis occurred at a higher incidence in subjects with age ≥65 years than the younger subjects in the 44 µg dose group.

Safety profile by race and ethnicity

Uveitis and choroiditis occurred at the highest incidence in Black/African American subjects in each dose group. Black/African American subjects also had the highest incidences of IOP Increased and iris adhesions among all race subgroups in the 880 µg dose group, and the highest incidence of dry eye in the 44 µg dose group. There were no consistent patterns by race or ethnicity apparent for the other SAEs.

Safety profile by gender

Incidence of cataracts and subcapsular cataracts observed were slightly larger in males than in females. Gender had no appreciable effect on the safety profile of DE-109 with regard to these common ocular AEs or SAEs in the study eye. There was no evidence for a higher risk of having the common systemic AEs in males compared to females.

Safety profile by etiology of uveitis

Ocular AEs of iridocyclitis, conjunctival haemorrhage, and increased IOP occurred at higher incidences in subjects with uveitis secondary to sarcoidosis compared to those with idiopathic uveitis. However, all 5 cases of serious non-infectious endophthalmitis occurred in subjects with idiopathic uveitis.

Safety profile by duration of uveitis

The trends toward higher incidence of AEs in subjects with longer time since diagnosis of uveitis may be due to recurrences in subjects with more severe or more chronic uveitis. A consistent dose response effect was not observed. There was no apparent pattern of SAEs by time since diagnosis of uveitis

Safety by Presence or Absence of Glaucoma at Baseline

The incidence of AEs of uveitis was numerically higher for the subgroup with glaucoma at baseline in the 440 µg dose group than in the subgroup without glaucoma at baseline; subjects with glaucoma at baseline appeared to have a higher incidence of increased IOP than those without glaucoma in each dose group.

Table 32: IOP-Related Events in the Study Eye ≥5% by Presence of Glaucoma at Baseline (Double-Masked Period)

	Glaucoma Present at Baseline			Glaucoma Absent at Baseline		
	44 µg	440 µg	880 µg	44 µg	440 µg	880 µg
Category	N=10 n (%)	N=14 n (%)	N=9 n (%)	N=107 n (%)	N=98 n (%)	N=108 n (%)
Elevation considered an adverse event						
Study Eye	2 (20.0)	5 (35.7)	5 (55.6)	18 (16.8)	13 (13.3)	15 (13.9)
Non-Study Eye	1 (10.0)	1 (7.1)	2 (22.2)	5 (4.7)	3 (3.1)	7 (6.5)
IOP increase ≥ 10 mmHg						
Study Eye	2 (20.0)	4 (28.6)	3 (33.3)	12(11.2)	8 (8.2)	14 (13.0)
Non-Study Eye	0	2 (14.3)	2 (22.2)	4 (3.7)	8 (8.2)	7 (6.5)
Elevation to >25 mmHg at any time						
Study Eye	2 (20.0)	4 (28.6)	2 (22.2)	13 (12.1)	6 (6.1)	13 (12.0)
Non-Study Eye	0	1 (7.1)	3 (33.3)	5 (4.7)	5 (5.1)	8 (7.4)
Elevation >30 mmHg at any time						
Study Eye	2 (20.0)	1 (7.1)	1 (11.1)	9 (8.4)	4 (4.1)	7 (6.5)
Non-Study Eye	0	0	1 (11.1)	3 (2.8)	3 (3.1)	2 (1.9)
IOP-Related Surgical Procedure						
Study Eye	0	0	1 (11.1)	0	1 (1.0%)	1 (0.9%)
Non-Study Eye	0	0	0	1 (0.9)	0	0
IOP-Related Laser Procedure						
Study Eye	0	0	0	0	0	0
Non-Study Eye	0	0	0	0	0	0
Vitrectomy						
Study Eye	1 (10.0)	0	0	3 (2.8)	1 (1.0)	4 (3.7)
Non-Study Eye	0	0	0	3 (2.8)	1 (1.0)	4 (3.7)

In general, subgroup analysis did not seem to show any relevant safety issues that determine the safety profile of this product. However, the multiple slices results in small sized group and it impairs achieving valid conclusions.

During the course of the assessment, the Applicant provided an analysis of the most relevant subgroups (i.e. age, gender, race, ethnicity, location of uveitis, etiology of uveitis and presence or absence of glaucoma at baseline) with independence of the dose (i.e. all treatment arms combined) in order to determine the main factors that may have an impact on the safety profile of Opsiria.

Slight tendencies were noted in increased AE reporting in the following subgroups:

- Older patients
- Black or African American patients
- Non-Hispanic or Latino patients
- Patients with a medical history of Sarcoidosis
- Patients with panuveitis or an anterior component of uveitis
- Duration of diagnosis longer than 12 months
- Use of IOP lowering medications at baseline or at Month 5
- Presence of glaucoma at baseline or at Month 5

Differences in AE reporting were also noted between the geographic regions. The effect of these differences on the overall profile of DE-109 is not considered substantial because the safety analyses have been conducted and reported on the entire ITT population rather than by geographic region.

Immunological events

Seven subjects were identified with systemic hypersensitivity (urticaria, face swelling, drug allergy), only one event occurred within 7 days of study drug injection: “mild drug allergy to Ofloxacin” and resolved within 20 days with treatment that included amoxicillin, loratidine and cetirizine.

Regarding the concept of a localized non-specific innate immune response to the 880 µg dose drug depot, in the monkey ocular toxicity study only the highest dose of 880 µg caused inflammatory responses, but mild in the severity and reversible. A correlation with the mass of drug particles and contact duration in the vitreous body was proposed.

