EMA/334174/2020
Committee for Medicinal Products for Human Use (CHMP)

Withdrawal assessment report

Xiidra

International non-proprietary name: lifitegrast

Procedure No. EMEA/H/C/004653/0000

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
ANCOVA	analysis of covariance
ANOVA	analysis of variance
ATs	artificial tears
AUC	area under the curve
AUC_{0-t}	area under the curve from the time of dosing to the last measurable concentration
BCVA	best corrected visual acuity
BID	twice daily
CAE	controlled adverse environment
CAE	controlled adverse environment
CFR	Code of Federal Regulations
CSR	clinical study report
C_{max}	maximum concentration occurring at t_{max}
DED	dry eye disease
EDS	eye dryness score
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICH	International Council on Harmonisation
ICSS	inferior corneal staining score
IOP	intraocular pressure
ISE	integrated summary of efficacy
ITT	intent-to-treat
LIF	Lifitegrast
LOCF	last observation carried forward
ODS	ocular discomfort score
OSDI	Ocular Surface Disease Index® (Allergan, Inc.)
PBO	Placebo
RMP	Risk Management Plan
SE	standard error
STT	Schirmer Tear Test
TEAE	treatment-emergent adverse event
US	United States
VAS	visual analogue scale
VR-OSDI	visual-related function subscale of Ocular Surface Disease Index

1. Joint Rapporteur's Recommendations

Based on the review of the data on quality, safety, efficacy, the application for **Xiidra** eye drop for the treatment of moderate to severe dry eye disease in adults for whom artificial tears has not been sufficient is **not approvable** since "major objections" have been identified, which preclude a recommendation for marketing authorisation at the present time. The details of these major objections are provided in the 2nd List of Outstanding Issues (see section VI).

In addition, satisfactory answers must be given to the "other concerns" as detailed in the List of Questions.

The major objections precluding a recommendation of marketing authorisation, pertain to the following principal deficiencies:

Clinical: Three clinical major objections have been raised. One relates to the lack of convincingly demonstration of clinically relevant effect across the different symptoms related to DED. The other clinical major objection regards the methods and lack of statistically significant difference compared to placebo, and the third clinical major objection concerns the indication.

Questions to be posed to additional experts

A SAG would be helpful now particularly to clarify the clinical meaningfulness of any improvement seen in clinical studies, (particularly against the background of improvement in symptoms but not of signs) as well as to clarify whether it is possible to identify patients for whom the treatment is indicated in the general practice setting.

The following questions are proposed:

1. The Experts are invited to discuss whether the efficacy profile of Xiidra can represent a clinically meaningful benefit. In the discussion, the Experts are invited to consider:
    a) the lack of statistically significant effect on signs and objective measures;
    b) the presence of effect on eye dryness but not on other symptoms;
    c) the effect size, also considering the potential sub-optimal comparator;
    d) the duration of effect, considering trial duration and apparent diminishing effect.
2. The Experts are invited to elaborate on whether the effect can be extrapolated to patients with DED due to recent refractory surgery, systemic diseases (e.g. diabetic retinopathy), glaucoma, medical treatment, iritis, uveitis, active ocular inflammation, blepharitis or meibomian gland dysfunction as these patients were excluded from the clinical studies?
3. Considering the fact that a large fraction of patients with DED are managed in primary care, please discuss:
    a) the applicability of an indication restricting its use in patients with a certain level of objective signs of severity of disease and;
    b) the place in therapy for Xiidra in the general population taking into account the unfavourable effects and if only authorized for short-term use

Inspection issues

No issues have been identified during assessment which call for a pre-approval inspection.

New active substance status

Based on the review of the data, the Rapporteurs considers that the active substance lifitegrast contained in the medicinal product Xiidra, 50 mg/ml, eye drops, solution in single-dose container, may be qualified as a new active substance in itself.

Similarity with authorised orphan medicinal products

It is considered that Xiidra is not similar to Oxervate within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. Please refer to the separate Similarity report.

2. Executive summary

2.1. Problem statement

2.1.1. Disease or condition

The targeted indication for lifitegrast is treatment of moderate to severe dry eye disease in adults for whom prior use of artificial tears has been insufficient.

The Applicant has supplied one phase 2 study and four phase 3 studies, hereof one long-term safety study. The target-population, i.e. patients with moderate to severe dry eye disease, was defined during the clinical development program, and not reflected in the phase 2 study or in the first phase 3 study.

2.1.2. Epidemiology and risk factors, screening tools/prevention

Reported prevalence estimates of DED vary widely depending on the population studied and the definition of DED used.

A recent systematic literature review and meta-analysis of 30 studies published between 1997 and 2015 from across the globe (range of respondents per study, N=200‑36,995) assessed the overall prevalence of self-reported DED by region, gender, and age (Ozer-Stillman et al., 2017).

Studies were found from America, Asia, and Oceania, while European studies (n=4) were very limited with the majority being not representative of the total population. The meta-analysis estimated the overall DED prevalence to be 12.6% and was higher in women than men (13.0% vs. 9.9%). Reported prevalence estimate for North America (USA) is 6.7%, while the prevalence of DED in Asia appears to be higher than in the West, with a reported overall prevalence of 22.5% (Ozer-Stillman et al., 2017).

Among adults in Europe, the overall prevalence of DED estimated from a meta-analysis of 3 studies was 13.9% (Ozer-Stillman et al., 2017), with country-specific estimates of 3.9% in Germany (Reitmeir et al., 2017), 9.6% in the United Kingdom (UK) for adult women, with diagnosis by clinician and current use of artificial tears (ATs) (Vehof et al., 2014), 11.0% in Spain (Viso et al., 2009), and 21.9% in France (Malet et al., 2014). The UK study is considered to provide the most representative and accurate estimate of prevalence-based on study design (population-based, cross-sectional), large sample size (n=3,824), age range (20 ‑ 87 years), and high diagnosis stringency (Vehof et al., 2014). This study reported a female-only DED prevalence (DED diagnosis by clinician). Using the male/female ratio from the GLIDE II UK study (female: male midpoint 2.35) (Shire, 2018), results were extrapolated to the overall UK adult population, providing an overall DED prevalence of 8.2% in the UK.

2.1.3. Aetiology and pathogenesis

Dry eye disease is the result of an immune-mediated disorder that is initially limited to the ocular surface. The integrity of the ocular surface epithelium is disrupted, which manifests as fluorescein staining of the cornea and lissamine green staining of the conjunctiva. Loss of the barrier function of the corneal epithelium exposes the underlying cells to the hyperosmolar tear film, which damages them directly, and indirectly through propagation of inflammation (Bron et al., 2017). Corneal nerves, terminating within the epithelium (Muller et al., 2003), are thus exposed to an abnormal tear film, resulting in decreased density and marked histopathologic changes (Cruzat et al., 2017;Labbé et al., 2013). These corneal nerves have receptors that are specialized and able to respond to particular stimuli, resulting in different qualities of sensation (Belmonte et al., 2015); the sensation of eye dryness is thought to be mediated by cold thermoreceptors (Belmonte and Gallar, 2011; Kovács et al., 2016; Belmonte and Gallar, 2011).

This aligns with the finding that shortened tear break-up time in DED is associated with lower corneal temperatures and greater symptomatology.

Although DED is considered a disease of the ocular surface, the pathology involves deeper corneal structures, ie, the corneal endothelium. In a recent series of studies, DED subjects were noted to have a lower corneal endothelial cell density than age-matched controls (Kheirkhah et al., 2015), and an accelerated mean annual rate of corneal endothelial cell loss: 2.1% over a mean follow-up period of 33 months when compared with the an annual loss rate of 0.22-0.6% in historic controls (Kheirkhah et al., 2017). Unlike the multilayered epithelial cells that can divide to heal an injury, the corneal endothelium is a single layer of cells that lines the inner surface of the cornea and that does not have the capacity to regenerate.

Once initiated, the vicious circle of DED is maintained by chronic inflammation. Early in the disease process, compensatory mechanisms maintain viability of critical ocular cells and structures. Longer term exposure of the corneal and conjunctival epithelia to inflammatory mediators appears to alter nerve structure and function, which disrupts the fine balance required to maintain ocular health. The ocular surface and deeper tissue, such as the corneal endothelium, are pathologically altered. Left untreated, the chronic nature of DED can progress to corneal scarring, ulcers, and ultimately vision loss.

2.1.4. Clinical presentation

The subjective symptoms in dry eye disease are often nonspecific. They include redness, burning, stinging, foreign body sensation, pruritus, and photophobia.

Conjunctival redness and damage to the ocular surface with punctate epithelial erosions (superficial punctate keratitis) are typical in dry eye; temporal conjunctival folds parallel to the lid margin are indicative. The lower tear meniscus is reduced. In addition, there are often signs of meibomian gland dysfunction with thickened eyelid margins and telangiectasia. The meibomian gland orifices are obstructed with a cloudy, granular or solid secretion that can only be expressed by exerting considerable pressure on the lower lid. If the meibomian gland dysfunction is associated with inflammation, blepharitis (inflammation of the lid margin) or meibomitis (inflammation of the meibomian glands) is present. In late stages or in severe forms of the disease, conjunctival scarring or corneal complications can occur. In addition to filamentary keratitis, persistent epithelial defects, ulceration, and even corneal perforation can complicate the course.

2.1.5. Management

The general goal of treatment is to restore homeostasis to the ocular surface (Craig et al., 2017a). In moderate to severe DED, successful treatment can stop disease progression, and prevent long-term consequences and permanent damage (Leonardi et al., 2017). Current treatment guidelines outlined by the 2017 DEWS II publication propose algorithms that are intentionally fluid, rather than strictly sequential, in order to encourage practitioners to treat patients on an individual basis.

The duration of treatment is defined by the patient' s response to a medication or therapy; if it is insufficient, treatment may be advanced until response is adequate. Patients should be assessed regularly and treatment adjusted when needed. Effective DED treatment places a substantial burden on clinical practitioners (Jones et al., 2017).

Early in the course of the dry eye disease process, supplementation of the tear film with nonprescription artificial tears, as recommended in Step 1 of the DEWS II management algorithm, may provide transient relief of symptoms. Artificial tears are ocular lubricants which mimic a layer of the tear film (Perry and Donnenfeld, 2003; Bron et al., 2009), but do not directly address hyperosmolarity, the core mechanism of DED. Many artificial tears contain chemical preservatives, such as benzalkonium chloride (BAK), to

protect multidose applications from contamination. Benzalkonium chloride is known to cause ocular damage and allergic reactions (Pucker et al., 2016). Patients with mild DED often respond to AT therapy such that ATs are the only treatment required (Jones et al., 2017) but for patients with more advanced DED, ATs do not provide a sufficient level of relief (Nichols et al., 2016).

In contrast to treating the symptoms of DED with artificial tears, the underlying inflammatory etiology may be targeted (Jones et al., 2017). Cyclosporine 0.1% (Ikervis®) is approved for "Treatment of severe keratitis in adult patients with dry eye disease, which has not improved despite treatment with tear substitutes" in Europe (IKERVIS SMPC). While cyclosporine is included as an option in the DEWS II Step 2 category, IKERVIS® is an appropriate treatment for DED patients with severe keratitis, which is a more advanced stage of DED (Ikervis®, 2015). Since cyclosporine primarily affects naïve T cells, activated T-cells will continue circulating throughout their lifecycle, which may be as long as 164 days (roughly 6 months). The onset of immunomodulation, and therefore treatment effect, is delayed until a critical mass of activated T-cells responsible for DED has been eliminated. Cyclosporine efficacy trials were 6 months in duration and a treatment effect was not seen until 3-4 months of continuous treatment (Baudouin et al., 2018;Leonardi et al., 2017;Sall et al., 2000).

2.2. About the product

Lifitegrast is a small molecule that has been formulated as a preservative-free sterile eye drop. Lifitegrast was designed to target the interaction between lymphocyte function-associated antigen 1 (LFA-1; also known as CD11a/CD18 or αLβ2), a cell surface integrin that mediates cell-cell interactions essential to immune and inflammatory response mechanisms, and intercellular adhesion molecule (ICAM)-1, its cognate ligand. ICAM-1 has been shown to facilitate many T-cell dependent immune functions through its interaction with LFA-1, including adhesion of T-cells to endothelial and epithelial cells, T-cell recruitment and trafficking, proliferation, and the release of inflammatory cytokines.

Studies indicate that T-cells play a critical role in the development of DED; consequently lifitegrast, by targeting the LFA-1/ICAM-1 interaction, may reduce components of inflammation and immune activation that have been correlated with the development and perpetuation of DED.

New active substance status is sought.

The proposed indication is:

Treatment of moderate to severe dry eye disease in adults for whom prior artificial tears has not been sufficient.

Xiidra is administered as one drop to each eye twice daily.

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

GMP:

Drug substance: An adequate Qualified Person`s declaration concerning GMP compliance of the active substance manufacturer has been provided.

Drug Product: An adequate documentation for GMP of the finished product manufacturing site and release site have been provided.

GLP:

All pivotal nonclinical safety studies finalized before a certain date in 2010, all paper raw data were destroyed. Applicant provided adequate justification for GLP compliance despite loss of paper raw data. Documentation of successful GLP audits by FDA was provided covering time-frames relevant for study conduct.

The whole bioanalysis program was conducted in the US. Plasma and tear methods were validated to GLP, whereas methods for ocular tissues were adequately qualified to save rare matrices (Non-GLP), which is considered acceptable.

GCP:

All studies with lifitegrast were conducted in accordance with ICH GCP, the principles of the Declaration of Helsinki, the US CFR, and the EU Clinical Trials Directive, as well as any other applicable local/regional regulations and guidelines regarding the conduct of clinical studies.

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

Legal basis

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC, as amended - a complete and independent application.

The Applicant has not applied for an accelerated assessment, authorisation under exceptional circumstances or as a conditional approval application.

Following the granting of a waiver against the requirement to perform studies in accordance with an agreed Paediatric Investigation Plan, no studies in the paediatric population have been conducted in support of the marketing authorisation application.

New active substance status

The Applicant requested the active substance lifitegrast contained in the medicinal product, Xiidra, to be considered as a new active substance in itself, as the Applicant claims that the active substance is not authorized in the EU, and furthermore it is not a salt, complex, or isomer or mixture of isomers, or a derivative of an authorized substance.

Orphan designation

Not applicable

Similarity with orphan medicinal products

The application contained a critical report pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, addressing the possible similarity with authorised orphan medicinal products. Assessment of this claim is appended.

Information on paediatric requirements

N/A

3. Scientific overview and discussion

3.1. Quality aspects

3.1.1. Introduction

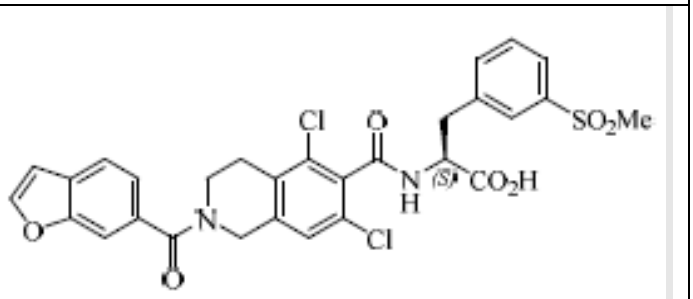
A summary of the documentation provided and the issues identified regarding active substance and finished product are presented below.

3.1.2. Active Substance

The documentation on the active substance, Lifitegrast, is presented as full-file. The active substance is not described in the European pharmacopeia and it is to be qualified as a new active substance.

General Information

Details on Lifitegrast:

International non-proprietary name (INN):	Lifitegrast
Chemical names:	(S)-2-(2-(benzofuran-6-carbonyl)-5,7-dichloro-1,2,3,4-tetrahydroisoquinoline-6-carboxamido)-3-(3-(methylsulfonyl)phenyl)propanoic acid
.Molecular structure:	
Molecular formula:	$C_{29}H_{24}Cl_2N_2O_7S$
Relative molecular mass:	615.5
General information and chemical features	It is a white to off-white powder. The active substance is slightly soluble in water, while it is very soluble at pH between 6.0-8.0, hence solubility of the active substance is low and pH dependent. It has a single chiral center and exists as the *S* stereoisomer, and is slightly hygroscopic. Polymorphism has been observed. Different polymorphs were identified.

Manufacture, process controls and characterisation

Manufacturing process and control of materials

The synthesis is described in four overall stages, where each of the stages consists of consecutive reaction steps. Hence, the synthesis is described in total seven steps, while comprises six actual synthetic steps (bond breaking/formation) and a recrystallization step. Considering this, in conjunction with the information provided on the starting materials proposed; the description the synthesis proposed is acceptable.

The Major objection relates to use of proven acceptable ranges (PARs) and design space are resolved satisfactory. The Applicant confirms that a design space has not been applied for and will not be used for commercial manufacture and that PARs will be deliberately changed one at a time. PARs for process parameters with the potential to impact product quality were investigated during development by design of experiment (DoE) studies to better understand the process and evaluate process robustness and reliability.

Three starting materials were proposed. The detailed information on the starting materials are discussed and the information provided have been found satisfactory. Adequate number of chemical transformation steps are in place to ensure elimination of possible impurities arising from the starting materials, hence the starting materials has been justified based on the chemical transformation steps.

No concerns have been identified, and the overall control strategy for chiral purity of the drug substance is considered adequate.

Analytical methods used to include validations have been addressed. Two manufacturers of each starting material are proposed. Equivalent quality of final active substance has been demonstrated; thus the use of multiple starting material manufactures has been justified.

Reaction schemes for the starting materials, including information on the reagents/solvents/catalysts used, as well as adequate details on manufacturers have been provided. Discussion on possible impurities has been presented. Impurities in the starting materials and their fate in subsequent synthesis have been adequately addressed as well as control strategy of impurities in starting materials has been justified by spiking/purge studies.

Solvents applied in synthesis of starting materials are controlled in the relevant starting material specification Furthermore, the catalysts is used in starting material syntheses, and are controlled in the relevant starting material specification.

Control of critical steps and intermediates

Satisfactory specifications are presented for all intermediate. Organic impurities in the intermediates and their fate in subsequent synthesis have been adequately addressed as well as control strategy of impurities in the intermediates has been justified. The fate and purging of impurities during the downstream chemistry is understood. A justified set of in-process tests, chemical intermediate specifications and critical process parameters has been developed for each stage of the manufacturing process to assure and confirm quality of the drug substance.

Descriptions of analytical methods used for determination of all IPCs have been presented as well as validation of the methods for their intended use has been addressed.

The Applicant has satisfactorily accounted for process development, including detailed overview of differences in processes. Bridging has been satisfactorily ensured and the synthesis proposed is supported by data enclosed in the dossier. The Applicant has conveyed confidence of knowledge on the synthesis proposed, including control of impurities (formation, fate and purge).

Characterisation

The structure of the active substance has been confirmed with Chemical Purity (HPLC), Chiral Purity (HPLC), FTIR, ^{1}H NMR, ^{13}C NMR, MS, XRPD, and elemental analysis. Data and spectra with interpretations have been presented.

Discussion on impurities is in general adequate (specified and unspecified organic impurities, genotoxic impurities, and elemental impurities). The Applicant has provided a detailed overview of organic impurities with indication of origin and fate for each impurity. Control and carry-over of potential impurities from the starting materials to the final active substance have been discussed. Fate of impurities as well as intermediates through processing seems well understood and supported by purge studies.