Healthy eyes used in the nonclinical monkey study seem to be relatively resistant to foreign objects and doses higher than 880 µg in monkeys (human equivalent dose of 1760 µg) may be required to elicit a similar response. In contrast, the eyes of the SAKURA Study subjects with active NIU-PS seem to be more susceptible to this innate immune response due to their pre-existing inflammatory condition so that lower equivalent doses (880 µg in human patients) may be sufficient to trigger this reaction.

According to the non-clinical toxicity studies and the main clinical study a localized non-specific immune response may well play a role in U–shaped dose response curve and in the relatively higher incidence of ocular inflammatory AEs with the higher (880ug) dose of DE-109.

The CHMP considered the impact in patients whose eye volume is smaller than the average, e.g. excessive hypermetropy, microphthalmus, phtysis bulbi. No data could be found regarding baseline bulbus lengths.

Safety related to drug-drug interactions and other interactions

No formal interaction studies have been performed. Since DE-109 administration results in systemic exposure below the levels required for systemic immunosuppression, no systemic interactions are anticipated. DE-109 has been used concomitantly with topical and systemic corticosteroids and topical IOP lowering medicinal products. In general, there does not seem to be any drug interactions.

Subjects who were treated with systemic corticosteroids at baseline experienced somewhat higher incidences of AEs and SAEs of uveitis and other common ocular AEs related to ocular inflammation (iridocyclitis, conjunctival haemorrhage, eye pain, intermediate uveitis and choroiditis) than subjects not treated with systemic corticosteroids.

The safety data from the SAKURA Study suggest that the use of IOP-lowering medications at baseline is associated with higher risk of AEs of increased IOP and recurrences of uveitis. Serious AEs of uveitis occurred at a higher incidence in subjects treated with IOP-lowering medications at baseline in the 440 µg dose group but not the other dose groups. Although the incidences of Uveitis and Macular Oedema were numerically higher in subjects with prior vitrectomy at baseline in the 440 and 880 µg dose groups than those without prior vitrectomy, there were too few subjects with prior vitrectomy to make a conclusion concerning the impact of vitrectomy on the safety profile of DE-109.

Not surprisingly, subjects who were treated with rescue therapy before Month 5 had higher incidences of AEs and SAEs of uveitis and AEs of iridocyclitis and intermediate uveitis than subjects who did not require rescue therapy (as rescue therapy was often used to treat these events).

For subjects treated with concomitant therapy before Month 5 which might have an impact on ocular inflammation, the incidences of ocular AEs that occurred AFTER subjects received any concomitant therapy were generally lower than those in the overall Safety Population during the Double-Masked Period.

The evaluation of AEs and SAEs after use of IOP-lowering Medications suggests a slightly higher incidence of AEs of Increased IOP than that in the overall Safety Population for the Double-Masked Period, which is not an unexpected observation; however, dose dependency was not apparent.

Discontinuation due to AEs

During the Combined till Month 12 analysis period, 30 subjects withdrew from the study due to AEs, nearly all of which were Ocular AEs. The most common AEs leading to discontinuation were panuveitis or posterior uveitis (44 µg, 4 subjects; 440 µg, 1 subject; 880 µg, 4 subjects) and IOP increased (44 µg, 3 subjects; 440 µg, 2 subjects; 880 µg, 0 subjects). Thirteen of the events that led to discontinuation were considered related to study medication or injection procedure: 3 subjects in 880 µg group due to panuveitis or posterior uveitis, 2 subjects in 880 µg group and 1 subject in 440 µg group due to sterile/non-infectious endophthalmitis and the rest were reported in the three groups due to several reasons. No dose-dependence in relation to withdrawals due to AEs is observed.

3.3.8. Discussion on clinical safety

The safety analysis of DE-109 (Opsiria) for IVT injection in patients with non-infectious uveitis in the posterior segment is mainly focused on the safety data obtained from the 12-month SAKURA Study 1. During the course of the assessment of this application, the Applicant submitted global (unblended) results from the SAKURA Study 2 (still ongoing). However, given that a placebo arm is lacking in both SAKURA pivotal trials, the real effect on safety derived from the IVT injection of sirolimus is unknown. In addition, 3 legacy studies comparing sirolimus administered intravitreally and subconjunctivally in

other ophthalmic indications (age-related macular degeneration and diabetic macular edema) are considered supportive. However, the differences in dosing (doses lower than that intended for marketing, most of patients received only one injection) and in conditions treated make the information provided only of limited value. Likewise, safety outcomes from the SAVE study did not indicate a different safety profile for IVT sirolimus in comparison to the one observed in SAKURA study. This study has several limitations (small sample size, dose intravitreally administered is lower than the dose intended to be authorised, absence of sham group) and no sound conclusion could be drawn.

Indirect comparisons between 44 µg DE-109 dose and sham arm from the HURON study (dexmethason implant) provide further safety information, which was considered supportive for the overall safety analysis.

The safety evaluation of IVT DE-109 covers a comprehensive battery of examinations, both ocular and systemic measurements which was deemed acceptable.

A total of 347 patients (348 eyes) were included in SAKURA study. Only 112 patients received treatment with 440 µg, the finally selected dose to be marketed. There is a more extensive population exposed to lower (44 µg) and higher doses (880 µg) in comparison to patients exposed to 440 µg dose. Additional safety data coming from 187 patients of the SAKURA Study 2 have been presented. Overall, the safety database could be considered large enough to characterize the safety profile of Opsiria. Around 70% of patients received 3 IVT injections during the double-masked period and approximately 50% of patients received 3 additional injections during the open label period.