Specification, analytical procedures, reference standards, batch analysis, and container closure

Control of drug substance

EU/ICH Q3A thresholds: Maximum daily dose 10 mg→ Reporting level: 0.05%; ID threshold: 0.10%; Qualification threshold: 0.15%. EU/ICH M7: Acceptable intake of potential genotoxic impurity taking into account indication and posology (>10 years)→1.5 µg/day. The active substance specification is adequately set. The revised limits proposed by the Applicant have been taking into consideration and were found acceptable based on the validation/registration batches presented in the documentation, and the conclusion from the non-clinical assessor.

The analytical methods have been adequately described. Where applicable, Ph. Eur. methods have been used. For the non-pharmacopoeial methods, full validation data have been provided. Overall, the validation of the in-house analytical procedures is sufficient and satisfactorily validated in accordance with the EU/ICH Q2 validation guidelines.

Batch data for active substance batches used for non-clinical, clinical, stability studies, process validation and commercial has been provided. All historical test results, including those used in the manufacture of the Phase II and Phase III pivotal clinical batches, the drug substance development, engineering and validation/stability comply with the specifications proposed. Data for the different batches show that there are no significant changes on impurity levels, which means that the process optimization and up scaling had no impact on impurity levels. Level of impurities is stable and low in the commercial batches (both validation and registration batches. In addition, the batch data for the active substance presented covers all of the manufacturers of the starting materials

Reference standards or materials

Information is adequate.

Container closure system

The active substance is packaged in one low-density polyethylene (LDPE) liner. It is placed into a second LDPE bag and sealed. The double-bagged material is then inserted into a HDPE drum. Specifications for the LDPE material have been presented.

Compliance of the primary packaging material with requirements of Regulation (EU) No 10/2011 on plastic materials and articles intended to come into contact with foods is presented.

Stability

The stability results justify the proposed retest period and storage conditions. Stability studies conducted in line with EU/ICH.

3.1.3. Finished Medicinal Product

Description of the product and Pharmaceutical Development

Description and composition of finished product

The finished product is a clear, colourless to slightly yellowish eye drops solution, 50 mg/mL (5%). The eye drops solution is to be marketed in a unit-dose ampules moulded of low-density polyethylene. A card of 5 ampules is packaged in an aluminium foil laminate pouch.

Pharmaceutical development

The development of the finished product has been described. The choice of excipients has been justified and their functions explained. The excipients are of pharmacopeial quality and are known for their use and function in the proposed pharmaceutical dosage forms (eye drop, solution), except for the antioxidant. Compatibility with the active substance have been demonstrated by stability data.

Development data supporting addition of antioxidant to the formulation has been provided. The Applicant has provided a detailed overview of the manufacturing development conducted and confidence is given that the manufacturing process developed is controlled and is suitable for intended use. The provided justification for selection of sterilizing filtration and aseptic filling by BFS The provided justification for the selection of the sterilisation method has been accepted. There is no concern regarding both safety and quality. The Applicant has provided robust assurance of sterility.

Manufacture of the product and process controls

Manufacture

The manufacturing process is well described. A clear description of the manufacturing process time and hold-times has been provided. All processing and hold times are and supported by validation studies.

Critical step/process parameters have been identified and control ensured. Overall, appropriate IPCs have been set and are justified by development and process validation data. The manufacturing process has been validated on three full scale batches at the proposed manufacturing site.Consistency in manufacture has been demonstrated.

Control of excipients

All the excipients are controlled in accordance with their respective Ph. Eur. and USP/NF monographs.

Product specification, analytical procedures, batch analysis

Overall, the specifications have been adequately set in accordance with EU/ICH Q6A, Ph. Eur. and the extensive development, batch and stability data available. The finished product specification includes appropriate test parameters for control of drug product quality throughout shelf life. The relevant limits for the impurities and assay in the specification are acceptable, based on qualification and the batch analysis results.

The risk assessment for the potential presence of N-nitrosamines has been provided. The assessment covers all process steps with regard to the potential formation of N-nitrosamines for the synthesis of the active substance lifitegrast. EMA guidance have been taking into consideration.

The applicant presented their conclusions regarding the potential risk of nitrosamine impurities formation, which were accepted. According to the risk assessment, there is no risk for the presence and/or introduction of N-nitrosamines during the drug product manufacturing process and/or their formation in the final drug product. No further actions are required. The analytical methods have been adequately described. Where applicable Ph. Eur. methods have been used. Overall, the methods have been satisfactorily validated in accordance with EU/ICH Q2.

Batch analyses data for several batches have been provided, which supports the composition, process, batch size and analytical methods proposed. Batch data demonstrates that the finished product is stable as well as consistency in manufacture.

Reference standards or materials

The same in-house reference standards as for the active substance are used. Information is adequate.

Container closure system

The finished product is packed in single dose LDPE ampoules and a card of five ampoules is packaged in an aluminium laminate foil pouch. The sealed foil pouches are packaged in external card boxes. Specification is provided for the LDPE resins . Furthermore, information regarding the sterilisation sites (the name and address) and the sterilisation method of the primary packaging have been provided.

Stability of the product

Stability studies conducted in line with EU/ICH. Some OOS results were observed and the root cause was being investigated at the time of the application. The following special precautions for storage are considered acceptable:

The proposed shelf-life of 2 years is accepted.

Store the single-dose containers in the original aluminium pouch until administration, in order to protect from light.

After opening the aluminium pouch, store remaining unopened single-dose containers in the original aluminiumpouch in order to protect from light.

Post approval change management protocol(s)

N/A

Adventitious agents

N/A

GMO

N/A

3.1.4. Discussion and conclusions on chemical, pharmaceutical and biological aspects

The chemical-pharmaceutical documentation and Quality Overall Summary in relation to Xiidra, 50 mg/ml eye drops, solution in single-dose container are overall of sufficient quality in view of the present European regulatory requirements.

3.2. Non clinical aspects

3.2.1. Pharmacology

Lifitegrast is a novel, potent, first-in-class small molecule that has been formulated as an unpreserved sterile eye drop. Lifitegrast was designed to target the interaction between lymphocyte function-associated antigen 1 (LFA-1; also known as CD11a/CD18 or αLβ2), a cell surface integrin that mediates cell-cell interactions essential to immune and inflammatory response mechanisms, and intercellular adhesion molecule (ICAM)-1, its cognate ligand. ICAM-1 has been shown to facilitate many T cell dependent immune functions through its interaction with LFA-1, including adhesion of T cells to endothelial and epithelial cells, T cell recruitment and trafficking, proliferation, and the release of inflammatory cytokines. Studies indicate that T cells play a critical role in the development of DED; consequently lifitegrast, by targeting the LFA-1/ICAM-1 interaction, may reduce components of inflammation and immune activation that have been correlated with the development and perpetuation of DED.

In vitro pharmacology

In vitro relevant functional activity of lifitegrast were demonstrated by several means:

Jurkat cells (V6308M)

Lifitegrast was shown to inhibit flourophore-labelled Jurkat T cell attachment to immobilized ICAM-1 in a concentration dependent manner (Report V6308M). EC50 indicated a similar potency to Compound 4, which is another potent inhibitor of LFA-1/ICAM-1 interaction (Gadek et al, 2002 and Keating et al, 2006).

Human PBMC (V6310M)

Human PBMC pre-treated with lifitegrast or positive control (cyclosporine) were stimulated with SEB for determination of effects on cytokine release profiles (Report V6310M by Sarcode, 2007). Lifitegrast effect on release of IL-2 and IL-4, is especially relevant for dry eye disease. EC50 for IL-2 and IL-4 and inhibition of release of IFNγ, MCP-1, MIP-1α and TNFα, suggested a relatively broad cytokine inhibition profile. On the other hand, Lifitegrast was typically several times less potent than cyclosporine, which is used in eye drops for the treatment of dry eye disease. It should be noted here, that the concentration in tear fluid of dry eye disease patients are expected to be above EC50 for relevant cytokines. This was demonstrated in tear fluid from rabbits (Report L6776M).

Human PBMC was used in a similar way by Ricerca in 2010 (report V6757M). The cytokine panel was extended and human PBMCs was also stimulated with SEB or LPS. The broad cytokine inhibition profile of lifitegrast was largely confirmed.

Human peripheral blood dendritic and CD 4+ T cells (V9919M)

In a recent study, T cells and activated dendritic cells (LPS and IFNγ) were co-cultured and evaluated for ICAM-1/LFA-1 synapse formation with and without positive control efalizumab (LFA-1 antibody), compound 4 and lifitegrast. Lifitegrast and compound 4 were both more potent than efalizumab and lifitegrast was less potent than compound 4. For lifitegrast, IC50 for inhibition of synapse formation of LFA-1 positive cells was 1.781 µM and for ICAM-1 positive cells IC50 was 3.842 µM. Compound 4 was more potent in this assay. Even though this study show lifitegrast to be of relatively poor potency, maximal concentration in tears in humans was demonstrated to be >100 µM (mean Cmax ~ 50 to 130 µg/mL corresponding to 81-211 µM, 2.7.2. Table 2, page 16), hence clinical effect of lifitegrast can be expected.

Human peripheral blood dendritic and CD 3+ T cells (V9975M)

In another recent study using confocal microscopy imaging (Report V9975M), the ability of lifitegrast to block ICAM-1/LFA-1 synapse formation between SEB activated dendritic cells and CD3+ T cells, when present at SEB addition. Compound 4 was included as comparator and positive control. Lifitegrast ability to prevent synapse formation was confirmed. Immune synapse formation was evaluated at 5 and 20 minutes past SEB addition. At 20 minutes, % interacting T cells was significantly lower than control level, already at 10 nM lifitegrast. A dose dependent decrease in % interacting T cells was observed. Hence, lifitegrast ability to prevent synapse formation was confirmed.

Lifitegrast ability to disrupt already established synapses was also evaluated. This was done in a similar way, but with addition of lifitegrast 20 minutes after SEB addition. The disruption process was found to be slightly less effective, however still dose dependent and significant already at 10 nM lifitegrast, 20 min after treatment with lifitegrast. At 5 minutes after lifitegrast treatment, only 1000 nM was showing significant decrease in % interacting T cells.

Lifitegrast ability to prevent downstream signalling by T cells (Zap70 phosphorylation) was also evaluated by flow cytometry, however no significant effect could be demonstrated for lifitegrast and only a trend for compound 4. This could be due to a narrow assay window.

Lifitegrast ability to antagonise T cell proliferation was evaluated by flow cytometry. Treatment of PBMC with SEB induced a strong proliferative response in both CD4+ and CD8+ T cells. Lifitegrast and compound-4 both significantly reduced T cell proliferation in a dose-dependent manner. IC50 on proliferation was determined for lifitegrast to be at 454.9, 567.7 and 402.2 nM on PBMC, CD4 and CD8 respectively.

Cell viability was also evaluated. In absence of lifitegrast, % viable cells was approximately 70% in the assay. It appeared that viability of lymphocytes were not significantly reduced in presence of lifitegrast, however a slight reduction was observed at concentrations at and above 250 nM (approximately 60% viable cells), which seemed to stabilise at 5000 nM (approximately 50% viable cells). *In vitro* proof of concept appear to be demonstrated.

In vivo pharmacology

Effects of Lifitegrast on Inflammatory Cell Infiltration in the Conjunctiva and Lacrimal Glands of MRL/MpJ-Faslpr/J Mice (M6758M, M6311M)

The effect of lifitegrast on inflammatory cell infiltration of the conjunctiva and eyelids was examined in two studies using MRL/MpJ-Faslpr/J mice. MRL/MpJ-Faslpr/J mice are homozygous for the

lymphoproliferation spontaneous mutation, Faslpr. These mice show systemic autoimmunity associated aberrant T-cell proliferation, and have been used as preclinical models for systemic lupus erythematosus and Sjögren's syndrome.

The effects of lifitegrast were compared to those of CsA and the anti-LFA-1 mAb, M17. In The first study, lifitegrast was administered to mice from 4 to 7 weeks of age. The second study differed however, in that lifitegrast was administered to mice from 4 to 10 weeks of age. Paradoxical results were obtained. The MRL/MpJ-Fas^{lpr}/J mice treated with vehicle had inflammation in 5.6% of the total acinar area. This was significantly greater than the 0.84% present in wild type mice. Lifitegrast- treated MRL/MpJ-Fas^{lpr}/J mice exhibited significantly more inflammatory cell infiltration, 10.25%-11.19%, than the vehicle control MRL/MpJ-Fas^{lpr}/J mice and MRL/MpJ-Fas^{lpr}/J mice treated IP with mAbM17 had the highest inflammation, 17.87%. The cyclosporine treated group was not significantly different from vehicle.

Results from this study demonstrate similarly increased leukocytic infiltration of the lacrimal gland with both lifitegrast (all doses) and the anti-LFA-1 mAb, M17. The paradoxical increase in inflammatory infiltrate observed in association with topical instillation of lifitegrast in MRL/MpJ-Fas^{lpr}/J mice was opposite to the results observed in canines with dry eye and suggests that this model may not be appropriate for studying ocular inflammation. The Applicant acknowledges the shortcomings of the mouse model used, and now places little or no weight on the overall conclusions derived from these studies. Instead in vitro and other in vivo data is relied upon. In vitro the relevant pharmacodynamics activity of lifitegrast was demonstrated. Study V9919M and study V9975 demonstrated the ability of lifitegrast to inhibit synapse formation using T-cells and activated dendritic cells. In addition, Study D6344M and Murphy et al., 2011, an in vivo study in dogs, demonstrated lifitegrast effects in reducing inflammation in keratoconjunctivitis sicca, which is thought to be mediated through the interaction of LFA-1 and ICAM-1. The totality of the data in these studies establishes proof of concept for lifitegrast.

Inhibition of Corneal Inflammation by Lifitegrast in a mouse model (Sun et al, 2013)

Sun et al in 2013 published a study in mice of lifitegrast ability to inhibit corneal inflammation induced by epithelial abrasion and exposure to inactivated pseudomonas aeruginosa or staphylococcus aureus in the presence of a silicone hydrogel contact lens. After 24 h, corneal thickness and haze were examined by *in vivo* confocal microscopy, and neutrophil recruitment to the corneal stroma was detected by immunohistochemistry. Topical lifitegrast inhibited P. aeruginosa- and S. aureus–induced inflammation, with the optimal application being a 1% solution applied either 2 or 3 times prior, i.e. prevention of inflammation rather than treating inflammation. Inflammation determined as neutrophils/section could be inhibited down to approximately 50% with this treatment regimen, whereas a single application of lifitegrast 1 h before and 1 h after could not inhibit neutrophil recruitment. Lifitegrast 1% showed consistently slightly better effects than 0.1 or 5% lifitegrast. This could be explained by bioanalysis of lifitegrast concentration in the cornea, which showed higher exposure of the 1% formulation as compared to 0.1 and 5% formulations.

Lifitegrast treating diabetic retinopathy in a rat streptozotocin model (Rao et al, 2010)

Diabetic rats were treated with lifitegrast by ocular instillation for 2 months. In this study it was demonstrated that lifitegrast could alleviate symptoms and consequences of diabetic retinopathy of blood-retinal barrier leakiness, retinal leukostasis and myeloperoxidase activity. In this study, the 5% lifitegrast formulation showed better efficacy than the 1%. Effect was compared to vehicle and a single intraocular delivery of micronized celecoxib, which acted as positive control. At most endpoints, 5% lifitegrast showed similar efficacy to celecoxib except for vitreous/plasma protein ratio, where only celecoxib showed significant effect. These results were backed up by a pharmacokinetic study of a single dose ^{14}C-lifitegrast in various ocular tissue (6.5%). This confirmed that ocular instillation of lifitegrast reach the posterior of the eye including vitreous humour and retina. See also PK section 3.3.1.

A study in dogs: Lifitegrast in treatment of keratoconjunctivitis sicca (KCS, D6344M, Murphy et al, 2011)

KCS is characterised by inflammation and decreased production of tears containing increased levels of cytokines. This is thought to be mediated through the interaction between LFA-1 and ICAM-1. Eighteen dogs with advanced KCS were included in the study to be treated for 12 weeks with lifitegrast 1% TID. Schirmers Tear Test (SST) was included as the primary end point. Cunjunctival biopsies for inflammatory cellular infiltration and a modified McDonald-Schadduck scoring system was included as secondary end points. SST reached statistical significance compared to baseline, even though 7 out of 18 dogs were non-responders. Five of 7 dogs which were non-responders had a baseline of 0 mm tear illustrating the severity of the disease in the dogs included in the trial. The secondary end points failed to reach significance compared to baseline, however a trend was observed, (p=0.07) for anti-inflammatory improvement in conjunctival biopsies. Only minor changes in McDonald-Shadduck scores were observed relative to baseline in conjunctival discharge, cunjunctival congestion and corneal opacity with no statistical significance reached. Nevertheless, this study in dog appear to confirm a somewhat modest beneficial effect of lifitegrast, which may be relevant for humans suffering from dry eye disease, which typically is less severe at onset of treatment compared to the dogs included in this study.

Proof of concept *in vivo* appear to have been reached for lifitegrast in animal disease models of mouse, rat and dog.

Secondary pharmacology (V6435*)*

A Cerep extensive selectivity screen on 105 known targets did not reveal any significant interaction above 50% with lifitegrast at 10 µM (Report V6435M). Hence, no off-target effects of lifitegrast is anticipated from systemic exposure.

Safety pharmacology

CNS (R6313M)

The modified Irwin screening in rat was used to evaluate CNS effects of lifitegrast (Report R6313M). Only male rats were taken into the Irwin study and single dosed via the intravenous route of administration (0.2, 1.0 or 10 mg/kg). Both male and female were used for pharmacokinetic analysis of the same doses to create composite PK profiles. Exposure of lifitegrast was confirmed. AUC appeared to be reasonably linear with dose AUC0-n of 20.9, 61.3 and 728 ng/mL*h for 0.2, 1.0 and 10 mg/kg, respectively. AUC at the lowest dose is far above clinical relevant systemic exposure (AUC0-8h 0.69 ± 0.47 ng/mL*h).

CNS effects of lifitegrast was limited to transient miosis, which was observed in animals administered 10.0 mg/kg lifitegrast at 1 minute (1 out of 6 animals), 1 hour (2 out of 6 animals), 2 hours (1 out of 6 animals), and 4 hours (2 out of 6 animals) post dose. This is not considered a concern, since exposure was demonstrated to be several fold above clinically relevant exposure at this dose (AUC0-8h in patients; 0.69 ng/mL*h).

Cardiovascular (D6338M)

Cardiovascular safety for lifitegrast was evaluated *in vitro* in the hERG assay and *in vivo* in telemetered beagle dogs (latin square design). Both studies were conducted to GLP. Lifitegrast inhibited hERG with an IC50 of 478 micromolar (>100,000 times higher than systemic exposure in patients, report V6312M). Dogs, dosed by the intravenous route with lifitegrast at 0, 1, 3 and 10 mg/kg, did not show any cardiovascular changes, except at one time point 3 hour post the low dose, where a slight increase in heart rate was observed (Report D6315M). Applicant's conclusion that this is not related to lifitegrast is supported, since the effect was not dose related and occurred at a later time point. Considering, that the route of administration is intravenous, any direct effect would be expected at an earlier time point if not

within minutes, depending on the mode of action. Pharmacokinetics was not part of the dog cardiovascular safety study however, this is acceptable since Day 1 data from the 4 week study provides supportive data (Report D6338M).

Respiratory (R6313M)

Potential effects of Lifitegrast on respiratory function was evaluated in the Head-Out Body Plethysmography Model in rats. Rats were single dosed 0.2, 1 or 10 mg/kg by the intravenous route and respiratory function was monitored for 6 hours. Pharmacokinetics was not part of the study, however, exposure documented in the CNS study in rat can be used as supportive data (Report R6313M).