It should be pointed out that data beyond 6 months using the dose intended to be authorised are limited and therefore long-term safety profile is at present uncertain. Although there is some experience with higher doses (117 patients received 880 µg) up to 12 months, no dose-dependency relationship with respect to the occurrence of adverse events has been identified. Therefore, long-term safety for the 880 µg dose provided limited value for the 440 µg dose and sound safety conclusions could not be established at the time of this report. Moreover, non-infectious uveitis is a chronic condition and the submission of only 6-month data for 440 µg dose is considered a source of concern. The Applicant submitted additional data coming from patients that received double-masked treatment for 12 months. However, the number of subjects that were retreated from month 6 to month 12 is considered very limited and no sound conclusions could be drawn. Data from SAKURA Study 2 have also been presented which provides supplementary information from a safety point of view,. It is of note that there is currently no experience with the use of intravitreal medicinal products containing sirolimus. Hence, long-the term safety profile for the 440 µg dose should be further characterised. Data from the SPRING study (ongoing) were expected to provide long-term efficacy and safety data of patients treated with the 440 µg dose, but a more comprehensive proposal from the Applicnt was to be provided.

Overall, AE incidence rates in the study between the two higher dose groups were remarkably similar, with the exception of AEs related to ocular inflammation which were higher in the 880 µg dose group. The most frequently reported ocular adverse events were iridocyclitis, uveitis, conjunctival haemorrhage, eye pain, choroiditis, intermediate uveitis, conjunctival hyperaemia, cataract and cystoid macular oedema. In general, no clear trend was observed in relation to the dose and none of the three doses showed an evident favorable safety profile. Several events were related to the worsening of the condition or they are complications of uveitis. A placebo arm would have been of value to clarify the role of the condition versus the medication itself.

The incidence of non-ocular systemic adverse events was low and no specific pattern indicating safety risks with the treatment was revealed. This is consistent with the low sirolimus levels detected in the systemic circulation after intravitreal administration of the product.

The occurrence of AE reported during the open label period, when all subjects were treated with the 880 µg dose were in general lower than the double-masked period, which may also indicate that no dose-dependent effect on safety is observed.

Regarding the study medication-related adverse events, it should be noted the characteristics of the formulation in relation to the safety profile. DE-109 forms a depot and slowly releases sirolimus in the ocular tissue. Consequently, it provides a high local drug concentration with very little systemic exposure. This effect correlates with the observation that the majority of AEs regarded as related to study drug or IVT injection procedure were ocular AEs and the incidence of non-ocular AEs was low. The most commonly drug-related AEs reported in the eye were iridocyclitis, uveitis, non-infectious endophthalmitis, medication residue and IOP. All of them were observed with higher incidence in DE-109 440 µg dose group in comparison to DE-109 44 µg dose group. During the double-masked period, iridocyclitis, uveitis and non-infectious endophthalmitis seem to be dose-dependent. However, the rest of AEs reported did not show a clear trend in relation to the dose administered. Non-ocular AEs reported with an incidence ≥3% were nasopharyngitis and headache.

The most common AE related to IVT injection was conjunctival haemorrhage. In general, higher doses are expected to cause more adverse events. However, in this case the concentration of sirolimus administered did not seem to match the AEs reported.

In relation to AEs occurring within 14 days of injection, conjunctival haemorrhage (14.3%), iridocyclitis (8.9%), uveitis (7.1%), eye pain (8.9%) and conjunctival hyperaemia (7.1%) were the most frequently reported. All but conjunctival hyperaemia followed a dose dependent trend.

An indirect comparison between the safety profile of DE-109 recalled in the SAKURA study and the sham group of the HURON study was performed in order to value the role of the low dose arm (44 µg) as a “control” arm. In general patients treated with sirolimus showed higher incidence of AEs than patients in the sham group in tehn HURON study, except for conjunctival haemorrhage, eye pain, visual acuity reduced and conjunctivitis. However, the two groups to be compared in this retrospective analysis have several differences in the administration schedule of both products, in the baseline characteristics of the population, in the treatments allowed during the studies and in the reporting of AEs. Moreover, the lack of dose-AE relationship of sirolimus intravitreal treatment rendered the value of this indirect comparison to be limited.

Legacy studies did not reveal any relevant AEs. Rather, several limitations of the studies mentioned above did not allow to draw valid conclusions.

Almost one third of patients (30.1%) of patients reported at least one serious AEs (SAE) during the 12 month treatment period. The majority of SAEs were related to ocular disorders. No systemic SAE was reported. As already identified with the most common AEs, there was no dose relationship in the incidence of SAEs. Medication residue and endophthalmitis seemed to occur with higher incidence over time and when the 880 µg dose was administered. This is not unexpected given that patients are exposed to more IVT injections over time and the strength of sirolimus administered is higher from month 6 to month 12. Medication residue was reported as an SAE in 8 patients and it slightly increased in the open-label analysis in comparison to the double-masked period. Therefore, the risk of sirolimus accumulation in the ocular tissue cannot be ruled out. Further justification concerning this potential risk and its influence in the proper functioning of the eye is required. The Applicant has explained that no accumulation of study drug with the repeated administration is expected. The main setback is based on

the possibility of migration of the drug depot/precipitate into the visual axis resulting in visual acuity disturbances. This occurrence has been classified as a SAE and the preferred term by MedDRA is "Medication residue". Adequate instructions concerning the appropriate technique for injection are included in the product information, which will minimize the injection of Opsiria in the visual axis.

Among the AEs of interest, the occurrence of endophthalmitis is worth mentioning with 10 episodes reported during the 12-month period (4 of them classified as serious). This information is adequately described in the SmPC. Additionally, specific recommendations included in section 4.4 of the SmPC in order to minimise this identified risk caused by the IVT injection (i.e. proper aseptic injection techniques and patients monitorisation) are considered sufficient.