No effects were observed, which was not also observed in the control group. Lifitegrast appear not to impact respiratory function.

Pharmacodynamic drug interactions

Pharmacodynamic drug interaction studies were not conducted due to the very low systemic exposure to lifitegrast after ocular instillation. This is accepted.

3.2.2. Pharmacokinetics

Nonclinical PK studies of lifitegrast were carried out to support the clinical use of lifitegrast by topical ocular instillation.

The ocular and systemic PK and TK of lifitegrast via 2 routes of administration (topical ocular instillation or IV) were characterized in a battery of nonclinical studies in 3 species (rats, rabbits,and dogs). Distribution was determined to characterize the lifitegrast disposition in the systemic or ocular tissues following IV and topical ocular instillation in 3 species (rats, rabbits, and dogs).

The binding of lifitegrast to plasma proteins, human serum albumin (HSA), alpha-1-acid glycoprotein (AAG), and melanin was also determined. *In vitro* metabolism studies in rat, dog, monkey, and human hepatocytes were conducted to examine hepatic metabolism and to determine whether there were any potential human-specific metabolites present (despite low systemic exposure following topical ocular instillation).

In vivo excretion was determined with [14C]-lifitegrast following topical ocular and IV administration in rats and dogs to further characterize lifitegrast disposition and the major elimination route. These findings were supported with a series of *in vitro* studies in animal and human-derived systems. The interactions of lifitegrast with CYP450 enzymes, absorption/efflux transporters (multiple drug resistance protein [MDRP]-1 and breast cancer resistance protein [BCRP]); and uptake transport systems (organic anion-transporting polypeptide [OATP]1B1, OATP1B3, organic cation transporter [OCT]2, organic anion transporter (OAT)1, and OAT3) were evaluated to assess the potential drug-drug interactions.

Additionally, the ocular tissue distribution of 2 different formulations of lifitegrast studied during clinical development (one being the formulation used in the Phase 3 OPUS-1 Study, the other being the intended commercial formulation) was evaluated following 5-day repeat-dose topical administration to pigmented rabbits.

Methods of analysis

Plasma, vitreous body and tear bioanalytical methods were validated to GLP. Methods for ocular tissues were adequately qualified to save rare matrices (Non-GLP), which is considered acceptable. For tear and vitreous body analysis, proxy matrices were used. This is also considered acceptable. Applicant provided a thorough discussion of all employed bioanalytical methods in PK Summary. Tables of bioanalytical methods validation performance was provided in PK tabulated Summary. Validation reports were

available for assessment. Several different methods had to be developed for the broad range of matrices including separate ocular tissues and tear obtained from tear strips. Methods were typically using conventional methods such as liquid/liquid extraction or protein precipitation followed by LC-MS/MS. Adequate stability in matrices was shown for lifitegrast. Units for concentration were ng/mL for plasma and vitreous body, µg/mL for tear and ng/g for ocular tissues. Other analytical methods were also thoroughly described in Pharmacokinetic Summary and appear to be fit for purpose. This included radiochemical procedures.

Absorption (R6319M, D6320M, R6313M)

Plasma pharmacokinetics of radiolabelled (14C) lifitegrast was evaluated in rat and dog after both intravenous and ocular route of administration. The doses in rat was 10 mg/kg and 1 mg/eye for intravenous and ocular administration, respectively. The doses in dog was 3 mg/animal and 3 mg/eye for intravenous and ocular administration, respectively. The pharmacokinetic calculation was handled differently, i.e. the unit for clearance and volume of distribution are not readily comparable between rat and dog.

Applicant recalculated the clearance and volume of distribution following intravenous administration of ^{14}C-lifitegrast in the dog in order to be able to compare with rat. The new values showed high similarity of primary pharmacokinetic parameters between the two species, i.e. the subtle differences can be ascribed to allometry. Dose normalised C_{max} appear different between the two species, however this can be ascribed to different sampling times with first time-point in rat of 5 minutes and first sampling time-point in dog of 15 minutes.

Terminal half-lives of lifitegrast related radioactivity after intravenous administration appear to be much longer (36-40 h in rat and 108-113 hours in dog) than for lifitegrast alone (approximately 0.5 hours in rat and 0.4-2.0 hours in dog). Applicant explained that the difference in half-life between radiolabelled and non-radiolabelled lifitegrast can be ascribed to differences in study design and the selection of time points for calculation of half-life. In the studies using radiolabelled lifitegrast, the half-life was calculated from data >24 hours post dosing and in the repeat-dose toxicity studies, data from <24 hours post dose was used. Since the pharmacokinetics of lifitegrast after i.v. administration is biphasic, this may give very different results. This explanation is accepted.

Bioavailability of the ocular route of administration could only be calculated for the rat and comprised to 3.37%. It was not possible to calculate bioavailability of the ocular route of administration in dog, since plasma radioactivity fell rapidly to below limit of quantification after administering via this route, hence bioavailability was estimated to 0%.

Single dose pharmacokinetics was evaluated as part of the Modified Irwin study in rat (Report R6313M). Both male and female were used for pharmacokinetic analysis of the same doses to create composite PK profiles. Pharmacokinetic analysis (Kinetica) was conducted without critical assessment of inclusion of data and the apparent 2-compartment PK profile, hence results of Vd, Cl and half-life are probably flawed and cannot be relied upon. Only AUC should be considered reasonably reliable based on mean of 6 animals on each dose. AUC appeared to be reasonably linear with dose AUC0-n of 20.9, 61.3 and 728 ng/mL*h for 0.2, 1.0 and 10 mg/kg, respectively.

For further details on repeat dose pharmacokinetics following intravenous and ocular administration, please refer to Toxicokinetics in section 4.2.

No studies to evaluate food effect on the absorption of lifitegrast were submitted. This is accepted, since lifitegrast is only intended for ocular instillation.

Distribution (R6319M, D6320M, L6776M, V6316M)

Systemic distribution of radiolabeled lifitegrast was investigated in rat (S-D and LE, RR6319M) and dog (Report D6320M) after a single dose via the intravenous route or the ocular route of administration (both eyes).

In these studies, the distribution to the eyes was also evaluated. After ocular administration, lifitegrast was found in highest concentrations in the anterior tissues. Bulbar and palpebral conjunctiva and cornea showed high concentrations in dog. Rats showed high concentrations in these same tissues and also in iris ciliary body. Rats showed much higher concentrations of radioactivity in eyes compared to dog. Apllicant explained the large difference in concentrations of lifitegrast in the eyes of rat and dog to be caused by 1) the difference in ocular surface area and 2) the higher dose in mg/kg in the rat. The explanation appears plausible and is supported. The posterior tissues showed much lower concentrations, however to an extent, which confirmed that lifitegrast diffused into the eye and resided there at least temporarily.

Applicant concludes that in rats some fraction of the lifitegrast dose administered passed through the nasal turbinates and into the esophagus, ultimately being excreted through the gastrointestinal tract. Since levels of radioactivity were detected in the liver and kidneys it is probable that (limited) systemic absorption did occur.

In rats and dogs, the distribution of radioactivity into tissues following an ocular dose of [14C]-lifitegrast was limited and radioactivity was generally associated with the gastrointestinal tract contents, the tissues associated with excretion, and the eye. These results indicate that lifitegrast-related radioactivity entered the eye via absorption from the topical ocular administration sites. This is supported.

After intravenous administration to rat, concentrations of radioactivity were detected in the anterior ocular tissues, but were not detectable in posterior tissues, with the exception of the sclera, demonstrating that [14C]-lifitegrast drug was distributed into the eye. This was not investigated in dog.

Study director concludes that after an intravenous bolus dose administration in rat, radioactivity was distributed into tissues at the first time point (Report R6319, Rat QWBA). The highest levels were generally associated with the gastrointestinal tract (supporting the excretion balance results), the tissues associated with excretion (in particular the liver and bile), and the glandular tissues. Concentrations declined rapidly and were not detectable in most tissues by 8 hours postdose.

Study director also concluded that a comparison of the distribution of radioactivity between Sprague Dawley (albino) and Long Evans (pigmented) rats, following either an ocular or intravenous dose administration, indicated that [14C]-lifitegrast derived radioactivity did not bind to melanin. This is supported.

An ocular distribution study was conducted in pigmented rabbit testing two different formulations of lifitegrast administered BID by ocular instillation for 5 days. Separate eye tissues were analysed for lifitegrast at 0.25, 0.5, 1, 3 or 8 hours post last dose. The study confirmed that lifitegrast was primarily residing in the anterior tissues of the eye. The half-life of lifitegrast was approximately 2 hours in anterior sclera and bulbar conjunctiva. In some tissues lifitegrast could not be quantified beyond 3 hours (e.g. choroid retinal pigment epithelium) and in others, no elimination was observed up until 8 hours, e.g. cornea. It appears that lifitegrast distribute to separate eye tissues/organs to a different extend with some tissues retaining lifigrast more than others. However, melanin containing tissues does not seem to be tissues in which lifitegrast is prone to accumulate. This could be due to the fact that lifitegrast is a weak organic acid and melanin is negatively charged (Rimpelä et al, 2018). See also section 3.3.2.

The binding of lifitegrast to rat, rabbit, dog, monkey, and human plasma proteins, HSA in solution, and AAG in solution was determined by equilibrium dialysis (RED Device) for 5 hours at concentrations of 50, 100, 250, 500, and 1000 ng/mL (Report V6316M). Lifitegrast was highly bound to plasma proteins from all species, with mean percentage bound values ranging from 96.1 to 99.5%. The relative rank order for

percentage bound was rabbit < dog < monkey = human < rat. Lifitegrast was highly bound to HSA (mean of 94.8 to 97.6%) and moderately bound to human AAG (mean of 31.6 to 51.1%).

The melanin binding of lifitegrast was determined by incubation of the test article in suspensions of Sepia officinalis melanin for 30 minutes at concentrations of 100, 500, and 1000 ng/mL. The results indicated that lifitegrast binding to melanin was concentration dependent, but only moderate (mean of 35.2 to 60.4% bound). The positive control chloroquine, a positively charged base, was highly bound at all tested concentrations (96.2 to 96.5%). Hence lifitegrast is not expected to bind to melanin to any level of concern.

Placental transfer of lifitegrast and milk excretion was not studied. This is considered acceptable, since systemic exposure is limited after ocular instillation and that no specific concerns of toxicity or off-target effects has been observed.

Metabolism (V6317M)

Applicant only discussed an in vitro study of lifitegrast in hepatocytes from rat, rabbit, dog, monkey and humans under this topic. Lifitegrast was apparently slowly metabolised in this system. Only phase 1 metabolites were observed. Metabolites formed were only equivocally identified, however none were specific for human hepatocytes. Identification of metabolites was hampered by the poor purity of the radiolabelled lifitegrast. However, since systemic exposure to lifitegrast is low in patients and that the majority of excreted lifitegrast is as parent compound, this study is considered sufficient.

It should be mentioned that the ADME study (Report R6319M) in rat suffered from the same poor purity of radiolabelled lifitegrast. In this study, attempts were made to identify metabolites, however only lifitegrast and impurities of lifitegrast were identified in excreta from rats. Lifitegrast accounted for the majority of excreted radioactivity in feces after both intravenous and ocular route of administration. This was also the case for urine following ocular administration, however after intravenous administration the major component was an impurity (deschloro-lifitegrast). The major circulating component in plasma was lifitegrast. See also section 3.5.

Excretion (R6319M and D6320M)

Lifitegrast appear to be eliminated primarily as parent compound by biliary excretion. The major part of lifitegrast related radioactivity was found in feces. This was demonstrated in both rat and dog and after both intravenous and ocular instillation of radiolabelled lifitegrast (Reports R6319M and D6320M). Studies of excretion after intravenous administration showed approximately 100% recovery of the administered radioactivity in both species. Recovery was acceptable in rat after ocular instillation (81-86%), but poor in dog using that route of administration (approximately 30%). Urinary excretion accounted for only 1-3% of the administered dose and feces 60 to 100% depending on route of administration. In dog after ocular instillation, feces still accounted for approximately 20% of the dose after 168 hours. It is acknowledged that mass balance studies performed for ocular instillation can be a challenge. The studies are considered adequate for characterising excretion of lifitegrast in nonclinical species.

Pharmacokinetic drug interactions (V6631M, V6632M, V6633M)

Lifitegrast potential for inhibition of cytochrome P450s was investigated in human liver microsomes (Report V6633M). Lifitegrast inhibited CYP2C9 and CYP3A4/midazolam and CYP3A4/testosterone with IC50 values of 4.1, 42 and 32 µM, respectively. No enhancement of inhibition response as a result of pre-incubation with NADPH compared to an identical pre-incubation in the absence of NADPH was observed for CYP2C9. The data demonstrated enhancement of inhibition response as a result of pre-incubation with NADPH compared to an identical pre-incubation in the absence of NADPH for CYP3A4 (midazolam and testosterone as substrates). A follow-on KI/kinact study was performed for CYP3A4 with

midazolam as the substrate. The KI and kinact values were found to be 107 µM and 0.16 min-1, respectively. A model based evaluation (according to FDA/EMA guidelines) of the clinical relevance of CYP3A4 inhibition concluded that there is a low potential for DDI based on systemic exposure.

A study in MDCKII cells, stably expressing human MDR1 or BCRP, showed that lifitegrast was not a substrate of these two transporters (Report V6632).

Lifitegrast is a substrate of OATP1A2 and OATP2B1, which are organic anion transporters involved in hepatic uptake from circulation (Report V6631M). OATP1A2 is expressed in choleangiocytes (epithelial cells of the bile duct) and not in hepatocytes (Lee et al, 2015). OATP2B1 is localised on the blood side of the hepatocyte and the gut side of enterocytes (Solvo home page). Applicant provided studies investigating the role of OATPs in vitro and *in vivo* and concluded that these two transporters could be involved in the uptake/elimination mechanism of lifitegrast. This is supported. These transporters can be saturated and this could be an explanation for the nonlinear kinetics observed in the repeat–dose toxicity studies of intravenous administration, where high exposure of lifitegrast is obtained. Since systemic and portal vein exposure in patients is expected to be much lower than systemic exposure obtained in animals after intravenous administration, saturation of these two transporters are not expected to occur in the clinical setting.

Other pharmacokinetic studies (L6340M)

Pharmacokinetics of lifitegrast after intravenous administration was also evaluated in pregnant rabbits (L6340M). Large variability in exposure was observed on GD 7, however bioanalytical data from Day 19 appear to be more reliable and less variable. Exposure was not proportional to dose, i.e. as observed in other species, clearance seem to be saturated at the high dose. Otherwise, no further pharmacokinetic testing should be required.

3.2.3. Toxicology

Topical ocular administration is the intended route of administration of lifitegrast and was evaluated in nonclinical studies following application 3 times per day, the maximum number of applications per day investigated in the clinic, for a duration of up to 39 weeks in dogs and rabbits. The safety of the intended commercial formulation was assessed in the 39-week topical ocular instillation toxicity study in dogs. A bridging 15-day repeat-dose ocular instillation toxicity study and a 5-day pharmacokinetic (PK) and ocular distribution study were performed in rabbits which assessed how different formulations might affect the toxicity, PK, or ocular distribution of lifitegrast. The dog and rat also had a lifitegrast metabolism profile similar to humans. Lifitegrast demonstrated pharmacological activity in both rat and dog models of eye disease. Despite not specifically evaluating the pharmacological relevance in rabbits, similar non-adverse findings of blinking and squinting were found in rabbits and dogs, so it can possibly be inferred that rabbits are pharmacologically relevant too. All species used in the nonclinical program appear to be pharmacologically relevant.

Single-dose toxicity (R6328M, L6756M)

Single-dose toxicity studies were performed in rat for the intravenous route of administration and in rabbit for ocular instillation. No findings of concern were observed in these two studies and the outcomes provided the basis for further testing in repeat-dose toxicity studies.

Repeat-dose toxicity

Lifitegrast was evaluated for toxicity in a range of studies in rat, rabbit and dog using both the intravenous and the ocular route of administration.

Intravenous administration (R6337M, D6331M, D6338M)

Lifitegrast was dosed by the intravenous route in rat and dog by once daily administration at doses of 0, 3, 10 or 30 mg/kg/day for 13 weeks in rat and 29 days in dog (GLP). These studies included recovery groups for control and high dose. A 7-day dose escalation study in dog with doses 0, 1, 3 and 10 mg/kg/day was also submitted (non-GLP). Lifitegrast was administered in phosphate buffered saline.

The rat study included expected endpoints such as necropsy and peripheral blood immuno-phenotyping of all animals and histopathology on control and high dose animals. The female rats reacted to lifitegrast by showing a decrease in food consumption of 9-11% in mid and high dose groups. Furthermore, both males and females showed a decrease in aspartate aminotransferase at the highest dose of 30 mg/kg/day. These effects were not considered adverse. No other lifitegrast related effects were observed. Apparently, despite high systemic exposure after intravenous administration to rats, no findings of concern were observed. This is supported.

The dose escalating study in dog (7-days) evaluated doses 0, 1, 3 and 10 mg/kg/day. No lifitegrast related findings were noted. The dog 29-days toxicity study used a higher dose range, same as in rat, namely 0, 3, 10 and 30 mg/kg/day. In this study expected endpoints such as necropsy and peripheral blood immunophenotyping of all animals and histopathology on control and high dose animals, were included. No lifitegrast related findings were observed. Dogs were apparently insensitive to high systemic exposure of lifitegrast - at least for 29 days. This is supported.

Ocular administration

Ocular toxicity was studied in rabbit and dog.

Rabbit (L6329M, L6332M, L6333M)

In rabbit, lifitegrast was dosed by ocular instillation three times a day (TID, 4 hours apart) in both eyes at doses of 0, 0.3, 1 and 3% for 13 weeks (2008, GLP) and 0, 0.3, 1 and 5% for 39 weeks (2011, GLP). Later on, a new vehicle, not containing parabens, was tested against the vehicle used in the pivotal toxicity studies. The vehicles alone were tested against 5% lifitegrast for 2 weeks (2012, GLP).

In the 13-week and 39-week studies, the only observed clinical sign, which was dose-related, was increase in blinking and squinting just after dosing. Apparently, this phenomenon was not observed in the 2-week study testing the new vehicle without parabens.

In the 13-weeks study, assessment of toxicity was based on mortality, clinical signs, qualitative food consumption, ophthalmic observations (clinical ophthalmic observations, ocular irritation scoring, intraocular pressure measurements, and pachymetry measurements), clinical and anatomic pathology. Blood, tear, and vitreous samples were collected for toxicokinetic evaluations.

A short-lived period of blepharospasm (blinking/squinting) appears to be a specific test article-related ocular finding in this study. Squinting was seen immediately after application of the test-article in a few Group 4 animals (3.0% lifitegrast).

This response was also rarely seen in eyes receiving 0.0 mg/eye/day (two occasions) and in an eye receiving 1% (one occasion). The duration of squinting ranged from 10 to 100 seconds, and rarely lasted longer than 90 seconds. Typically, it was seen in only 1 or 2 animals at a given time point, and most often it was noted after the second or third instillation of the test article on the same day.

Female rabbits receiving 3.0% of lifitegrast had a statistically significantly higher intraocular pressure (IOP) on Day 90 than did vehicle treated female animals, however values were still within normal levels. Mild conjunctival congestion was inconsistently observed over all dosing groups. Mild conjunctival congestion can be a normal background finding in rabbits and has been associated with the animal being manually restrained or becoming excited. The findings of higher IOP and mild conjunctival congestion is considered not related to lifitegrast. This is supported.