In addition, retinal detachment AE was also reported with higher incidence in the study eye versus the fellow eye (5 AEs in the study eye versus 1 AE in the fellow eye). Furthermore, cataract events slightly increased in the study eye with respect to the fellow eye (2.6% vs. 2%).

Medication errors were identified in 13 patients during the 12-month study. In order to minimize these potential errors in clinical practice, it should be guarantee that all the ophthalmologists qualified to administer this product by intravitreal use have all the necessary material for the injection (i.e. needles and syringe) available. The Applicant has confirmed that the needles and the syringe are not included in the same container as the vial of Opsiria. Given that there were six patients where different syringe/needle was used, the Applicant is strongly recommended to include the syringe and the two needles required in the same package as the vial in order to minimize this potential risk. In addition, in order to assure a safe use of the product, a pre-filled syringe was recommended. The Applicant is not intended to change the presentation. However, it was acknowledged that several risk minimisation measures that seem to be appropriate to prevent or reduce any risk of medication errors have been submitted. In addition, extensive instructions for use of vials, syringes and needles will be included in the product information.

There were no clinically significant changes in the mean laboratory results, vital signs, physical examinations, and electrocardiograms. The intraocular pressure significantly increased in the study eye with respect to the fellow eye, treated with standard treatment. Therefore, this AE seems to be more linked to the IVT drug administration rather than to the uveitis condition.

Ophthalmic examinations such as lid hyperemia, lid edema, conjunctival hyperemia, corneal oedema, etc. clinically assessed with slit-lamp biomicroscopy did not reveal significant changes from baseline. A slight increasing trend in the severity of cataract was observed.

The Applicant has submitted safety data of DE-109 by different subgroups covering age, gender, race and ethnicity, location of uveitis, duration of uveitis, etiology of uveitis, vitreous haze score at baseline, baseline BCVA, lens status at baseline, presence or absence of glaucoma at baseline and present and absence of macular oedema at baseline. In general, subgroup analyses did not seem to show any relevant safety issues. The differences observed between groups may also be due to the small sample size of some groups, which prevents achieving valid conclusions. During the course of the assessment, the Applicant was requested to provide an analysis of the most relevant subgroups irrespective of the dose in order to determine the main factors that have an impact on the safety profile of DE-109. These data have been presented and a slight increase of AEs were noted in some subgroups (older patients, black or African American patients, non-Hispanic or Latino patients, patients with a medical history of sarcoidosis, patients with panuveitis or an anterior component of uveitis, duration of diagnosis longer than 12 months, European an US patients, use of IOP lowering medications at baseline or at Month 5 and presence of glaucoma at baseline or at Month 5)

Concerning the subgroup analysis based on the presence of glaucoma at baseline, a higher incidence of IOP increase was observed in the study eye versus the non-study eye. Patients with glaucoma at baseline presented a higher incidence of IOP with respect to those patients with glaucoma absent at baseline. These data indicate that IOP increase and intravitreal injection of sirolimus are connected, especially when glaucoma is present. The potential worsening of glaucoma condition with the intravitreal administration of DE-109 was considered worrying. The Applicant has adequately justififed this concern and detailed information concerning the management of the intraocular pressure increased has been described in section 4.4 of the SmPC. However, the Applicant was asked to provide information concerning the number of patients without glaucoma at baseline that developed glaucoma during the study.

Data on prostaglandins analogs use and its influence on anterior and posterior uveitis were requested. The Applicant has submitted these data showing that the incidence of AEs seems to be higher when using prostaglandin analogs. Additional clarifications are needed.

There does not seem to be any drug interactions between sirolimus and other medication usually administered in patients with uveitis such as systemic corticosteroids and IOP lowering medication.

A potential interaction between repeated IVT injection procedure and eye structure may occur. Theoretically, the repeated IVT injection over long time – even if bimonthly - might damage the structure of sclera and other layers of the eyeball while inserting, expelling the content and pulling back. As sirolimus might interfere with wound healing, formation of scar tissue and thereby change in shape of the eyeball may happen. Data on bulbar lengths and discussion on the potential deformation of eyeball shape was requested from the Applicant. According to the responses, no bulbus length was measured in the Sakura Study. Some additional concerns in relation to the scarring tendency following repeated intravitreal injections were raised.

There were two deaths during SAKURA study (one in 44 µg dose group and one in 880 µg dose group). Both of them were unrelated to study drug.

The majority of patients discontinued the treatment due to panuveitis, posterior uveitis or increased IOP. The 440 µg dose showed less patient discontinuations due to AEs, which is reassuring. However, no dose-dependent relationship with respectto withdrawals due to AEs is observed.

3.3.9. Conclusions on clinical safety

The Applicant general approach for the safety analysis was considered acceptable. However, some weaknesses have been identified such as the absence of a placebo arm in the SAKURA study. This prevents from defining the real safety profile of IVT DE-109 in the treatment of non-infectious uveitis. SAKURA Study 2, legacy studies in other ophthalmic indications and SAVE study providedsupportive data.

The local administration of DE-109 appeared to be well tolerated in patients with non-infectious uveitis. The most frequently reported ocular AEs were iridocyclitis, uveitis, conjunctival haemorrhage, eye pain, choroiditis, intermediate uveitis, conjunctival hyperaemia, cataract and cystoid macular oedema. Nevertheless, the incidence of AEs was similar in the three sirolimus groups (44, 440 and 880 µg) and none of the three doses showed a clearly favorable safety profile. Moreover, the lack of dose proportionality in relation to the incidence of AEs may pose some difficulties for the extrapolation of the results.

The most commonly drug-related AEs reported in the eye were iridocyclitis, uveitis, non-infectious endophthalmitis, medication residue and IOP. All of them were observed with higher incidence in the

440 µg dose group in comparison to the 44 µg dose group and the majority were associated to the worsening of the condition, the drug product or the intravitreal injection. Non-ocular AEs reported with an incidence ≥3% were nasopharyngitis and headache.

The main uncertainty at the time of this report was related to the long-term safety profile of DE-109 in the treatment of non-infectious uveitis. Only 112 patients were exposed during 6 months to the dose intended to be authorised (440 µg). Considering that the proposed indication for this product is a chronic condition and a slightly higher incidence of some important adverse events such as IOP increased, endophthalmitis and medication residue were observed over time, the limited data available beyond 6 month was a concern. In addition, other concerns such as the number of patients that develop glaucoma during the study, the causality assessment of some ocular AEs, the scarring tendency following repeated IVT injections, the worsening of AEs in patients treated with prostaglandin analogues and the content of the packaging required further discussion.

3.3.10. Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the Applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

3.3.11. Risk management plan

The RMP review is presented in the PRAC Rapporteur Assessment Report (separate report, not published).

4. Orphan medicinal products

According to the conclusion of the COMP (EC Decision dated 30 August 2011) the prevalence of the "condition" chronic non-infectious uveitis is 4.1 per 10000 individuals in the EU.

5. Benefit risk assessment

Opsiria is an intravitreal solution containing sirolimus (rapamycin) intended for the chronic treatment of non-infectious uveitis of the posterior segment of the eye. Sirolimus is already available on the market (oral route of administration) for the prophylaxis of organ rejection in adult patients at low to moderate immunological risk receiving a renal transplant. The therapeutic action in uveitis is based in the same mechanism of action claimed for the systemic administration.

The Applicant has performed two Phase 3 trials (the 2nd was ongoing at the time of this report). One of them, SAKURA Study 1, a double-blind, low dose-controlled trial was the basis of this application.

Benefits

Beneficial effects

Though steroids are effective in controlling inflammation, they cannot be used long-term without serious side effects. However, chronic treatment is required in some severe cases of posterior or intermedia uveitis. Immunosuppresants allow corticosteroids to be tapered off (corticosteroid-sparing agents) while providing effective control of the chronic eye inflammation. None of these had been approved in uveitis in first-line therapy at the time of this report. Opsiria is the first

immunosuppressant seeking indication for intravitreal treatment of uveitis. This represents also a novel route of administration for sirolimus, i.e. directly at the target location, with a very low systemic exposure to the product. This has the potential to result in a more favourable safety profile.

When Opsiria was administered to patients with posterior uveitis in the pivotal clinical trial SAKURA 1, after five months (three injections) of treatment the proportion of VH 0 responders at Month 5 (i.e., achieved complete resolution of ocular inflammation) was statistically significantly (p=0.0252) higher in the 440 µg dose group (22.8%) compared with the 44 µg dose group (10.3%) which served as low dose control. The proportion of VH 0 responders at Month 5 was numerically higher in 880 µg dose group (16.4%) compared with the 44 µg dose group, but the difference was not statistically significant (p=0.1823).

The key secondary endpoint, VH 0 or 2 unit responder rate, which was considered a clinically meaningful improvement in inflammation, at Month 5 was 28.0% in the 440 µg dose group vs 16.2% in the 44 µg dose group which was maintained over the study period with bimonthly IVT injections. The proportion of subjects who achieved clinical quiescence of NIU-PS with a VH score of 0 or 0.5+ at Month 5 (p=0.0081) was significantly higher in 440 µg dose group vs 44 µg dose group.

A numerically favourable response was measured in corticosteroid tapering success (76.9% vs 63.6%), need of rescue therapy (14.0% vs 22.2%), and improvement of visual acuity, although statistical significance was not reached.

A subgroup of patients with uveitis without an anterior component (also panuveitis) was identified in which a better response in terms of reduction of inflammatory activity was observed. The proportion of patients with VH 0 was 30% vs 9.2% in the control group (percentages for the primary analysis in the global population were 22.8% vs 10.3%). A similar response was reported when response was defined as VH improvement.

Uncertainty in the knowledge about the beneficial effects

The population recruited in the study reasonably represented the spectrum of the proposed target population. A total of 78% of patients included had an idiopathic uveitis, a higher percentage than that usually reported. Although highly variable depending on geographical region and anatomical location of uveitis (Wakefield 2005, Nguyen 2013), it might also be reflecting differences between countries (especially with those with limited diagnostic resources). In this respect, only 11.1% of patients were recruited in EU countries. Given the relevance of geographical differences, it may compromise the extrapolation of the results. In fact, the responder rates between regions were rather different. The responder rate in India was 31.4% compared to the 11.8% value in the EMEA region. Paradoxically, the placebo group responder rate in the EMEA was higher than in the 440 µg dose group, with both being very small, slightly above 10% rate out of few participants.

The clinical relevance of the size of the effect is questionable. The treatment effect observed in vitreous haze was not convincingly translated into a clear benefit when other relevant outcomes such as visual acuity, macular edema, corticosteroid tapering or need of rescue therapy were examined. Without submitting new data during the procedure, the Applicant has pointed out some groups of patients in which the benefit was more evident (patients with macular oedema without epiretinal membrane, n=7; patients with worst VA at baseline, n=14). However the small size of these subgroups and the fact that they were explored *a posterior* do not allow ruling out a chance finding.

Also, the majority of patients on corticosteroids tapered them and maintained the inflammation controlled regardless of the sirolimus dose. In general, the response achieved by the intermediate dose

was better than that observed for the high and low dose but the size of the differences between groups was of uncertain relevance.