In the 39-weeks study, assessment of toxicity was conducted using the same endpoints as for the 13-weeks study supplemented by electroretinography (ERG) data. There was no evidence for a decrease in amplitude in the ERG in the dosed groups. Thus, lifitegrast at the dosages used in this study did not result in compromised retinal function as assessed by ERG. Similar to the 13-week study, mild conjunctival congestion was sporadically observed with no dose related incidence. Lifitegrast-related blinking and squinting were noted in treated animals sporadically in a dose-dependent manner shortly following dosing, however of insufficient severity to generate more overt signs of ocular irritation such as conjunctival hyperemia, chemosis, or corneal changes. No other findings were reported. The findings observed were found non-adverse and the high dose (5%) was considered NOAEL. This is supported.

In the 2-weeks study, assessment of toxicity was based on mortality, clinical signs, body weight, qualitative food consumption, clinical ophthalmic examinations, intraocular pressure (IOP) measurements, pachymetry, clinical and anatomic pathology and plasma exposure determination. This is considered acceptable for this kind of study. The clinical ophthalmic examinations showed that mild conjunctival congestion (Grade 1) was noted in a few animals given lifitegrast in either Vehicle on Day 1 of the dosing phase. Minor corneal staining (Grade 1 in corneal staining and area of corneal staining) was present sporadically in all groups post dose on Days 1 and/or 15 of the dosing phase. These findings occurred at these frequencies in normal rabbits and were not considered to be lifitegrast-related. No test article-related changes in IOP or pachymetry were noted in any animals in this study.

Dog (D6330M, D6335M, D6336M)

Lifitegrast toxicity was evaluated in the dog by the ocular route of administration (TID, 4 hours apart) in three studies, one dose-escalating study with doses of 1.0, 3.0 and 10% lifitegrast (2007, non-GLP), a 13-week study with doses 0.3, 1.0 and 3.0% (2008, GLP) and finally a 39-week study with doses 1.0%, 3.0% and 5.0% lifitegrast (2015, GLP). The 39-week study was conducted with the new vehicle not containing parabens.

For all three studies, the only lifitegrast related effect was blinking and squinting at doses at or above 3% lifitegrast. Hence this was also evident using the new vehicle without parabens in the 39-week study.

In the dose escalation study, assessment of ocular tolerance was based on ocular examinations (including irritation scoring), intraocular pressure and pachymetry measurements, and ocular histopathology. General animal health was monitored based on survival, clinical signs, body weight, and necropsy findings. Plasma, tear, and vitreous toxicokinetic evaluations were also done.

At the 1% concentration, no clinical effects of the test article were observed. When a 3% concentration was employed, a transient irritative response characterized by squinting and tearing was observed that all animals acclimated to. At a 10% concentration, the transient irritative response was more pronounced and of slightly longer duration (still <60 seconds). This mild irritation was not considered to be adverse. This conclusion is supported. No other findings were present on clinical ophthalmic examination. No macroscopic pathology findings were noted in any animals at sacrifice right after the dosing phase. No significant abnormalities were seen on histopathology. Therefore, Applicant's conclusion that up to 10% lifitegrast is tolerated is supported, despite slight irritability potential of 3 and 10% lifitegrast.

In the 13-week study in dog, assessment of systemic toxicity was based on mortality, clinical signs, body weights, food consumption, clinical pathology, and anatomic pathology. Assessment of the effects of dose administration on ocular parameters was based on ophthalmic observations, tear analysis, and vitreous fluid collections. Toxicokinetic analysis was also conducted.

The main lifitegrast-related ocular finding was a variable, short-lived, period of squinting immediately after application of the test-article to the eye. The frequency of squinting generally followed a dose-response pattern over the course of the study. In general, in all 4 groups, the frequency of

blinking/squinting tended to be somewhat greater at the third scoring interval on a given day when compared to the frequency seen at the first scoring interval on that day.

Baseline pachymetry and intraocular pressure measurements were typically within normal limits for young beagle dogs in a laboratory setting. There were no significant differences for either sex of animals for the IOP and pachymetry data. Lifitegrast showed no effect on clinical pathology parameters, organ weights, and no macroscopic or microscopic findings (all animals for eyes, other organs only high dose group versus control). Applicant's conclusion that the highest dose (3%) applied in this study can be considered NOAEL. This conclusion is supported.

In the 39-week study using the new vehicle, assessment of toxicity was based on mortality, clinical signs, body weights, food consumption, ocular squinting observations, slit lamp and indirect ophthalmic examinations, intraocular pressure (IOP) measurements, pachymetry, electroretinography (ERG), and clinical and anatomic pathology. Tear, blood, and vitreous samples were collected for toxicokinetic evaluations.

Lifitegrast potential adverse effects on eyes were evaluated by slit lamp biomicroscopy, indirect ophthalmoscopy, IOP and axial corneal thickness. No effects were identified. Furthermore, administration of lifitegrast had no effect on retinal function as assessed by scotopic and photopic ERGs recorded during weeks 18 and 38 of the dosing phase.

Ocular treatment with lifitegrast revealed no effects on clinical signs, qualitative food consumption or body weight changes, or clinical or anatomic pathology. Histopathology was conducted on eyes from all animals and on other organs in high dose group and control. The few and sporadic findings, which were observed, were not considered related to lifitegrast treatment. This conclusion is supported.

Similar to the other studies with ocular administration of lifitegrast, blinking or squinting occurred immediately post dose and exhibited a clear dose-related effect because it was not noted in control animals and was mostly observed in animals given 5% lifitegrast. The frequency of blinking or squinting lasting for >60 seconds also increased with increasing dose such that it was not seen in animals given 0 or 1% lifitegrast, on only 4 occasions in animals given 3% lifitegrast, and on 28 occasions in animals given 5% lifitegrast.

Given the blinking and squinting was transient and mild in severity and did not translate into any abnormal ocular observations, Applicant's proposal that the high dose of 5% lifitegrast can be considered NOAEL, is supported. This dose in this vehicle is similar to drug product used in clinical trials and is intended for marketing authorization.

Genotoxicity (V6322M, V6323M, M6324M)

The genotoxicity of lifitegrast has been studied with respect to gene mutations in bacteria and mammalian cells and chromosomal aberrations in-vitro and in-vivo. Additionally, tests of primary DNA damage in-vitro and malignant cell transformation have been conducted.

The study in bacteria was conducted with doses up to 5000 µg/plate with or without S9. Lifitegrast appeared to remain in solution for all test concentrations. Positive controls were used; i.e. benzo[a]pyrene and 2-aminoanthracene with S9 and 2-nitrofluorene, sodium azide, ICR-191 and 4-nitroquinolone-N-oxide without S9. Target concentrations were verified to be within 92.7 to 101%. It is agreed that Lifitegrast did not cause an increase in the mean number of revertants per plate with any of the tested strains either in the presence or absence of microsomal enzymes prepared from Aroclor™-induced rat liver (S9). Background lawn was normal for all plates, hence no toxicity to bacteria was observed.

The confirmatory study in mammalian cells was also conducted using doses up to 5000 µg/plate. At doses of 3500 and 5000 µg/plate without metabolic activation (3 h treatment, 20 h harvest time) mitotic

index was reduced by 56% and 97% respectively. At the dose 3500 µg/plate, increased total percentage of cells showing structural chromosomal aberrations from 1 in the vehicle to 34 in plates with 3500 µg/plate lifitegrast. The positive control showed 85, hence this must be consider as a signal. Applicant classifies the signal as equivocal. This is supported, since the dose is toxic, but not 100% lethal as the mitotic index indicates. Furthermore, a slight reduction in dividing cells and confluence of monolayer compared to vehicle control was observed. The lifitegrast cytotoxicity increased with longer treatment time (20 hours). The increase in chromosomal aberrations was not observed with microsomal activation or with 20 hours treatment time. Microsomal activation appears to decrease lifitegrast cytotoxicity, i.e. no reduction in dividing cells were evident in plates incubated with up to 5000 µg/plate. The initial study was only conducted with 20 hours treatment time, hence the positive chromosomal aberration finding was only observed in the confirmatory assay and was not repeated. Guideline S2R1 (Guidance on genotoxicity testing and data interpretation for pharmaceuticals intended for human use) recommend that if the effect only occurs at the most toxic concentrations and the growth is suppressed ≥50%, then weight of evidence indicate lack of genotoxic potential and a single *in vivo* test can be considered sufficient.

Lifitegrast was evaluated for *in vivo* clastogenic activity and/or disruption of the mitotic apparatus by detecting micronuclei in polychromatic erythrocytes in CD-1 mouse bone marrow. Based on the results of the dose range-finding study, the maximum tolerated dose was estimated to be 500 mg/kg/day. In the dose-range finding study both genders were dosed. Since no difference in toxicity of lifitegrast was observed, only males were used in the micronucleus study. At 500 mg/kg/day, the test article, lifitegrast, induced death in 1 of 5 animals and signs of clinical toxicity, which included irregular respiration, slight hypoactivity, rough haircoat, and/or hunched posture. The doses used are considered in line with S2(R1) as the highest dose is expected lead to lethality. The sampling time of bone marrow (24 hours post last dose) is in line with OECD guideline on Mammalian Erythrocyte Micronucleus Test. Lifitegrast did not induce statistically significant increases in micronucleated PCEs at any test article dose examined (125, 250, and 500 mg/kg/day administered by the intravenous route of administration for three days to male mice, N=5) in the main study. Since, lifitegrast was not cytotoxic to the bone marrow either, Applicant's conclusion that lifitegrast is not considered clastogenic, is supported. It should be noted, that toxicokinetics for this study is missing. However, since lifitegrast was administered at high doses by the intravenous route and clinical signs were evident in the high dose group, this deficiency can be accepted.

Carcinogenicity

ICH Guideline S1A states: "Pharmaceuticals administered by the ocular route may not require carcinogenicity studies unless there is cause for concern or unless there is significant systemic exposure." Applicant's position that the carcinogenic potential of lifitegrast has been adequately evaluated without the long term carcinogenicity testing in rodents is supported. This is based on the *in vitro* and *in vivo* genotoxicity testing, which did not give rise to concern. Furthermore, the repeat dose toxicity studies by the intravenous (up to 13 weeks in rats) or ocular route of up to 39 weeks in rabbits and dogs did not reveal any concerns for carcinogenic potential or immunotoxicity either.

Reproductive and developmental toxicity

Fertility and early embryonic development

Rat combined fertility/embryo-foetal development study (R6341M)

Lifitegrast potential impact on male and female fertility and early embryonic development was evaluated in rat. Male and female rats were dosed IV premating, through mating and gestation. Females were evaluated daily for oestrous cyclicity starting two weeks before dosing and extending through the pairing phase until mating was confirmed. Caesarean sections were performed on all surviving females on GD 21, at which time placentas and amniotic sacs were examined for gross abnormalities, and the number

of corpora lutea, implantation sites, and early or late resorptions were recorded. Individual foetuses were sexed, weighed and examined for external, visceral, and skeletal anomalies (variations and malformations). Males were necropsied after at least 10 weeks of dosing, at which time the reproductive organs were weighed and preserved, followed by assessments of sperm motility and total concentration. Male and female reproductive performances were evaluated based on results of confirmation of mating and female pregnancy. Clinical signs of alopecia, especially on the front legs and feet appeared to increase slightly with increasing dose (R6341M) in both male and female rats, but was also observed in the control group. Lifitegrast administration had no effects on any parameter except male body weight at one time interval (Day 21-28) and a slight decrease in adjusted mean prostate weight (~16% when compared to controls). No other test article-related toxicities (including effects on testicular or epididymal weights) were noted in the males. Exposure was not determined in this study. Exposure to adult animals can be extrapolated from the 13-week repeat-dose toxicity study. This is considered adequate for lifitegrast for ocular instillation, since systemic exposure in patients is expected to be <1000 times the exposure at NOAEL in this combined fertility/embryo-foetal development study.

Rabbit embryofoetal development and toxicokinetics (L6340M)

The purpose of this study was to evaluate the maternal and embryo/foetal toxicity and determine the toxicokinetics of lifitegrast administered daily via intravenous injection to pregnant rabbits during the period of organogenesis during gestation days 7 to 19 (L6340M). Clinical observations, body weights, and food consumption were monitored. A toxicokinetic evaluation was conducted on the first and last day of dosing (GD 7 and 19 respectively). Cesaerean sections were performed on all surviving animals on GD 29, at which time classical end points for embryofetal development were evaluated including the number of corpora lutea, implantation sites, early and late resorptions, and viable and dead foetuses were recorded. Individual foetuses were sexed, weighed and examined for external, soft tissue (visceral) and skeletal anomalies (variations and malformations). Findings observed in rabbit foetuses were not attributed to lifitegrast as incidences were similar or only slightly higher than in control group or historical controls. This is supported, except for findings of variations in supernumerary branches of the subclavian vein, which incidence appear to increase with dose, se inserted table below. However, since systemic exposure in rabbit is >1000 times higher than in patients at the highest dose of 30 mg/kg/day, this is considered acceptable.

Exposure was well documented in this study. Large variability in exposure was observed on GD 7, however bioanalytical data from Day 19 appear to be more reliable and less variable. Exposure was not dose linear, i.e. clearance seem to be saturated at the high dose. This has been observed in other species and is therefore not unexpected. No maternal toxicity was observed. None of the early terminations were attributed to lifitegrast.

Prenatal and postnatal development, including maternal function

Lifitegrast potential impact on prenatal and postnatal development was not evaluated. This is considered acceptable, since no findings were observed in repeat-dose toxicity, fertility and embryofoetal development studies and exposure at NOAEL were generally much higher than systemic exposure to patients.

Studies in which the offspring (juvenile animals) are dosed and/or further evaluated

No studies were submitted. The lack of studies in juvenile animals is accepted, since a full waiver for paediatric studies was granted by the PDCO. A paediatric indication will not be pursued, since lifitegrast is not anticipated to represent a significant therapeutic benefit over existing treatments for paediatric patients.

Local Tolerance (R6356M, Z6357M)

Lifitegrast seem to be well tolerated after ocular instillation as evaluated throughout the pivotal toxicity studies except for squinting of dose-related duration, see also repeat-dose toxicology section. Local dermal tolerance of lifitegrast was also evaluated in rat and minipig in various formulations by topical or intradermal administration in DMSO (rat only), however without control groups. The formulations were tested by both single dose and repeated dose. It was concluded that after topical application of lifitegrast as Gel (1%) or Ointment (1%), no dermal reaction was observed in either rat or minipig. Other topical formulations and intradermal administration gave adverse local reactions. Since lifitegrast is for ocular instillation, local tolerance is considered adequately evaluated.

Other toxicity studies

In vitro toxicity evaluation of lifitegrast on corneal epithelial cells (V6325M)

An *in vitro* study of lifitegrast toxicity to primary corneal epithelial cells plated into 96-well plates revealed that exposure to lifitegrast for 1-24 hours at concentration of ≤ 1% was toxic (V6325M). Applicant argues that the constant exposure is not clinically relevant as the formulation of lifitegrast will quickly be diluted when instilled into the eye of the patient (Meadows, 2002). As no findings of concern was observed in eyes of rabbits after repeated-dose of lifitegrast by ocular instillation using the formulation similar to that used in clinical trials (5%), this is supported. It should also be noted here that lifitegrast appeared to reside in cornea tissue beyond 8 hours post last dose at concentrations of 1-2 µg/g (1.6-3.2 µM) after administering 1.75 mg/eye/dose (5% formulation) BID to rabbits for 5 days without any visible detrimental effects (Report L6776M).

Hemolytic potential and plasma compatibility testing with lifitegrast (V6326M)

Lifitegrast was hemolytic in dog blood at concentrations of 3 and 10% and caused macroscopic and microscopic changes in the plasma of both dogs and humans at concentrations of 1, 3, and 10%. It should be noted that hemolysis was not apparent when human blood was mixed with any concentration of lifitegrast or the control article. Since systemic exposure is very low after ocular instillation, these findings are not of concern.

Antigenicity

No studies were submitted. This is considered acceptable, since lifitegrast is a small molecule and no antibody formation against lifitegrast is expected. Sensitization potential is covered by local tolerance studies.

Immunotoxicity

The potential immunotoxicity of lifitegrast was assessed in the repeat-dose IV and ocular toxicity studies; no indication of immunotoxicity or immunosuppression was observed in any of these studies. Since long term nonclinical and clinical studies did not indicate increased incidence of ocular infections, the lack of specific immunotoxicity investigations is well justified and consistent with ICH S8.

Dependence

No studies of lifitegrast potential to induce dependence or withdrawal effects were submitted. This is considered acceptable, since no concerns in this regard arose either from selectivity screening, CNS safety pharmacology or repeat-dose toxicity studies of both intravenous and ocular administration.

Metabolites

No studies of human specific metabolites were submitted, since none were identified.

Studies on impurities

Genotoxic risk assessment of lifitegrast API process (API-2013-0041)

The relatively complicated synthetic route of lifitegrast was evaluated for potential genotoxic impurities to end up as impurities in the final product. The strategy included a Genotoxic risk assessment as performed by Aptuit (API-2013-0041), which is supported. The genotoxic risk assessment concluded that the only compound of concern was benzylchloride. In a follow up report evaluating purging factors, benzene and SSP-005602 was added to this list. Benzylchloride and benzen were deemed adequately purged, however SSP-005602 was present in the intermediate Synthon B. Therefore, Synthon B was evaluated in a GLP *in vitro* bacterial gene mutation test where it was concluded to be non-genotoxic. Synthon B and SSP-005602 share the same structural alerts, therefore these conclusions are supported.

Toxicological support for commercial specifications (R6706M)

Five impurities are present in drug substance above the ICH Q3A(R2) qualification threshold of 0.15%: SSP-005517, SSP-005495, SSP-005528, SSP-005543, and SSP-005574. Therefore, these were qualified by *in vivo* toxicology studies. Three of those impurities were spiked into lifitegrast at 0.5% level and dosed for 28 days by the intravenous route to rats. It should be noted here that some findings, although of mild character, were found to be more pronounced in the group of rats dosed with lifitegrast with the 3 impurities. However, the findings were considered of no toxicological importance. This conclusion is supported. The other two impurities were found adequately qualified in one of the pivotal toxicity studies conducted by the intravenous route in rat (13-weeks). This is also supported.

Local (ocular) safety of impurities

The impurities SSP-005517 and SSP-005495 were identified in drug substance used for the 13- and 39-week pivotal toxicity studies by the ocular route of administration in rabbits (L6333M and L6329M). The impurities SSP-005528, SSP-005543, and SSP-005574 were later quantified in the batches of lifitegrast used for the 13- and 39-weeks studies by using an updated analytical method. Since the impurities are not degradation products, the post hoc analysis and quantification are considered adequate for qualification. Safety margins were based on mg/kg dose of impurities in rabbits compared with theoretical dose of impurities to patients in case of presence of 0.5% of the impurities. This strategy is supported, although the safety margins were low (in the range of 1.6 to 18). In conclusion, the 5 impurities can be considered qualified in terms of local tolerance after ocular instillation.

Genotoxic assessment of impurities

All five impurities SSP-005543, SSP-005574, SSP-005528, SSP-005495, and SSP-005517 were negative in Ames assay. Although some were slightly toxic at the high dose and some precipitated at doses ≥ 1600 microgram/plate, no increase in revertants were observed for any strain with or without S9 activation, so this conclusion is supported.