Without a placebo/sham group of reference, the clinical value is difficult to establish. Of note, the size of the effect is smaller than that initially estimated (a difference of 16% between groups). For comparison, 60% of patients treated intravitreally with sirolimus 352 µg in the SAVE study (Nguyen 2013) showed a reduction of two steps or more of vitreous haze at month 3 and 40% of patients at month 6. In the HURON study, where patients with posterior non-infectious uveitis were treated with dexamethasone, 31.2% of patients treated with 700 µg and 28.9% of patients treated with 350 µg achieved vitreous haze score of zero, compared to 14.5% of those treated with sham at Week 26.

Although corticosteriod tapering was possible in a large proportion of patients, the question remains to what extent DE-109 represents a steroid sparing drug. Another practical aspect of the study outcome is, whether the responder rate is large enough to allow clinicians withdraw systemic steroid or other systemic immunmodulant treatment. Is there any threat that withdrawing a definitely effective treatment results in undertreatment and worsening of posterior uveitis? There are no comparative studies available for DE-109 with other therapies like corticosteroids or immunomodulators. Therefore positioning of IVT sirolimus and determining it's place in therapy was difficult at the time of this report.

Also, the fact that an effect was only observed with the 440 µg dose (and not with the higher active dose) does not help to clarify the efficacy of the product. The response exhibited by patients treated with 880 µg was unexpectedly lower than that of patients treated with the intermediate dose. This inverted U-shaped (or bell-shaped) pattern of response has been explained by the Applicant by the development of a non-specific innate immune response related to the mass of drug particles and contact duration in the vitreous body. The local reaction resulting in exacerbated inflammation would mask or reduce the anti-inflammatory efficacy of the product. Preservatives, mechanical/rheologic stress due to physical contact, the use of high doses and the pre-existing inflammatory condition have additionally been proposed by the Applicant as relevant factors with potential influence. This dose-dependent inflammatory response has been already described for triamcinolone and correlated with the presence of precipitated particles in ocular tissues. It has been described as sterile endophthalmitis reported in rare instances (< 2%). Five cases of non-infectious endophtalmitis were described during the double-blind period of the SAKURA 1 study. The incidence of this event (1.4%) was within the range expected according to literature. No additional case of sterile endophthalmitis was reported during the open label phase (month 6 to month 12) where all patients were treated with the high dose on a bi-monthly basis. In this period no dramatic change in efficacy was observed in the 440 µg group of patients (or in the 44 µg) that could be explained by this dose-response local immune reaction. Therefore, although theoretically possible, the proposed mechanism is not supported by clinical observations.

With respect to long-term efficacy data, there is limited data of the intended dose beyond 6 months. This represents one of the drawbacks of this application. The fact that patients are being treated (from Month 12 to Month 24) with a dose already discarded due to lack of efficacy is also an issue. As a consequence of the results from SAKURA 1 the Applicant informed the CHMP that the following amendments have been implemented in the second SAKURA study: the study has been shortened to 6 month double-blind period (no open label phases are going to be performed) and patients on 880 µg dose have been withdrawn from the study. It means that the population recruited in SAKURA 2 will be composed by patients treated under different regimens according to the recruitment date.

Some global results on the second SAKURA study have been submitted during the course of the assessment. They only provide a general picture (blinded) on the overall population included. Although consistent with the previous Study these results are of limited supportive value.

A 1-year open-label extension study (SPRING Study) is providing access to the 440 μg dose, as needed, for up to one year, for patients completing the SAKURA study. As there is limited efficacy and safety data for this proposed dose beyond 6 months these results will provide supporting information on the safety profile and likely, on the persistence of the effect.

The application is based on a single pivotal trial not finalised yet, which could in principle be sufficient to support indication MAA application provided convincing and robust data on the efficacy and safety are provided. The concerns raised above suggest that further reassurance is needed. At the time of this report, the confirmation of an effect appears necessary. It should be given by the second SAKURA study, still ongoing.

Risks

Unfavourable effects

In general, the majority of AEs were related to eye disorders. The most frequently observed ocular AEs were iridocyclitis, uveitis, conjunctival haemorrhage, eye pain, choroiditis, intermediate uveitis, conjunctival hyperaemia, cataract and cystoid macular oedema. Those regarded as related to the study medication included non-infectious endophthalmitis (44 μg: 0%, 440 μg: 0.9% and 880 μg: 3.4%), medication residue (44 μg: 0.9%, 440 μg: 5.4% and 880 μg: 5.1%) and IOP (44 μg: 6.0%, 440 μg: 10.7% and 880 μg: 8.5%). Iridocyclitis and uveitis were the most frequently reported AEs, most likely due to the study design because subjects with baseline diagnosis of panuveitis and/or anterior uveitis were also enrolled, and all subjects were tapered off topical corticosteroids before randomization. The most frequent AE related to IVT injection was conjunctival haemorrhage (44 μg: 14.5%, 440 μg: 13.4% and 880 μg: 15.4%), eye pain, conjunctival hyperemia and IOP increased. In relation to AEs occurring within 14 days of injection, conjunctival haemorrhage, iridocyclitis, eye pain, uveitis and conjunctival hyperaemia were the most frequently observed.

Non-ocular AEs reported with an incidence ≥3% were nasopharyngitis and headache.

Almost one third of patients (30.1%) reported at least one SAE during the 12 month treatment period. The majority of SAEs were related to ocular disorders. No systemic SAE was reported. Medication residue, endophthalmitis and medication errors are important unfavourable effects identified.

Medication residue was reported as a SAE and slightly increased in the open-label analysis in comparison to the double-masked period was observed. This event is related to the the possibility of migration of the drug depot/precipitate into the visual axis resulting in visual acuity disturbances. Information on the proper injection technique is already included in the SmPC. In addition, no risk of sirolimus accumulation in the ocular tissue after repeated administrations is expected.