All five impurities were also tested in the chromosomal aberration assay in CHO cells with negative outcome. Some of the impurities induced slight toxicity to the cells at the higher test concentrations in the 23 hour treatment regime, but no indication of increased chromosomal aberrations above vehicle control were observed. Therefore, the conclusion that these five impurities can be considered qualified according to ICH3A(R2) to 0.5% is supported.

Other studies

Assessment of potential phototoxicity of lifitegrast (V9041M)

Lifitegrast was evaluated for phototoxic potential by characterisation ultraviolet (UV) absorbance spectrum. Lifitegrast absorbs light primarily in the UVB spectrum. Phototoxicity was then tested in the 3T3 Neutral Red Phototoxicity assay by employing appropriate wavelengths including the UVB range at adequate intensity. Lifitegrast was not phototoxic at any concentration up to 100 µg/mL. According to ICH S10, a negative outcome of this test generally provides low probability of phototoxicity for systemic toxicity in humans. The predictivity of this assay for ocular phototoxicity is less clear. Lifitegrast absorbs

highly to the anterior part of the eye, however no significant increase in photophobia was observed in patients. Hence, lifitegrast potential for inducing phototoxicity is considered low.

3.2.4. Ecotoxicity/environmental risk assessment

In phase I, the PEC calculation of 0.05 µg/L exceeded the action limit of 0.01 µg/L thereby triggering a phase II, Tier A evaluation. The experimentally derived $LogK_{ow}$/$LogD_{ow}$ values were all significantly below the trigger value of 4.5 so that PBT screening in phase II was not indicated. An endocrine effect study was not indicated based on nonclinical mammalian reproductive toxicity study results.

As the vapour pressure of lifitegrast is low, no release to the atmosphere was indicated and testing was limited to aqueous and terrestrial analysis as indicated by further testing. This is considered acceptable.

The Phase II aquatic toxicity studies were performed under full GLP requirements using validated test methods. No significant toxic effects were observed in algae, daphnia or fish, and as the most sensitive species was fish with a NOEC of 11.827 mg/L, this value was used in subsequent calculations.

As lifitegrast did not exhibit adsorption to sewage sludge, no assessment in the terrestrial compartment was considered necessary. Lifitegrast shows less that 1% biodegradation and when tested in water-sediments systems, showed a significant shift into sediment and persistence in the sediment, thus triggering a phase IIb sediment organism toxicity assessment. Degradation occurred to Unknown 1 (maximum 14.3 % AR), minor extractable metabolites unextracted sediment residues (maximum 28.8 % AR) and carbon dioxide (< 1% AR).

PECsediment/PNECsediment was below 1 indicating an acceptable risk to sediment dwelling organisms.

However, the Applicant clarified that the transformation product "unknown 1" is classified as persistent both in water (DT50, 12 °C: 56.7 d) and in the total system (DT 50, 12 °C: 141.0 d).

A proposal for structural formula of unknown 1 was presented. The proposal of dealkylation of the benzofuran carbaldehyde moiety from the lifitegrast appears likely.

The Applicant should submit the ERA report updated with the new information on the degradation product Unknown 1 **(OC)**.

Conclusion

Lifitegrast is neither a PBT nor vPvB substance. The substance is not very biodegradable but shows significant shifting to and persistence in fresh water sediment. Considering the above data, lifitegrast is not expected to pose a risk to STP, surface water or sediment compartments and is therefore not expected to pose a risk overall to the environment when used in accordance with the proposed product posology for the treatment of dry eye disease. It is noted and supported that the statement "Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer needed. These measures will help protect the environment." is included in the PIL in line with the EMA's 'Guideline on the environmental risk assessment of medicinal products for human use' (EMEA/CHMP/SWP/4447/00 corr 2).

However, The ERA report should be updated with new information regarding the degradation product Unknown 1.

3.2.5. Discussion on non-clinical aspects

In general, the nonclinical safety package appears sufficient.

Pharmacology

Overall, *in vitro* and *in vivo* pharmacology studies provided adequate proof of concept of lifitegrast in dry eye disease. Safety pharmacology studies of CNS, cardiovascular and respiratory end-points did not reveal any findings of concern, neither did a Cerep selectivity screen. Exposure in these studies appeared to be well above clinically relevant systemic exposure. Pharmacodynamic drug interaction studies were not performed, since clinical systemic exposure is low.

Pharmacokinetics

The pharmacokinetics of lifitegrast was investigated after both ocular and intravenous administration. The intravenous route of administration is not clinically relevant, however provided valuable information on the systemic distribution and clearance mechanisms.

Toxicology

The toxicity of lifitegrast was evaluated in single- and repeat-dose studies in rat, rabbit and dog after both intravenous and ocular administration. The choice of nonclinical species is considered justified. Lifitegrast appeared to be well tolerated even after intravenous administration resulting in high systemic exposure. Ocular exposure resulted in squinting of dose-related duration, but no macro- or microscopic changes were found in the eyes.

Lifitegrast was adequately evaluated in other toxicity studies such as genotoxicity, reproductive and developmental toxicity and local tolerance. When topics were not studied, these were well justified. Furthermore, impurities were qualified by dedicated *in vivo* and *in vitro* studies supplemented by referencing to repeat-dose toxicity studies.

3.2.6. Conclusion on non-clinical aspects

Apart from a missing updated ERA report, lifitegrast can be recommended for marketing authorisation from the nonclinical point of view.

3.3. Clinical aspects

- ***Tabular overview of clinical studies***

Table 1: Listing of Clinical Studies

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
PK and safety	SAR 1118-001 (Phase 1)	Module 5.3.3.1	Primary: - To assess safety and tolerability Secondary: - To determine the PK profile in plasma and tears	Phase 1, randomized, double-masked, placebo-controlled, dose-escalation study	Lifitegrast 0.1, 0.3, 1.0, or 5.0% or placebo ophthalmic solution; Period 1: single dose, single drop Period 2: single drop BID Period 3: single drop TID	28 subjects (28 males/ 0 females)	Healthy subjects	21 days of treatment separated by observation days (Period 1: 1 day; Period 2: 10 days; Period 3: 10 days)	Complete; Full

Table 1: Listing of Clinical Studies

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
Efficacy and safety	1118-KCS-100 (Phase 2 dry eye)	Module 5.3.5.1	Primary: - To evaluate efficacy as assessed by inferior corneal staining measured without use of the CAE at Day 84 Secondary: - To evaluate subjective and objective efficacy measures with and without use of the CAE - To evaluate safety and tolerability	Phase 2, multicenter, randomized, prospective, double-masked, placebo-controlled, parallel arm study	Lifitegrast 0.1, 1.0, or 5.0% or placebo ophthalmic solution; single drop BID	230 subjects (51 males/ 179 females)	Subjects with dry eye disease	84 days (12 weeks)	Complete; Full

Table 1: Listing of Clinical Studies

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
Efficacy and safety	1118-KCS-200 (SPD606-301; OPUS-1)	Module 5.3.5.1	Primary: - To evaluate efficacy as assessed by change from baseline to Day 84 in inferior corneal fluorescein staining and VR-OSDI - To evaluate safety and tolerability Secondary: - To evaluate efficacy as assessed by STT (means at Days 14 and 84) and total OSDI score (mean changes from baseline to Days 14 and 84)	Phase 3, multicenter, randomized, prospective, double-masked, placebo-controlled, parallel arm study	Lifitegrast 5.0% or placebo ophthalmic solution; single eye drop BID	588 subjects (142 males/ 446 females)	Subjects with dry eye disease	84 days (12 weeks)	Complete; Full

Table 1: Listing of Clinical Studies

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
Efficacy and safety	1118-DRY-300 (SPD606-302; OPUS-2)	Module 5.3.5.1	Primary: - To evaluate efficacy as assessed by change from baseline to Day 84 in inferior corneal fluorescein staining score and eye dryness score - To evaluate safety and tolerability Secondary: - To evaluate efficacy as measured by change from baseline to Day 84 in total corneal staining score, nasal conjunctival lissamine green staining score, eye discomfort score, and ODS	Phase 3, multicenter, randomized, prospective, double-masked, placebo-controlled, parallel arm study	Lifitegrast 5.0% or placebo ophthalmic solution; single eye drop BID	718 subjects (168 males/ 550 females)	Subjects with dry eye disease with a history of artificial tear use within 30 days of screening	84 days (12 weeks)	Complete; Full

Table 1: Listing of Clinical Studies

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
Efficacy and safety	SHP606-304 (OPUS-3)	Module 5.3.5.1	Primary: - To evaluate efficacy as measured by eye dryness score (mean change from baseline to Day 84) Key Secondaries: - To evaluate efficacy as measured by eye dryness score (mean change from baseline to Day 42) - To evaluate efficacy as measured by eye dryness score (mean change from baseline to Day 14) Secondary: - To evaluate efficacy as measured by the visual analogue scale and ODS - To evaluate safety and tolerability	Phase 3, multicenter, randomized, double-masked, placebo-controlled, parallel arm study	Lifitegrast 5.0% or placebo ophthalmic solution; single eye drop BID	711 subjects	Subjects with dry eye disease with a history of artificial tear use within 30 days of screening	84 days (12 weeks)	Complete; Full

Table 1: Listing of Clinical Studies

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
Safety	1118-DRY-400 (SPD606-303; SONATA)	Module 5.3.5.1	Primary: - To evaluate safety as assessed by ocular and non-ocular adverse events Secondary: - To evaluate ocular safety measures	Phase 3, multicenter, randomized, prospective, double-masked, placebo-controlled, parallel arm study	Lifitegrast 5.0% or placebo ophthalmic solution; single eye drop BID	332 subjects (82 males/ 250 females)	Subjects with dry eye disease	360 days (1 year)	Complete; Full
Efficacy and safety	1118-ACJ-100 (Phase 2 allergic conjunctivitis study)	Module 5.3.5.4	Primary: - To evaluate efficacy as assessed by signs and symptoms of allergic conjunctivitis Secondary: - To evaluate safety and tolerability	Phase 2, single center, randomized, prospective, double-masked, placebo-controlled, parallel arm study	Lifitegrast 0.1, 1.0, or 5.0% or placebo ophthalmic solution; single drop TID	60 subjects (31 males/ 29 females)	Subjects with allergic conjunctivitis	14 days (2 weeks)	Complete; Full

BID=twice a day; CAE=controlled adverse environment; ODS=ocular discomfort score; OSDI=Ocular Surface Disease Index© (Allergan, Inc.); PK=pharmacokinetic; STT=Schirmer Tear Test (unanesthetized); TID=3 times daily; VR-OSDI=visual-related function Ocular Surface Disease Index subscale

3.3.1. Pharmacokinetics

Introduction

Lifitegrast binds to lymphocyte function-associated antigen-1 (LFA-1) and prevents interaction with its cognate ligand, intercellular adhesion molecule-1, thus diminishing the recruitment of leukocytes to sites of inflammation and inhibiting the leukocyte component of inflammation and immune activation including lymphocyte adhesion, infiltration, proliferation, and cytokine release. As a potent LFA-1 antagonist, lifitegrast may provide symptomatic and functional clinical benefit for patients with dry eye disease (Gao et al. 2004).

Clinical studies in the lifitegrast development program contributing pharmacokinetic data

Study	Phase	Design	Population	Intervention
SAR 1118-001	1	Randomized, double-masked, placebo-controlled, dose-escalation	28 healthy volunteers	Lifitegrast 0.1% (N=5 active, N=2 placebo) Lifitegrast 0.3% (N=5 active, N=2 placebo) Lifitegrast 1.0% (N=5 active, N=2 placebo) Lifitegrast 5.0% (N=5 active, N=2 placebo)
SONATA	3	Multicentre, randomised, double–masked and placebo-controlled study evaluating safety	332 patients with dry eye disease	Lifitegrast 5.0% twice daily Vs. Placebo (2:1 randomisation)

Primary endpoint of SAR 1118-001

To measure safety and tolerability as assessed by physical examinations, ECGs, vital signs, clinical laboratory measurements, and AEs to measure the systemic effects of lifitegrast and slit lamp biomicroscopy, IOP, STT, TFBUT, and BCVA to measure the local effects of lifitegrast.

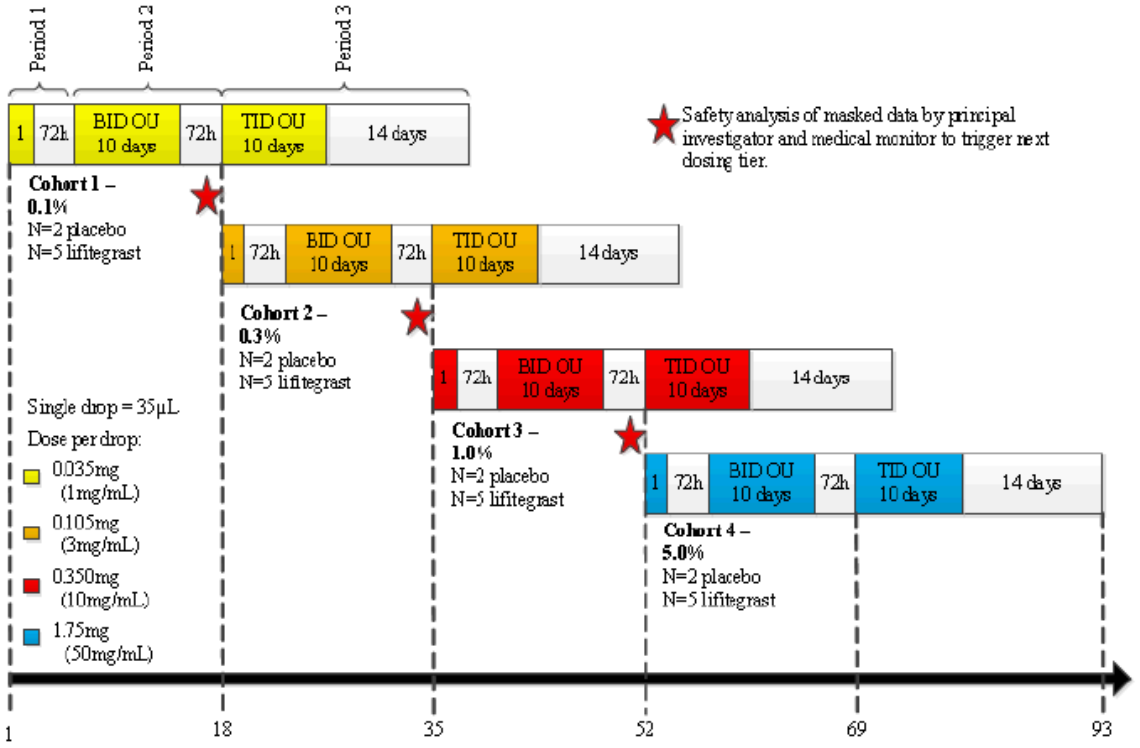
Secondary endpoint of SAR 1118-001

To determine the pharmacokinetic profile in plasma and tears of single and multiple doses of 4 escalating concentrations of lifitegrast.

Design of SAR 1118-001

Figure 1: SAR 1118-001 Study Design Schematic

Period 1 Single Dose	Period 2 Multiple Dose BID	Period 3 Multiple Dose TID and Follow-up
Subjects received a single drop of investigational product administered in 1 eye and a single drop of placebo in the opposite eye + observation (Cohort Days 1-4)	Subjects received a single drop of investigational product to each eye twice daily (single drop) + observation (Cohort Days 5-17)	Subjects received a single drop of investigational product to each eye 3 times daily + observation (Cohort Days 18-29) Subjects underwent post-dose visits at 24 hours and 48 hours and were then discharged from the study center. Subjects return for follow-up visits at 1 week (Cohort Day 34) and 2 weeks (Cohort Day 41) from last dose. Study completion at end of Cohort Day 41.



BID=twice daily; OU=both eyes; TID=3 times daily

A total of 28 subjects were enrolled in the study and assigned to 1 of 4 cohorts that corresponded to the 4 escalating dose cohorts of lifitegrast or placebo. Within each cohort, 5 subjects were randomised to receive lifitegrast and 2 subjects were randomised to receive placebo. All subjects who enrolled completed the study.

The starting dose for this study was determined based on results from non-clinical toxicology studies of lifitegrast and FDA guidelines for the selection of starting dose. The subsequent dose levels were selected to allow gradual escalation to doses considered likely to have a therapeutic effect in subsequent studies.

The study included healthy males and females, age 18–50 years, BCVA at least 20/40 without any relevant comorbidity.

Investigational Product(s) Administered

Subjects received single and multiple daily doses of either lifitegrast (0.1, 0.3, 1.0, or 5.0%) or placebo ophthalmic solution administered to the ocular surface as an eye drop.

Bioanalytical Methodology

Plasma and tear samples were assayed for lifitegrast with validated mass spectroscopy methods.

Methods were linear over the range 0.500-100ng/mL with a LLOQ of 0.500ng/mL and 5.00-1000ng/mL with a LLOQ of 5.00ng/mL for plasma and tear analysis respectively.

Pharmacokinetic Measurements

Pharmacokinetic parameters were determined from the plasma and tear concentration-time data for lifitegrast by non-compartmental analysis. Pharmacokinetic variables included:

Cmax	Maximum concentration occurring at tmax
tmax	Time of maximum observed concentration sampled during a dosing interval
AUC0-4	Area under the curve from the time of dosing to 4 hours
AUC0-8	Area under the curve from the time of dosing to 8 hours
AUC0-t or AUC last concentration	Area under the curve from the time of dosing to the last measurable

The following procedures were used for tear and plasma concentrations below the LLOQ:

- Tear and plasma concentrations that were BLQ were reported as zero on the data listings
- Concentrations that were BLQ were treated as zero in the calculation of summary statistics (e.g., mean, SD) for the plasma concentrations at individual time points
- Mean concentrations were reported as zero if all values were BLQ, and no descriptive statistics were reported. If the calculated mean (±SD) concentration was less than the LLOQ, the value was reported as calculated.

Primary Analyses

The primary endpoint was to measure safety and tolerability as assessed by physical examinations, ECGs, vital signs, clinical laboratory measurements, and AEs to measure the systemic effects of lifitegrast and slit lamp biomicroscopy, IOP, STT, TFBUT, and BCVA to measure the local effects of lifitegrast.

Secondary Analyses

The secondary endpoint was to determine the pharmacokinetic profile in plasma and tears of single and multiple doses of 4 escalating concentrations of lifitegrast.

Disposition of Subjects

A total of 28 subjects were enrolled in the study and assigned to 1 of 4 cohorts that corresponded to the 4 escalating dose cohorts of lifitegrast or placebo. Within each cohort, 5 subjects were randomised to receive lifitegrast and 2 subjects were randomised to receive placebo. All subjects who enrolled completed the study (see Table 3).

Table 3: Subject Disposition

	Lifitegrast				Placebo N=8 n (%)	Total N=28 n (%)
	0.1% N=5 n (%)	0.3% N=5 n (%)	1.0% N=5 n (%)	5.0% N=5 n (%)		
Enrolled	5 (100)	5 (100)	5 (100)	5 (100)	8 (100)	28 (100)
Completed study	5 (100)	5 (100)	5 (100)	5 (100)	8 (100)	28 (100)
Discontinued from study	0	0	0	0	0	0

Source: Section 14, Table 14.1.1

Baseline demographic characteristics were similar between treatment groups.

Subjects' age ranged from 19-47 years, with the mean (SD) being 30.5 years (8.9). Over half of subjects (57%) were 18-29 years of age. All subjects were male, and the majority of subjects were Hispanic (89%). The mean (SD) body mass index was 25.6kg/m2 (2.3).

Pharmacokinetic parameters of lifitegrast in plasma derived from SAR 1118-001

Table 1: Summary of Lifitegrast Plasma Pharmacokinetic Parameters in Healthy Subjects Receiving Single and Multiple Dose Regimens of Lifitegrast (Pharmacokinetic Population)

	N	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-t} (ng·h/mL)	AUC_{0-8} (ng·h/mL)	AUC_{0-4} (ng·h/mL)
Lifitegrast 1.0%						
Period 2, Day 10	5[a]	0.18 ± 0.40	0.08	NC	0.04 ± 0.10	NC
Period 3, Day 10	5[b]	0.27 ± 0.37	0.09 ± 0.01	NC	NC	0.07 ± 0.10
Lifitegrast 5.0%						
Period 1, Day 1	5[c]	0.65 ± 0.68	0.22 ± 0.24	0.35 ± 0.48	NC	NC
Period 2, Day 1	5[c]	0.50 ± 0.49	0.22 ± 0.24	NC	0.20 ± 0.22	NC
Period 2, Day 10	5[d]	1.70 ± 1.36	0.09 ± 0.01	NC	0.69 ± 0.47	NC
Period 3, Day 1	5[d]	1.31 ± 1.04	0.19 ± 0.17	NC	NC	0.56 ± 0.48
Period 3, Day 10	5[d]	0.95 ± 0.60	0.08 ± 0.00	NC	NC	0.64 ± 0.65

AUC_{0-4}=area under the curve from the time of dosing to 4 hours; AUC_{0-8}=area under the curve from the time of dosing to 8 hours; AUC_{0-t}=area under the curve from the time of dosing to the last measurable concentration; C_{max}=maximum concentration occurring at t_{max}; NC=not calculated; t_{max}=time of maximum observed concentration sampled during a dosing interval

Note: AUC_{0-t} is reported for Period 1 (single dose), AUC_{0-8} is reported for Period 2 (twice daily), and AUC_{0-4} is reported for Period 3 (3 times daily).

[a] N=1 for t_{max}

[b] N=2 for t_{max}

[c] N=3 for t_{max}

[d] N=4 for t_{max}

Source: SAR 1118-001 Clinical Study Report, Section 14, Table 2.1.4

Limited plasma exposure to lifitegrast was observed following ophthalmic administration. All lifitegrast plasma concentrations were below the quantifiable limit of the assay (0.5ng/mL) for administration of single- and multiple-dose regimens of placebo, lifitegrast 0.1%, and lifitegrast 0.3%. For the lifitegrast 1.0% group, lifitegrast plasma concentrations were only measurable in the plasma samples collected 5 minutes after administration on Period 2, Day 10 (n=1 of 5 subjects) and Period 3, Day 1 (n=2 of 5 subjects) with all plasma concentrations values below the quantifiable limit of the assay in the next pharmacokinetic sample collected 30 minutes after administration. For the lifitegrast 5.0% group, lifitegrast plasma concentrations were only measurable in the plasma samples collected 5 minutes and 30 minutes after administration and all other plasma concentrations were below the quantifiable limit of

the assay with the exception of a few sporadic concentrations measured for Period 3, Day 1 (1 measurable concentration at 8 hours after administration) or Period 3, Day 10 (1 measurable concentration each at 1 and 8 hours after administration).

Pharmacokinetic parameters of lifitegrast in tears derived from SAR 1118-001

Table 2: Summary of Lifitegrast Tear Pharmacokinetic Parameters in Healthy Subjects Receiving Single and Multiple Dose Regimens of Lifitegrast (Pharmacokinetic Population)

Treatment	N	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-t} (ng·h/mL)	AUC_{0-8} (ng·h/mL)	AUC_{0-4} (ng·h/mL)
Lifitegrast 0.1%						
Period 1, Day 1	5	2234 ± 2193	1.15 ± 1.45	3760 ± 3650	NC	NC
Period 2, Day 1	5	2132 ± 1289	0.22 ± 0.10	NC	3916 ± 3652	NC
Period 2, Day 10	5	1587 ± 1647	0.53 ± 0.27	NC	3304 ± 3315	NC
Period 3, Day 1	5	1652 ± 993	0.33 ± 0.00	NC	NC	1196 ± 668
Period 3, Day 10	5	2886 ± 2388	2.52 ± 3.33	NC	NC	2548 ± 1594
Lifitegrast 0.3%						
Period 1, Day 1	5	10756 ± 11337	0.34 ± 0.02	24551 ± 19259	NC	NC
Period 2, Day 1	5	39259 ± 38735	0.33 ± 0.00	NC	41487 ± 54267	NC
Period 2, Day 10	5	24395 ± 35782	0.31 ± 0.03	NC	24987 ± 27156	NC
Period 3, Day 1	5	16367 ± 15799	5.59 ± 11.48	NC	NC	10938 ± 8239
Period 3, Day 10	5	7490 ± 6337	0.30 ± 0.04	NC	NC	7616 ± 3581
Lifitegrast 1.0%						
Period 1, Day 1	5	16222 ± 15639	1.12 ± 1.53	52245 ± 55837	NC	NC
Period 2, Day 1	5	72701 ± 92677	1.87 ± 3.45	NC	168360 ± 300626	NC
Period 2, Day 10	5	34763 ± 39828	0.99 ± 1.50	NC	62490 ± 77785	NC
Period 3, Day 1	5	18304 ± 12538	5.09 ± 10.36	NC	NC	12607 ± 7575
Period 3, Day 10	5	27457 ± 17918	0.42 ± 0.14	NC	NC	29851 ± 35598
Lifitegrast 5.0%						
Period 1, Day 1	5	74792 ± 67753	5.14 ± 10.44	311734 ± 342330	NC	NC
Period 2, Day 1	5	48681 ± 56903	0.34 ± 0.01	NC	75493 ± 99762	NC
Period 2, Day 10	5	91413 ± 43308	0.44 ± 0.22	NC	127697 ± 66418	NC
Period 3, Day 1	5	119031 ± 106536	0.33 ± 0.01	NC	NC	77395 ± 58225
Period 3, Day 10	5	126383 ± 99675	0.31 ± 0.02	NC	NC	115757 ± 73976

Note: AUC_{0-t} is reported for Period 1 (single dose), AUC_{0-8} is reported for Period 2 (twice daily), and AUC_{0-4} is reported for Period 3 (3 times daily).

AUC_{0-4}=area under the curve from the time of dosing to 4 hours; AUC_{0-8}=area under the curve from the time of dosing to 8 hours; AUC_{0-t}=area under the curve from the time of dosing to the last measurable concentration; C_{max}=maximum concentration occurring at t_{max}; NC=not calculated; t_{max}=time of maximum observed concentration sampled during a dosing interval

Source: SAR 1118-001 Clinical Study Report, Section 14, Table 2.1.3

The first tear sample collected around 30 minutes after single dose administration of lifitegrast on Period 1, Day 1 typically had the highest lifitegrast concentration, but the lifitegrast tear Cmax occasionally occurred at a later time point, around 4, 8, or 24 hours after administration in a few instances. For single dose administration, the lifitegrast tear concentrations increased in a roughly dose-proportional manner

with the 50-fold increase in dose between lifitegrast 0.1 and 5.0% solutions producing a 33.5-fold increase in mean lifitegrast tear Cmax on Period 1, Day 1 (74792 vs. 2234ng/mL) and a 82.9-fold increase in mean lifitegrast tear AUC0-t (311734 vs. 3760ng·h/mL). However, the lifitegrast single-dose tear pharmacokinetic parameters exhibit large variability with the coefficient of variation ranging from 90.6-105.4% for tear Cmax and from 78.4-109.8% for tear AUC_{0-t} across the 4 doses.

Allowing for the high tear pharmacokinetic variability, there were no obvious differences between twice daily (Period 2) and 3 times daily (Period 3) dosing schedules in tear pharmacokinetic results. Moreover, there was no unexpected accumulation of lifitegrast in tears during the twice daily and 3 times daily regimens.

ADME

Absorption

Tear: C_{max} = 91413 ±43308 ng/ml, $AUC_{0-8hours}$ = 127697 ±66418 ng·h/ml and T_{max} 0.44 ±0.22 hours. There was no accumulation of lifitegrast in tears during twice daily and 3 times daily administration of lifitegrast.

Plasma: T_{max} of 0.09 ±0.01 hours (approximately 5.4 minutes). Lifitegrast is also rapidly eliminated from plasma with lifitegrast concentrations typically being measurable for only up to 30 minutes after administration. Systemic exposure to lifitegrast is extremely low with C_{max}=1.70 ±1.36 ng/ml and $AUC_{0-8hours}$ = 0.69 ±0.47 ng·h/ml when administered twice daily for 10 days; therefore, lifitegrast disposition half-life (t½) cannot be determined accurately. The overall plasma profile demonstrated no systemic accumulation of lifitegrast when administered twice daily over 10 days.

Distribution

Lifitegrast was highly bound to plasma proteins in rat, rabbit, dog, monkey, and human plasma, with mean percentage bound values ranging from 96.1-99.5%. Lifitegrast is highly bound to human serum albumin (mean of 94.8 to 97.6%), and was moderately bound to human α1-acid glycoprotein (mean of 31.6-51.1%). In vitro study results suggest that lifitegrast is a substrate for OATP1 and OATP4 uptake transporters. The clinical relevance of these findings is unknown given that systemic exposure to lifitegrast via the topical ocular route of administration is very low. The binding to melanin was found to be moderate (mean of 35.2-60.4% bound).

Excretion

The majority of the drug is excreted unchanged via the faecal route. The main route of excretion following ocular administration was the faeces, accounting for approximately 60% of the administered radioactivity up to 168 hours post-dose. Urinary excretion accounted for up to 2% of the administered radioactivity.

Metabolism

The metabolism of [14C]-lifitegrast was examined in isolated primary hepatocytes from male Sprague-Dawley rat, male beagle dog, male cynomolgus monkey, and female human, and the metabolism was slow in all species with no human specific metabolite identified (Study Report V6317M-SPD606). Lifitegrast (10μM) significantly inhibited CYP2C9 (94%), and further investigation revealed the IC50 to be 11μM (Study Report V6435M-SPD606). However, due to the low clinical exposure (mean plasma Cmax of 1.7ng/mL [2.7nM] at the therapeutic dose), drug-drug interactions are not expected with CYP2C9 substrates, and no clinical drug-drug interaction studies were conducted.

Pharmacokinetics in target population (SONATA)

There was no evidence of accumulation of lifitegrast in plasma over time; the mean trough concentration of lifitegrast in plasma was below the lower limit of quantification (0.500ng/mL) at Days 0, 180, and 360 (Months 0, 6, and 12) (see Table 3).

Table 3: SONATA Lifitegrast Plasma Concentration (Safety Population)

	Lifitegrast N=220	
	n	Mean (SD), ng/mL
Day 0 (Month 0, Visit 2, baseline)	52	0.000 (0.0000)
Day 180 (Month 6, Visit 5)	47	0.308 (0.8264)
Day 360 (Month 12, Visit 7)	43	0.047 (0.2187)

Note: Sensitivity of detection is 0.50ng/mL.
SD=standard deviation
Source: SONATA Clinical Study Report, Section 14, Table 2.1

Special populations

No PK studies of lifitegrast in special populations have been conducted. Based on the elimination pathways, no impact of impaired renal or hepatic function is expected. Further, neither gender, age nor weight are expected to alter the PK of lifitegrast. An OC has been raised regarding binding of lifitegrast to iris melanin and possible implications for PK in different races.

Interactions

In vitro studies have found that lifitegrast is a significant inhibitor of CYP2C9. A study to determine the potential of OATP inhibitors to alter lifitegrast excretion was conducted in rats (Study Report V6390M-SPD606). Co-administration of CSA or probenecid with lifitegrast modulated the pharmacokinetic parameters of lifitegrast. The clearance of lifitegrast significantly decreased and the AUC significantly increased when co-administered with an OATP transport inhibitor (the plasma clearance remained high, >15mL/min/kg). However, as lifitegrast following ophthalmic administration only enters systemic circulation to a very limited degree. Consequently, it is considered unlikely that the in vitro and non-clinical impact on CYP2C9 and OATP, respectively, will have any impact on the PK parameters of lifitegrast or other concomitantly administered medicinal products in a clinical setting and no dedicated DDI studies have been conducted. However, drug transporters are known to be expressed in the ocular epithelium. Possible implications for pharmacokinetic drug-drug interactions between lifitegrast and other topically applied ophthalmic drugs have been raised as an OC.

3.3.2. Pharmacodynamics

Mechanism of action

Lifitegrast targets the interaction between lymphocyte function-associated antigen-1 (LFA-1), a cell surface protein found on leukocytes, and intercellular adhesion molecule-1 (ICAM-1), its cognate ligand. By targeting the LFA-1/ICAM-1 interaction, lifitegrast reduces elevations in cytokines that have been correlated with the development and perpetuation of dry eye disease.

Primary pharmacology – Dose selection

The starting dose in Study SAR 1118-001 (single dose of lifitegrast 0.1%) was determined based on results from non-clinical toxicology studies of lifitegrast and Food and Drug Administration guidelines for the selection of starting dose. The subsequent dose levels in Study SAR 1118-001 (lifitegrast 0.1, 0.3, 1.0, and 5.0%; single dose, twice daily, and 3 times daily) were selected to allow gradual escalation to doses considered likely to have a therapeutic effect in subsequent studies.

Nonclinical studies in which the distribution of either 14C-labeled lifitegrast or unlabelled lifitegrast were determined following topical administration at doses ranging between 1mg/eye in rats to 3mg/eye in dogs, demonstrate that the highest levels of radioactivity or of lifitegrast itself occur in anterior ocular tissues (bulbar and palpebral conjunctiva, cornea, and iris ciliary body) at 0.25-0.5 hours across several species. The distribution to anterior ocular tissues was not always dose-dependent. Nevertheless, the pharmacokinetics of lifitegrast distribution in pre-clinical species supported a clinical dose regimen of up to 3 times daily topical ocular instillation and at doses included in the clinical exposures.

The lifitegrast 0.3% dose strength was not used in Phase 2 studies because the majority of adverse events were observed in this dose strength in Phase 1. Therefore, the Phase 2 dry eye study evaluated the efficacy of lifitegrast 0.1, 1.0, and 5.0% twice daily. The greatest treatment effect was observed with lifitegrast 5.0% twice daily, so this dose regimen was chosen for the Phase 3 studies.

Secondary pharmacology

The in vitro effects of lifitegrast on the hERG channel current (a surrogate for I_{Kr}, the rapidly activating, delayed rectifier cardiac potassium current) was evaluated in voltage-clamped human embryonic kidney cells (HEK293) transfected to stably express the hERG channel. The IC_{50} for the inhibitory effect of lifitegrast on hERG potassium current was 478 µM, which is considerably higher than the mean plasma lifitegrast C_{max} for the therapeutic dose of 5.0% lifitegrast administered twice daily (mean C_{max} of 1.7ng/mL [2.7nM]). Therefore, lifitegrast is not expected to affect cardiac repolarization or prolong the QTc interval of the electrocardiogram.

Pharmacodynamic interactions with other medicinal products

No information has been submitted. There is a potential risk of pharmacodynamic interactions e.g. a synergistic effect for topically applied medical products like antibiotics, corticosteroids, ciclosporine A and pilocarpine. No safety issues or lack of efficacy are expected.

3.3.3. Discussion on clinical pharmacology

Discussion of Pharmacokinetics

Lifitegrast is being developed for the treatment of dry eye disease and is to be administered locally in the eye. Based on the non-clinical program to characterize the pharmacokinetics of lifitegrast, systemic exposure following topical administration was expected to be minimal.

There is no adequate model of DED and since Xiidra is locally acting, has no significant systemic absorption and is eliminated rapidly it is considered to be acceptable that no specific clinical pharmacology studies were conducted in Humans. As inflammation has been shown to be key to the pathology of DED and has been postulated to sustain a vicious cycle leading to self-sustained disease state, it is plausible that anti-inflammatory therapies can be effective in the treatment of DED.

One randomised, double-masked, placebo-controlled, dose-escalation phase 1 study in 28 healthy volunteers was conducted from which the PK characteristics of lifitegrast were elicited. Further, the SONATA study, which was a multicentre, randomised, double-masked, placebo-controlled phase 3 study in 332 patients contributed PK data in the target population of patients with dry eye disease.

Bioanalytical methodology

The bioanalytical analyses are appropriate.

Plasma PK

Systemic absorption following topical administration in humans was very limited. The exact magnitude of the absorption could not be determined but it is justified to assume that it is of a similar magnitude

as that observed in animal studies (0% to approx. 3.5%). The absorption that did occur was rapid (with a T_{max} of 5-13 minutes following topical administration) and lifitegrast was also cleared rapidly (not detectable beyond 30 minutes following topical administration). C_{max} increased with increasing dose although no robust dose-response relationship was apparent. Determination of Cmax was somewhat uncertain, as overall concentrations were very low. Overall, AUC determination was challenged by the very low systemic exposure. A dose-response relationship was present as evidenced by the 5% dose being the only one to yield systematic detection of lifitegrast in plasma. Neither the 2-daily nor the 3 times daily study indicated any plasma accumulation following multiple exposure.

Lifitegrast is highly bound to human serum albumin (94.8-97.6%). Further, lifitegrast appears to be a substrate of the OATP family but it is considered unlikely that this will affect the PK of topically administered lifitegrast to a clinically important degree. The main route of excretion of lifitegrast is unchanged via faeces. Only about 2% of lifitegrast is recovered in urine. While systemically administered lifitegrast is metabolized by CYP2C9, any impact of inhibitors of inducers of CYP2C9 on the PK of topically administered lifitegrast is considered unlikely due to the very limited systemic absorption.

Tear PK

A dose-response relationship between dose of lifitegrast administered and concentration of lifitegrast measured in tears is overall present. Tear lifitegrast C_{max} was typically observed at the initial measurements (30 min or 1 hour) while for some samples, C_{max} was reached at later time points. A dose-response relationship between administered lifitegrast concentration and concentration measured in tears was sufficiently demonstrated for both C_{max} and AUC, albeit single-dose lifitegrast PK parameters exhibited large variability. It is considered documented that a twice-daily regimen and a 3 times daily regimen display no apparent differences of PK expected to be of clinical relevance. No unexpected accumulation of lifitegrast was detected.

It was questioned why several samples from placebo-treated eyes had measurable concentrations of lifitegrast as well as several tear samples from subjects receiving only placebo. An overview of the tear concentration values presented during assessment by the Applicant confirmed that the detected concentrations were low, besides the two values (1632.91 ng/mL in the 0.3% cohort on Day 1 and a 0.5 hr post-dose sample with a concentration of 2644.23 ng/m). Re-analysis of the samples were not possible, and the explanation of cross-contamination due to lack of change of glows is a concern. However, it is unlikely that the reported PK parameters are affected in a degree that compromise the overall conclusions, and the issue of positive placebo samples is not further pursued.

Additional PK data

Overall, similar PK of lifitegrast in healthy volunteers and the target population has been demonstrated. No studies in special populations have been conducted but based on the PK characteristics of lifitegrast, no differences of PK in special populations are expected. Lifitigrast binds moderately to melanin, but there are no indications of accumulation in melanin containing tissues that could translate to concerns of racial differences. Non-clinical data support that lifitigrast accumulation is low. No drug-drug interaction studies have been conducted, but systemic exposure is minimal and no clinically relevant DDIs are expected with concomitant systemic administered medicinal product. Drug transporters are known to be expressed in the ocular epithelium, and there are potential drug-drug interactions for non-systemically available ophthalmic drugs, due to transporters at the ocular surface, if they were co-administered. Therefore, there should be at least 15 minutes between administrations of ophthalmic medicinal products.