Retinal detachment AE was reported with higher incidence in the study eye versus the fellow eye (5 AEs vs. 1 AE). Furthermore, cataract events slightly increased in the study eye with respect to the fellow eye (2.6% vs. 2%). This incidence is not surprising considering the administration route of the product. Cataracts in phakic patients showed a trend of increasing severity with time, which was dose dependent. The changes in cataract severity might be reflection of the baseline uveitis and of previous corticosteroid therapy.

Regarding IOP increased, data indicated that intravitreal injection of sirolimus and the increase of IOP are known to be connected especially when glaucoma is present.

An analysis of the most relevant subgroups irrespective of the dose was provided in order to determine the main factors that have an impact on the safety profile of DE-109. A slight increase of AEs were noted in some subgroups (older patients, black or African American patients, non-Hispanic or Latino

patients, patients with a medical history of sarcoidosis, patients with panuveitis or an anterior component of uveitis, duration of diagnosis longer than 12 months, European and US patients, use of IOP lowering medications at baseline or at Month 5 and presence of glaucoma at baseline or at Month 5).

Uncertainty in the knowledge about the unfavourable effects

DE-109 administered intravitreally is not free of AEs. The lower dose (44 μg) showed a similar safety profile compared to the other two doses (440 μg and 880 μg). No dose relationship in the incidence of AEs was observed and the lack of placebo is an important limitation of the study.

Data beyond 6 months using the dose intended to be authorised (440 μg) are limited. Although there is some experience with higher doses up to 12 months (117 patients received 880 μg), no dose-dependency relationship with respect to the occurrence of adverse events has been identified. Therefore, the behaviour of the 880 μg dose is unexpected and it cannot be considered as the "worst-case scenario". Moreover, given that non-infectious uvetitis is a chronic condition, long-term treatment may be necessary for the management of this condition. In general, there is currently no experience with the use of intravitreal medicinal products containing sirolimus and at least one year exposure at dosage levels intended for clinical use would be necessary. Hence, although additional data have been submitted, long-term safety is at present uncertain and should be further characterised. Data from the SPRING study (ongoing) is expected to provide long-term efficacy and safety data of patients treated with the 440 μg dose.

The majority of AEs reported were related to the study medication (i.e. non-infectious endophthalmitis, medication residue, IOP increased), to the IVT injection (i.e. conjunctival haemorrhage, eye pain, conjunctival hyperaemia, IOP increased) and to the worsening of the underlying disease or complications derived from the disease (i.e. uveitis, iridocyclitis). However, the following minor uncertainties need to be addressed.

The IVT procedure itself is invasive, traumatizing the sclera and other layers of the eye, even if a fine needle is used by experienced person. By repeated injections there might be a chance for formation of series of fine scars which may lead to changing the shape of the eyeball. Additional questions have been raised on this issue.

Medication errors were identified in 13 patients during the 12-month study. In order to assure a safe use of the product, a pre-filled syringe was recommended. The Applicant is not intended to change the presentation. However, several risk minimisation measures that seem to be appropriate to prevent or reduce any risk of medication errors have been submitted. In addition, extensive instructions for use of vials, syringes and needles will be included in the product information. Regarding the packaging, the Applicant has confirmed that the needles and the syringe are not included in the same container as the vial of Opsiria. Given that there were six patients where different syringe/needle were used, the Applicant is strongly recommended to include the syringe and the two needles required in the same package as the vial in order to minimize this risk.

Data on prostaglandine analogs use and its influence on anterior and posterior uveitis were requested. The Applicant has submitted these data showing that the incidence of AEs seems to be higher when using prostaglandin analogs. Additional clarifications are needed.

Data on bulbar lengths and discussion on the potential deformation of eyeball shape was requested to the Applicant. According to the responses, no bulbus length was measured in Sakura Study. Some additional concerns in relation to the scarring tendency following repeated intravitreal injections were also raised.

Patients with glaucoma at baseline presented a higher incidence of IOP increased with respect to those patients with glaucoma absent at baseline. Although the intravitreal injection procedure and the occurrence of IOP increased are known to be connected, further discussion on the potential worsening of glaucoma condition in relation to the intravitreal administration of DE-109 was required. The Applicant has adequately justifiifed this concern and detailed information concerning the management of IOP increased is described in section 4.4 of the SmPC. However, the Applicant should provide information concerning the number of patients without glaucoma at baseline that developed glaucoma during the study.

Effects Table

Table 33: Effects Table for DE-109 in the chronic treatment of non-infectious uveitis of the posterior segment of the eye.

Effect	Short Description	Unit	44 µg	440 µg	880 µg	Uncertainties / Strength of evidence	Refs.
Favourable Effects							
VH Response	VH score of 0 at Month 5	%	10.3	22.8[a]	16.4[b]	Lack of a placebo arm limits the assessment of the clinical value. Small differences with respect to the control group. Borderline statistical significance. Questionable clinical relevance of the effect size. Discrepancies in the response between groups according to geographical distribution. Lower effect of the high dose than the intermediate dose.	
	VHscore of 0 or 2-unit response at Month 5		16.2	28.1[a]	19.0[b]		
	VH score of 0 or 0.5+ at Month 5		35.0	52.6[a]	43.1[b]		
Corticosteroid tapering success	Success if the overall prednisone-equivalent dose being tapered off to ≤ 5 mg/day at Month 5	%	63.6	76.9	66.7	The lack of a relevant differences between groups raises concerns related to the role of sirolimus as corticosteroid-sparing.	
Reduction in the need for rescue therapy	Use of rescue therapy before Month 5	%	22.2	14.0	18.1	The effect observed in vitreous haze was not convincingly translated into clear benefit on need of rescue therapy.	
BCVA	% subjects with improvement of 15 letters	%	11.4	13.1	9.5	Small difference with respect the control group.	
Unfavourable Effects							
Endophthalmitis (infectious/non-infectious)	Incidence of endophthalmitis (Combined till Month 12 analysis period)	%	0	0.3	3.8	AEs of non-infectious endophthalmitis may be related to innate immune response associated with higher doses, to study medication or to injection procedure. AEs of infectious endophthalmitis are associated with the injection procedure.	