Discussion of Pharmacodynamics

Pharmacodynamic data were generated in pre-clinical studies as well as Study SAR 1118-001.

The mechanism of action of lifitegrast is targeting of the interaction between lymphocyte function-associated antigen-1 (LFA-1), a cell surface protein found on leukocytes, and intercellular adhesion molecule-1 (ICAM-1), its cognate ligand. Studies performed in vitro using a human T-cell line have demonstrated that through its interaction with LFA-1, lifitegrast inhibits T-cell adhesion to ICAM-1, and inhibits the secretion of key inflammatory cytokines, including T-cell regulating cytokines IL-2 and IL-4 and several cytokines associated with the clinical severity of dry eye (IL-1α, IL 1β, IL-6, IL-10, IFN-γ, MIP-1α). Through this mechanism, lifitegrast reduces elevations in cytokines that have been correlated with the development and perpetuation of dry eye disease. Clinical studies of lifitegrast have not contradicted this mechanism of action.

Lifitegrast was well tolerated across test doses, and no accumulation was detected at the highest dose (5%) following multiple exposure. Systemic exposure was very low. Non-clinical studies indicated that a dosing regimen of up to 3 administrations daily would be well-tolerated. However, the 5% dose, which showed the greatest treatment effect, was carried forward into studies to determine clinical efficacy and safety. As a twice-daily and a three times daily regimen showed similar efficacy, the twice-daily regimen was chosen.

In vitro studies found that hERG channels are inhibited at lifitegrast concentrations several orders of magnitude larger than those concentrations that therapeutic doses of lifitegrast yield. Thus, it may be assumed that lifitegrast administered at therapeutic doses will not affect cardiac repolarization or prolong the QTc interval.

It is considered possible that lifitegrast may exhibit pharmacodynamic interactions, in particular with other medicinal products administered topically in the eye. Although patients receiving concomitant treatment (and patients with concomitant diseases) were excluded from the clinical trials, it is considered very likely that the target population for lifitegrast will be receiving other medicinal products to treat dry eye disease. Such medicinal products include antibiotics, corticosteroids, potent immunosuppressants such as cyclosporine, and tear-stimulating medicinal products such as pilocarpine.

There is a risk of pharmacodynamic interactions, including potential synergetic interactions between lifitegrast and for topically applied products like antibiotics, corticosteroids, ciclosporine A and pilocarpine. However, as there is no expected safety issues or expected lack of efficacy related to potential PD interactions, and the issue is not pursued further. It is stated in the SmPC that no DDI studies have been performed. This is considered acceptable. 15 minutes between administrations of ophthalmic medicinal products is considered acceptable.

Efficacy of lifitegrast does not depend on lifitegrast reaching systemic circulation and thus, establishment of a relationship between plasma concentrations and effect of lifitegrast is not clinically meaningful.

3.3.4. Conclusions on clinical pharmacology

Conclusion of Pharmacokinetics

Overall, the PK characterisation of lifitegrast has been limited but this is overall justified by the PK characteristics established in Study 1118-001.

Conclusion of Pharmacodynamics

Overall, the PD characterisation of lifitegrast has been limited but this is considered overall justified particularly in light of the mechanism of action and overall confinement of lifitegrast to the eye following topical administration.

3.3.5. Clinical efficacy

The lifitegrast DED clinical development program consists of 6 randomised, double-masked, placebo-controlled clinical studies involving 2,607 subjects:

- 1 Phase 1 study in healthy subjects and
- 4 multicenter, prospective, randomised, double-masked, placebo-controlled safety and efficacy studies:
  - 1 Phase 2 (1118-KCS-100) and
  - 3 Phase 3 (1118-KCS-200/OPUS-1, 1118-DRY-300/OPUS-2, and SHP606-304/OPUS-3)
- 1 long-term multicenter, prospective, randomised, double-masked, placebo-controlled, parallel-arm safety study (1118-DRY-400; referred to as SONATA).

A total of 2,247 subjects with DED have participated in clinical efficacy studies, with 1,181 of these exposed to lifitegrast. A total of 177 subjects have been exposed to lifitegrast for >6 months and 170 subjects have been exposed to lifitegrast for ≥12 months (defined as ≥355 days). A brief description of the Phase 2 and Phase 3 studies is presented below.

- The Phase 2 DED study was a multicenter, randomised, prospective, double-masked, placebo-controlled, parallel-arm study. A total of 230 subjects with DED were randomised to lifitegrast 0.1, 1.0, or 5.0% or placebo (1:1:1:1) and were treated twice daily for 12 weeks (84 days). Efficacy and safety results from this study are described in this submission.
- OPUS-1, OPUS-2 (pivotal study), and OPUS-3 (pivotal study) were Phase 3, multicenter, randomised, prospective, double-masked, placebo-controlled, parallel-arm studies. A total of 588, 718, and 711 subjects were randomised to either lifitegrast 5.0% or placebo (1:1) in OPUS-1, OPUS-2, and OPUS-3, respectively, and were treated twice daily for 12 weeks (84 days). Efficacy and safety results from these studies are described in this submission.
- SONATA was a Phase 3, multicenter, randomised, double-masked, placebo-controlled, parallel-arm study comparing the safety of lifitegrast 5.0% in which subjects were instructed to follow a twice daily dosing regimen for 1 year (360 days). A total of 332 subjects were randomised to either lifitegrast 5.0% or placebo (2:1). Safety results from this study are described in this submission.

All studies were conducted in the US.

Table 2 Summary of Key Elements of the Lifitegrast Clinical Efficacy Studies in Dry Eye Disease

	Phase 2	OPUS-1	OPUS-2	OPUS-3
Sample size	230	588	718	711
Primary sign endpoint	ICSS	ICSS	ICSS	Not specified
Primary symptom endpoint	Not specified	VR-OSDI score	EDS	EDS
Study arms	Placebo, 0.1%, 1.0%, 5.0% lifitegrast	Placebo, 5.0% lifitegrast	Placebo, 5.0% lifitegrast	Placebo, 5.0% lifitegrast
Schedule	BID for 84 days	BID for 84 days	BID for 84 days	BID for 84 days
Key I/E	• Adults with DED • Cornea score of ≥2.0 in any eye • Redness score ≥1.0 in ≥1 eye • STT ≥1 and ≤10 • Change in ICSS ≥+ 1 pre-post CAE • ODS ≥+ 3 at 2 consecutive time points intra-CAE	• Adults with DED • Cornea score of ≥2.0 in any eye • Redness score ≥1.0 in any eye • STT ≥1 and ≤10 • Change in ICSS ≥+ 1 pre-post CAE • ODS ≥+ 3 at 2 consecutive time points intra-CAE	• Adults with DED • Cornea score of ≥2.0 in any eye • Redness score ≥1.0 in any eye • STT ≥1 and ≤10 • EDS ≥40 at screening and baseline • ICSS >0.5 at screening and baseline • Recent AT use required	• Adults with DED • Cornea score of ≥2.0 in any eye • Redness score ≥1.0 in any eye • STT ≥1 and ≤10 • EDS ≥40 at screening and baseline • ICSS ≥0.5 at screening and baseline • Recent AT use required
CAE	Yes	Yes	No	No
Rescue treatment/ Artificial Tears	No	No	No	No
Key sign measurements	• Corneal fluorescein score • Conjunctival lissamine score • STT	• Corneal fluorescein score • Conjunctival lissamine score • STT	• Corneal fluorescein score • Conjunctival lissamine score • STT	Ad hoc analyses of[a]: • ICSS • Total corneal staining score
Key symptom measurements	• ODS • 7-item VAS • OSDI	• ODS • 7-item VAS • OSDI	• ODS • 7-item VAS • OSDI	• ODS • 7-item VAS

AT=artificial tears; BID=twice daily; CAE=controlled adverse environment; DED=dry eye disease; EDS=eye dryness score; ICSS=inferior corneal staining score; I/E=inclusion/exclusion criteria; ODS=ocular discomfort score; OSDI=Ocular Surface Disease Index; STT=Schirmer Tear Test without anesthesia (mm/5min); VAS=visual analogue scale; VR-OSDI=visual-related function subscale of OSDI

[a] Sign endpoints were measured as safety endpoints in the OPUS-3 study and ad-hoc efficacy analyses were conducted.

Dose-response studies and main clinical studies

The phase 2 dose-finding study:

Study design

The study included 3 periods: screening, treatment, and follow-up observation. The study duration was 14 weeks in total.

A total of 5 challenges with the CAE were scheduled during screening and treatment (1 CAE at each visit). Ocular assessments and subject self–assessments were conducted prior to, during, and following each CAE in both eyes.

The Screening Period consisted of 2 visits (Visits 1 and 2 (Days -14 and 0). Each visit included exposure to the CAE. Subjects had to have a positive response in at least 1 eye at Visit 1 (Day -14,) and in the same eye at Visit 2 (Day 0) to be considered for study eligibility.

A positive response was defined as meeting all of the following criteria in the same eye:

- Change from pre-CAE to post-CAE in inferior corneal fluorescein staining score ≥+1
- ODS ≥3 at 2 consecutive time points (or score of 4 at 2 consecutive time points if the pre-CAE score=3 at the same visit)
- STT (without anaesthesia) ≥1 and ≤10mm.

The worst eye meeting these requirements was designated as the study eye.

The Treatment Period started at Visit 2 (Day 0) and included Visits 3-5 (Days 14-84). Site staff administered the first dose of randomised investigational product at Visit 2 and at each scheduled visit.

Subjects self-administered investigational product for all other doses (1 drop BID) until Visit 5 (Day 84). Subjects were asked to rate and record ocular symptoms in daily diaries for 7 consecutive days prior to each visit.

Approximately half of those randomised took or were taking a concomitant ocular medication of these most were using artificial tears.

In- and exclusion criteria

The key in- and exclusion criteria are presented in table 2 above. However, the exclusion criteria also comprised *"Pre-auricular lymphadenopathy or any ocular condition that, in the opinion of the investigator, could affect study parameters including, but not limited to, glaucoma, diabetic retinopathy, blepharitis, meibomian gland disease, follicular conjunctivitis, iritis, uveitis, and/or active ocular inflammation. Use of any topical medication and/or antibiotics for the treatment of blepharitis or meibomian gland disease. Active or history of ocular herpes; any other ocular infection within the last 30 days."*

Primary objective

To evaluate the efficacy of 3 different concentrations (0.1, 1.0, 5.0%) of lifitegrast compared to placebo in the treatment of dry eye as assessed by inferior corneal staining measured without use of a controlled adverse environment (CAE). Comparisons were to be made during 12 weeks of treatment with BID dosing.

Secondary objectives

The secondary objectives were as follows:

Ocular Signs:

- To evaluate the efficacy of lifitegrast compared to placebo in the treatment of dry eye as assessed by STT (mm/5 minutes) measured by the mean at Day 14 (Visit 3)
- To evaluate the efficacy of lifitegrast compared to placebo in the treatment of dry eye as assessed by STT (mm/5 minutes) measured by the mean at Day 84 (Visit 5).

Ocular Symptoms:

- To evaluate the efficacy of lifitegrast compared to placebo in the treatment of dry eye as assessed by the total OSDI score (0-100 scale) measured by mean change from baseline to Day 14 (Visit 3)
- To evaluate the efficacy of lifitegrast compared to placebo in the treatment of dry eye as assessed by the total OSDI score (0-100 scale) measured by mean change from baseline to Day 84 (Visit 5).

Endpoints

There was one pre-specified 'sign'-endpoint, namely the ICSS. There was not a primary symptom endpoint specified for the Phase 2 study. Secondary Symptom measurements: ODS (ocular comfort score), 7-item VAS (the items included burning/stinging, itching, foreign body sensation, blurred vision, eye dryness, photophobia, and pain.), OSDI (Ocular Surface Disease Index) as shown in the table below:

Study	Endpoint	Sign Measures	Symptom Measures
Phase 2	Primary	• ICSS (mean at Day 84)	• Not applicable
	Secondary	• Corneal fluorescein staining score (total, inferior, superior, central) • STT • Conjunctival lissamine green staining score (temporal, nasal, total) • Blink rate[a] • Conjunctival redness score • Tear film break-up time • Ocular Protection Index[a]	• OSDI score (total, symptom subscale, VR-OSDI, trigger subscale) • ODS • VAS by symptom[b] • 5-symptom assessment[c]

Secondary efficacy endpoints were meant to be exploratory in nature.

Results

Study participants

A total of 230 subjects with DED were randomised to lifitegrast 0.1, 1.0, or 5.0% or placebo (1:1:1:1) and were treated twice daily for 12 weeks (84 days). LIF 0.1%, N=57, LIF 1.0%, N=57, LIF 5.0%, N=58, Placebo, N=58.

Demographics

Table 4: Subject Demographics (ITT Population)

	0.1% LIF N=57	1.0% LIF N=57	5.0% LIF N=58	Placebo N=58	Total N=230
Age (years)					
Mean (SD)	63.14 (13.100)	63.63 (11.883)	62.26 (12.220)	60.38 (12.930)	62.34 (12.523)
Minimum, maximum	26.0, 89.0	35.0, 91.0	31.0, 85.0	26.0, 89.0	26.0, 91.0
≥50 years, n	51	50	51	47	199
Sex, n (%)					
Female	47 (82.5)	40 (70.2)	47 (81.0)	45 (77.6)	179 (77.8)
Male	10 (17.5)	17 (29.8)	11 (19.0)	13 (22.4)	51 (22.2)
Ethnicity, n (%)					
Not Hispanic or Latino	56 (98.2)	57 (100.0)	58 (100.0)	58 (100.0)	229 (99.6)
Hispanic or Latino	1 (1.8)	0	0	0	1 (0.4)
Race, n (%)					
White	53 (93.0)	53 (93.0)	53 (91.4)	54 (93.1)	213 (92.6)
Asian	2 (3.5)	2 (3.5)	3 (5.2)	1 (1.7)	8 (3.5)
Black or African American	1 (1.8)	1 (1.8)	2 (3.4)	3 (5.2)	7 (3.0)
American Indian or Alaska Native	1 (1.8)	0	0	0	1 (0.4)
Other	0	1 (1.8)	0	0	1 (0.4)
Iris color, n (%)					
Brown	46 (40.4)	46 (40.4)	36 (31.0)	42 (36.2)	170 (37.0)
Blue	34 (29.8)	44 (38.6)	42 (36.2)	40 (34.5)	160 (34.8)
Hazel	24 (21.1)	18 (15.8)	30 (25.9)	20 (17.2)	92 (20.0)
Green	10 (8.8)	4 (3.5)	6 (5.2)	12 (10.3)	32 (7.0)
Gray	0	2 (1.8)	2 (1.7)	2 (1.7)	6 (1.3)

ITT=intent-to-treat; LIF=lifitegrast; SD=standard deviation
Source: Section 14, Table 14.1.2

Primary endpoint:

One primary 'sign'-endpoint was selected, namely the inferior corneal fluorescein staining score (ICSS). There were no primary symptoms measures.

Table 6: Inferior Corneal Fluorescein Staining Score (Ora Scale) at Day 84 (Week 12, Visit 5) (ITT Population with LOCF)

	0.1% LIF N=57	1.0% LIF N=57	5.0% LIF N=58	Placebo N=58
Baseline (Day 0, Week 0, Visit 2)				
n	57	56	58	58
Mean (SD)	1.78 (0.473)	1.82 (0.508)	1.77 (0.515)	1.65 (0.513)
Day 84 (Week 12, Visit 5)				
n	57	55	54	55
Mean (SD)	2.03 (0.868)	1.92 (0.768)	1.83 (0.680)	2.05 (0.715)
Treatment effect (SE)[a]	0.06 (0.138)	0.20 (0.139)	0.27 (0.140)	
95% confidence interval	(-0.26, 0.39)	(-0.13, 0.53)	(-0.06, 0.60)	
p-value	0.9381	0.3585	0.1375	

[a] Analysis of covariance model with treatment, baseline, and site. P-value compared to placebo from Dunnett's test.

Note: Ora corneal fluorescein staining scoring is as follows with 0.5 increments: 0=no staining; 1=occasional; 2=countable; 3=uncountable, but not confluent; 4=confluent.

Note: Results presented in this table are from the study eye only.

ITT=intent-to-treat; LIF=lifitegrast; LOCF=last observation carried forward; SD=standard deviation; SE=standard error

Source: Section 14, Table 14.2.1.1

Secondary endpoints

There was a somewhat greater improvement at D84 for 5% lifitegrast in the Shirmer Tear test measurement (-2.02 mm) compared to placebo (+0.56 mm), lifitegrast 0.1% (+12 mm) and lifitegrast 1% (+0.85 mm).

The Ocular surface disease index (OSDI) was used a measure of symptomatic burden. All lifitegrast doses reduced the total score from baseline at D 84 (see Table below), however the greatest reduction was seen with the 1% concentration.

Ocular surface disease index								
	0.1% LIF		1% LIF		5% LIF		Placebo	
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
Total score Day 0	57	29.46 (19.92)	57	32.76 (15.963)	58	31.77 (21.312)	58	28.84 (16.499)
Change from baseline to D14	56	-5.14 (14.702)	56	-6.14 (14.67)	54	-3.25 (14.629)	55	-1.53 (9.776)
Change from baseline to D42	57	-5.36 (16.479)	56	-5.89 (14.671)	54	-4.65 (15.223)	55	-0.09 (13.633)
Change from baseline to D84	57	-5.35 (15.859)	56	-5.71 (13.333)	54	-5.15 (14.149)	55	-0.09 (10.069)

At Day 84 symptomatic improvements from baseline greater than placebo was observed using the Visual Analogue Scale (symptoms) for the following VAS symptoms, burning and stinging, and eye dryness. A numerical dose response was seen for both symptoms [(burning stinging: -8.61, -10.24, and -12.92 for 0.1%, 1% and 5%) and (eye dryness: -10.67, -11, and -15.49 for 0.1%, 1% and 5% respectively)].

In summary there was no evidence of efficacy for any of the dose concentrations based on statistically significant improvement in signs (ICFSS) of DED, however there was greater numerical improvement from baseline noted for the 5% concentration compared to the 0.1% and 1% concentrations at D84.

There was some numerical evidence of improvement in symptoms for all lifitegrast concentrations as assessed by the OSDI but without any major difference between the concentrations. In addition, symptoms assessed by a VAS showed an improvement in burning and stinging and eye dryness with a dose response for both.

There is limited evidence for a dose response relationship in symptoms only and contradictory evidence for signs.