Effect	Short Description	Unit	44 µg	440 µg	880 µg	Uncertainties / Strength of evidence	Refs.
Retinal detachment	Incidence of retinal detachment	N	2	3	0	AEs associated with the injection procedure.	(3)
Cataract	Incidence of cataracts	%	5.1	5.4	8.5	AEs mainly associated with the injection procedure.	(1)
Increased IOP	Incidence of increased IOP	%	18.8	17.9	21.4	AEs associated with the active substance/injection procedure	(1)
	Incidence of IOP increased and glaucoma: Glaucoma at BL Absence of glaucoma at BL	%	 20.0 16.8	 35.7 13.3	 55.6 13.9	Potential for worsening of pre-existing glaucoma condition is currently unknown.	(2)
Drug depot in the visual axis (medication residue)	Incidence of medication residue Double masked Combined 12 months study	%	 0.9	 6.3	 5.1 6.1	AE related to the injection technique and/or to other factors such as subject position and vitreous consistency and other characteristics that might influence depot migration. Drug depot in the visual axis may lead to a transient decrease in vision.	(1)
Medication errors	Incidence of medication errors in the 12-month study	N	7	4	2	A safe use of the product is questioned. Clear instructions for use of vials should be provided in the PI.	
Macular oedema	Incidence of macular oedema oedema	%	1.7	7.1	6.0	Potential for worsening of macular oedema in patients with pre-existing macular oedema.	(1)

Abbreviations: µg: micrograms; BL: baseline; N: number; U: Unit; Refs.: References, AE: Adverse event; IOP: intraocular pressure; VH: Vitreous haze; BCVA: Best corrected visual acuity; PI: Product Information

Notes: a: $p<0.05$ vs 44 µg dose; b: non-statically significance vs 44 µg dose.

Data presented in the above table is extracted from SAKURA study

Discussion on the benefit-risk assessment

The modest efficacy of intravitreal sirolimus in the treatment of non-infectious uveitis of posterior is the main concern. Several findings provide additional sources of concern:

a) In the SAKURA Study 1 the response of Opsiria (440 µg dose) both in terms of resolution (VH 0 response) and clinically relevant improvement of inflammation (VH 0 or 2-unit response; VH 0 or 0.5+ response) was far from being compelling. The difference between the intermediate 440 µg dose and the 44 µg dose used as control (~12%) reached statistical significance although the clinical relevance of the differences are still a question of concern.

b) The lack of effect of the high (880 µg) dose does not provide further reassurance on the observed effect.

c) The low number of EU patients and the discrepancies in the response between groups according to geographical distribution raise doubts about the extrapolation of any effect.

The Applicant is expected to further justify the positive benefit-risk ratio of Opsiria in the treatment of posterior uveitis. Moreover, a new attempt should be made to estimate the benefit/risk ratio of Opsiria in the European population.

Non-infectious uveitis of the posterior segment of the eye is a chronic condition and long term treatment may be required. Efficacy results for 12 month-treatment are available for the 880 µg, a dose discarded as inefficacious. The maintenance of the effect of the intended to be marketed 440 µg dose is unknown and some analyses would suggest a waning effect at the end of 6 month treatment period. Given the fact that Opsiria is a first-in-class product for the treatment of posterior uveitis robust short- and long-term efficacy results and a comprehensive safety database are necessary. In case that a relevant benefit is identified, it should be prospectively confirmed in the ongoing SAKURA 2 study. Also, the absence of efficacy data beyond 6 months with the intended dose is a matter of concern. The ongoing SPRING study will provide information on the persistence of the effect beyond 1 year. The safety profile seemed to be favourable. However, given that DE-109 will be administered for long periods of time and considering the uncertainty related to the effect of some adverse events over time, the absence of comprehensive long-term safety data is a significant limitation.

Moreover, DE-109 is not free of adverse events and surprisingly the three dose groups showed similar incidence of adverse events. In particular in light of the lack of dose-dependence between groups in the incidence of adverse events, a placebo arm would be required in order to be able to clearly define the safety profile of DE-109. Additional safety concerns are related to the number of patients that develop glaucoma during the study, the causality assessment of some ocular AEs, the scarring tendency following repeated IVT injections, the worsening of AEs in patients treated with prostaglandin analogs and the content of the packaging.

At this stage, it is considered that the single study results are not sufficiently convincing to support the clinical benefit of the product. In case that a population with a relevant benefit is identified, it should be prospectively confirmed in the ongoing SAKURA 2 study. Of special relevance, a new attempt should also be made to estimate the benefit/risk ratio of Opsiria in the European population.

The limitations of efficacy data beyond 6 months with the intended dose were a matter of concern. Moreover, the safety data show several limitations that prevent to draw clear conclusions. The ongoing SPRING study will provide information on the persistence of the effect and the safety profile beyond 1 year.

5.1. Conclusions

The overall benefit-risk balance of Opsiria was considered negative at the time of this report.

6. Recommended conditions for marketing authorisation and product information

Not applicable at the time of this report.

User consultation

The submitted report is considered acceptable and no further user testing of the PIL would in principle be needed.