Main studies

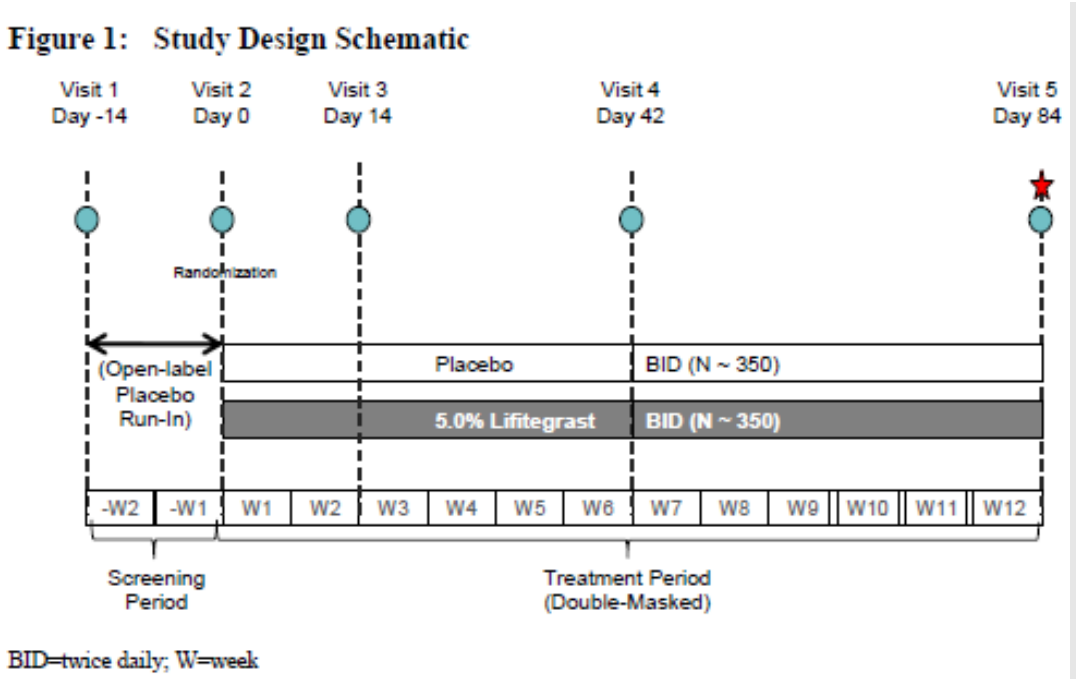
Two of the phase 3 studies (OPUS-2 and OPUS-3) are considered pivotal studies. The OPUS-1 study is considered supportive due to the use of CAE by the inclusion and randomisation. All three OPUS-studies were of 12 weeks' duration. Additionally, a 1-year phase 3 study, the SONATA study provides supportive long-term efficacy data. The SONATA study is described in section 3.6 and in the safety section.

OPUS 1-3 studies

Methods

All three clinical OPUS-trials were prospective, multi-center, randomised, double-masked, placebo-controlled parallel-arm studies conducted in the United States. The three studies were similar in design, which is shown in the graph below:

Figure 1: Study Design Schematic



BID=twice daily; W=week

Study Participants

Main in- and exclusion criteria are as follows:

Ocular related inclusion criteria were as follows:

- As-needed or scheduled use of non-prescription (over-the-counter) artificial tear substitute for symptoms of DED within 30 days prior to the screening visit (Visit 1) and willingness to suspend use of tear substitutes 72 hours prior to the screening visit and for the duration of the study (OPUS-2 and OPUS-3)
- Best corrected visual acuity (BCVA) of 0.7 logMAR or better (logMAR <0.7; Snellen equivalent score of 20/100 or better) in each eye at the screening visit (Visit 1)
- Subject-reported history of DED in both eyes
- Corneal fluorescein staining score ≥2 (0-4 point scale) in at least 1 region in at least 1 eye at Visits 1 and 2
- Conjunctival redness score ≥1 (0-4 point scale with allowance for 0.5 point increments) in at least 1 eye at Visits 1 and 2
- Eye dryness score ≥40 (0-100 point VAS, both eyes) at Visits 1 and 2 (OPUS-2 and OPUS-3)
- A positive response in at least 1 eye, defined as meeting ALL of the following criteria in the same eye at both Visits 1 and 2 (OPUS-1 only):
  (a) Inferior corneal fluorescein staining score ≥0.5 (0-4 point scale with allowance for 0.5 point increments)
  (b) Schirmer tear test (STT; without anaesthesia) ≥1 and ≤10 mm

Exclusion criteria were mostly acceptable however patients with conditions such as lid margin disorders (e.g. blepharitis, Meibomian gland disease) or other co-morbid ocular conditions which in the opinion of the investigator could have affected study parameters were excluded from the study. Some subjects with DED secondary to scarring, except for those with scarring secondary to refractory surgery where the investigator believed that the scarring would not have interfered with compliance or outcome measures were also excluded.

Treatments

The treatment was similar for the three OPUS-studies. During the 2-week Screening Period, open-label placebo was administered twice daily to the ocular surface of both eyes as an eye drop. During the 12-week double-masked Treatment Period, subjects received twice daily doses of either placebo or lifitegrast, administered to the ocular surface as an eye drop. Subjects were instructed to administer a single drop of investigational product twice daily (in the morning and just before bedtime in the evening) in both eyes.

Investigational product

Investigational product was supplied as a sterile, clear, colourless liquid solution containing 5.0% lifitegrast concentration in 5 cavity single dose, 0.99 mL low–density polyethylene unit dose vials with a fill volume of approximately 0.2 mL. Each mL of a 5.0% solution contained 50 mg of lifitegrast.

Reference product

The placebo solution consisted of all components of the investigational product solution with the exception of lifitegrast. The traditional control arm of a placebo-controlled trial uses the active formulation of a drug, minus the active ingredient.

Treatment Compliance

Subject compliance with the dosing regimen was assessed by reconciliation of the used and unused investigational product and review of the returned diaries. Non-compliance with dosing was recorded as a protocol deviation if >20% of the expected number of doses since the last visit had been missed or if >120% of the expected number of doses since the last visit had been expected.

Prohibited medications

Prohibited medications included topical cyclosporine or use of any other ophthalmic medication (e.g., glaucoma medication, topical anti–inflammatory eye drops) for the duration of the study. The appropriate pre–study washout period was defined in the study protocol.

Objectives

Study	Primary objective	Secondary objectives
OPUS-1	• To evaluate the efficacy of lifitegrast compared to placebo in the treatment of dry eye as assessed by the co-primary endpoints of o inferior corneal fluorescein staining (0-4 point Ora scale, ocular sign) and o VR-OSDI (0-4 point mean composite score; items 6-9 regarding reading, driving at night, use of computer, and watching television) of the OSDI (Allergan, Inc.) (ocular symptom), each measured by mean change from baseline to Day 84 (Visit 5). • To evaluate the safety and tolerability of lifitegrast compared to placebo in subjects with dry eye when administered twice daily for 12 weeks.	Ocular Signs: • To evaluate the efficacy of lifitegrast compared to placebo in the treatment of dry eye as assessed by STT (mm/5 minutes) measured by the mean at Day 14 (Visit 3) • To evaluate the efficacy of lifitegrast compared to placebo in the treatment of dry eye as assessed by STT (mm/5 minutes) measured by the mean at Day 84 (Visit 5). Ocular Symptoms: • To evaluate the efficacy of lifitegrast compared to placebo in the treatment of dry eye as assessed by the total OSDI score (0-100 scale) measured by mean change from baseline to Day 14 (Visit 3) • To evaluate the efficacy of lifitegrast compared to placebo in the treatment of dry eye as assessed by the total OSDI score (0-100 scale) measured by mean change from baseline to Day 84 (Visit 5). The secondary objectives defined here differ from those listed in the study protocol (final amendment dated 05 Aug 2011). As the SAP was drafted (final dated 09 Feb 2012), the list of secondary endpoints was further refined, and hence the secondary objectives defined here supersede those listed in the protocol.

		Refer to the clinical study protocol for the original list of objectives.
OPUS-2	The co-primary objectives of the study were: • To evaluate the efficacy of lifitegrast compared to placebo in the treatment of dry eye in subjects currently using artificial tears as assessed by the co-primary endpoints of: o Sign – inferior corneal fluorescein staining score (0–4 point scale) measured by mean change from baseline to Day 84 (Week 12, Visit 5) in the designated study eye o Symptom – eye dryness score (0–100 point VAS, both eyes) measured by mean change from baseline to Day 84 (Week 12, Visit 5) • To evaluate the safety and tolerability of lifitegrast compared to placebo in subjects with dry eye when administered twice daily for 84 days (12 weeks).	The secondary objectives of the study were to evaluate the efficacy of lifitegrast compared to placebo in the treatment of dry eye in subjects currently using artificial tears as assessed by: Ocular Signs • Total corneal staining score (0–12 point scale), measured by mean change from baseline to Day 84 (Week 12, Visit 5) in the designated study eye • Nasal conjunctival lissamine green staining score (0–4 point scale), measured by mean change from baseline to Day 84 (Week 12, Visit 5) in the designated study eye. Ocular Symptoms • Eye discomfort score (0–100 point VAS, both eyes), measured by mean change from baseline to Day 84 (Week 12, Visit 5) • ODS (0–4 point scale), measured by mean change from baseline to Day 84 (Week 12, Visit 5) in the designated study eye.
OPUS-3	To evaluate the efficacy of lifitegrast compared to placebo in improvement of symptoms of DED as measured by the mean change from baseline to Day 84 in the EDS (0-100 point visual analogue scale [VAS], both eyes)	<u>Key Secondary Objectives</u> To evaluate the efficacy of lifitegrast compared to placebo in improvement of symptoms of dry eye disease as measured by: • Mean change from baseline to Day 42 in the EDS (0-100 point VAS, both eyes) • Mean change from baseline to Day 14 in the EDS (0-100 point VAS, both eyes) <u>Secondary Objectives</u> • To evaluate the efficacy of lifitegrast compared to placebo in improvement of symptoms of DED as measured by: o Mean change from baseline to each visit in the 6 additional items of the 7-item VAS (0-100 point scale, both eyes) o Mean change from baseline to each visit in the designated study eye in the ocular discomfort score (ODS; 0-4 point scale)

		• To evaluate the safety and tolerability of lifitegrast compared to placebo

Outcomes/endpoints

Table 6: Primary, Secondary, and Tertiary Sign and Symptom Efficacy Measures in the OPUS-1, OPUS-2, and OPUS-3 Studies

Study	Endpoint	Sign Measures	Symptom Measures
OPUS-1	Primary	• ICSS (mean change from baseline to Day 84)	• VR-OSDI (mean change from baseline to Day 84)
	Secondary	• STT (mean at Days 14 and 84)	• Total OSDI score (mean changes from baseline to Days 14 and 84)
	Tertiary	• Corneal fluorescein staining score (total, superior, central, inferior) • STT • Conjunctival lissamine green staining score[d] • Blink rate[a] • Conjunctival redness score • Tear film break-up time • Subgroup analysis of subjects with and without a history of AT use for all tertiary variables	• OSDI score (total score, symptom subscale, VR-OSDI, trigger subscale) • ODS • VAS by symptom[b] • Subgroup analysis of subjects with and without a history of AT use for all tertiary variables
OPUS-2	Primary	• ICSS (mean change from baseline to Day 84)	• EDS (VAS; mean change from baseline to Day 84)
	Secondary	• Total corneal fluorescein staining scores (mean change from baseline to Day 84) • Nasal conjunctival lissamine green staining score (mean change from baseline to Day 84)	• Eye Discomfort Score (VAS; mean change from baseline to Day 84) • ODS (mean change from baseline to Day 84)
	Tertiary	• Corneal fluorescein staining score (total, superior, central, inferior) • STT • Conjunctival lissamine green staining score (temporal, nasal, total) • Conjunctival redness score	• OSDI score (total score, symptom subscale, VR-OSDI, trigger subscale) • ODS • VAS by symptom[b]
OPUS-3	Primary	• Not specified	• EDS (VAS; mean change from baseline to Day 84)
	Key Secondary	• Not specified	• EDS (VAS; mean change from baseline to Day 42)
			• EDS (VAS; mean change from baseline to Day 14)
	Secondary	• Not specified[e]	• ODS • VAS by symptom[b]

AT=artificial tear; EDS=eye dryness score; ICSS=inferior corneal staining score; ODS=ocular discomfort score; OSDI=Ocular Surface Disease Index; STT=Schirmer Tear Test; VAS=visual analogue scale; VROSDI=visual-related function subscale of Ocular Surface Disease Index

Notes: All measures are mean and change from baseline at each visit unless otherwise specified. Sign measures and ODS are in the designated study eye. Symptoms other than ODS are in both eyes.

[a] Visits 2-5 only

[b] VAS symptoms: EDS, eye discomfort (OPUS-2 and OPUS-3 only), burning/stinging, itching, blurred vision (Phase 2 and OPUS-1 only), foreign body sensation, photophobia, and pain

[c] 5-symptom assessment symptoms: ocular discomfort, burning, dryness, grittiness, and stinging

[d] Regions: nasal conjunctival, temporal conjunctival, inferior cornea, central cornea, superior cornea, and total ocular surface

[e] Sign endpoints were measured as safety endpoints in the OPUS-3 study and ad-hoc efficacy analyses were conducted.

Randomisation and blinding (masking)

In all three OPUS-studies, the patients were randomly assigned to receive lifitegrast or placebo based on a 1:1 ratio (lifitegrast: placebo) within the randomisation strata. Stratification strata were different between the three studies.

OPUS-1: Randomisation was centralised across sites and was stratified by the pre-CAE ICSS in the study eye at Visit 2 and by the prior use of AT (defined as subjects who had routinely used over-the-counter AT or topical ophthalmic lubricants until 72 hours before Visit 1). An IWRS was used to facilitate subject randomisation, accounting for the stratification factors. Upon a subject's qualification to enter the study, his/her Visit 2 pre-CAE ICSS and prior active use of AT was input into the IWRS system to classify the subject into 1 of the following strata:

- Visit 2 pre-CAE ICSS ≤1.0 in the study eye and subject was not actively using AT
- Visit 2 pre-CAE ICSS ≤1.0 in the study eye and subject was actively using AT
- Visit 2 pre-CAE ICSS >1.0 in the study eye and subject was not actively using AT
- Visit 2 pre-CAE ICSS >1.0 in the study eye and subject was actively using AT.

OPUS-2 and OPUS-3: Subjects were randomly assigned to receive lifitegrast or placebo based on a 1:1 ratio within the randomisation strata using permuted blocks.

Randomisation was centralised across study centers, stratified by Visit 2 (Day 0, Week 0) inferior corneal fluorescein staining score and EDS in the study eye in order to ensure balance amongst the treatment groups. An interactive web response system was used to facilitate subject randomisation accounting for the stratification factors. Subjects were classified into 1 of the following strata based on site calculation and entry in the interactive web response system:

- Visit 2 (Day 0, Week 0) ICSS ≤1.5 in the study eye and EDS <60
- Visit 2 (Day 0, Week 0) ICSS ≤1.5 in the study eye and EDS ≥60
- Visit 2 (Day 0, Week 0) ICSS >1.5 in the study eye and EDS <60
- Visit 2 (Day 0, Week 0) ICSS >1.5 in the study eye and EDS ≥60

In all three OPUS-studies, randomisation was centralised across study centers, an in all three OPUS-studies, treatment was blinded for study personnel and patients (double-masked).

Statistical methods

The statistical methods are described separately for the OPUS 1-3 apart from general considerations and definitions of populations.

General considerations

Continuous variables were summarized using descriptive statistics including the number of observations, mean, SD, median, minimum, and maximum values. Categorical variables were summarised using frequencies and percentages. Hypothesis testing, unless otherwise indicated, was performed using 2-sided tests at the α=0.05 significance level. Baseline for all efficacy analyses was defined as the value for the efficacy assessment at Day 0/Visit 2.

Analysis populations

The screened set consisted of all subjects who signed an ICF. The randomised population included all subjects screened for whom a randomisation number was assigned. The safety population included all randomised subjects who received at least 1 dose of investigational product. The intent-to-treat (ITT) population included all randomised subjects who took at least 1 dose of investigational product. Analyses conducted using the ITT population and randomised population were based upon the treatment assigned; analyses conducted using data from the safety population were based upon the treatment received. All ITT subjects with at least 1 post-baseline efficacy assessment were included in the efficacy analysis.

OPUS 1

Primary efficacy endpoints

The primary analysis of the following co-primary endpoints was performed using a 2-sample t-test comparing lifitegrast to placebo in the ITT Population with LOCF:

- Ocular Sign: Mean change from baseline to Day 84 (Visit 5) in ICSS (0-4 Ora scale)
- Ocular Symptom: Mean change from baseline to Day 84 (Visit 5) in the VR-OSDI (0-4 point mean composite score; Items 6-9).

Type I error control for the primary endpoints

Statistical significance is required for both the sign and the symptom in order to conclude that the study was successful; hence no additional adjustment for multiplicity was necessary for the co-primary endpoints.

Sensitivity analysis for the primary endpoints

The co-primary efficacy endpoints were also analysed using additional statistical methods as pre-specified sensitivity analyses, including a non-parametric Wilcoxon rank sum test and a repeated-measures ANCOVA (adjusted for baseline and site) including data collected at Visits 3, 4, and 5 for confirmation. All analyses were also repeated for the ITT Population with WOCF and the Per-protocol Population with observed data only.

The stratification factors used at randomisation were not included as covariates in the analysis.

Secondary endpoints

Ocular Signs:

- To evaluate the efficacy of lifitegrast compared to placebo in the treatment of dry eye as assessed by STT (mm/5 minutes) measured by the mean at Day 14 (Visit 3)
- To evaluate the efficacy of lifitegrast compared to placebo in the treatment of dry eye as assessed by STT (mm/5 minutes) measured by the mean at Day 84 (Visit 5).

Ocular Symptoms:

- To evaluate the efficacy of lifitegrast compared to placebo in the treatment of dry eye as assessed by the total OSDI score (0-100 scale) measured by mean change from baseline to Day 14 (Visit 3)

To evaluate the efficacy of lifitegrast compared to placebo in the treatment of dry eye as assessed by the total OSDI score (0-100 scale) measured by mean change from baseline to Day 84 (Visit 5).

Type I error control for the secondary endpoints

If both co-primary endpoints were significant, Simes modified Bonferroni procedure was applied to control the Type I error rate across the secondary endpoints within an analysis population.

Handling of Dropouts or Missing Data

The method of LOCF was used for the primary efficacy analysis on the ITT Population. In the case of missing data post-screening, post-challenge assessments were not carried forward. Additional imputation methods were used for the Per-protocol Population analyses. The WOCF (post-challenge assessments were not carried forward) and multiple imputation using MCMC methods were applied to the ITT Population for the primary and secondary efficacy endpoints.

OPUS 2

Primary Efficacy endpoints

The co-primary efficacy outcome variables were the mean change from baseline to Day 84 (Week 12, Visit 5) in inferior corneal fluorescein staining score in the designated study eye and in eye dryness score.

Each analysis was performed using a stratified 2-sample t-test (i.e., ANOVA) comparing lifitegrast to placebo in the ITT Population with LOCF. The ANOVA model included treatment, strata, and the interaction between treatment and strata. The stratification factors used for randomisation will be used for this analysis. The interaction between treatment and strata is included in the model to allow for inconsistency across strata to be examined. The study is not powered to detect the effect of interaction between treatment and strata.

Type I error control of the primary endpoints

Statistical significance is required for both the sign and the symptom in order to conclude that the study was successful; hence no additional adjustment for multiplicity was necessary for the co-primary endpoints.

Secondary endpoints

The secondary ocular sign variables were the mean change from baseline to Day 84 (Week 12, Visit 5) in total corneal fluorescein staining score and nasal conjunctival lissamine green staining score in the designated study eye.

The secondary ocular symptom variables were the mean change from baseline to Day 84 (Week 12, Visit 5) in eye discomfort score and ODS in the designated study eye.

The secondary efficacy endpoints were analysed using the same ANOVA model as for the co-primary efficacy endpoints comparing lifitegrast to placebo in the ITT Population with LOCF.

Type I error control of the secondary endpoints

Hochberg's (1988) procedure was applied to control the type I error rate at 5% level across all secondary endpoints.

Handling of dropouts or missing data

For the efficacy data, subjects were analysed either based upon observed data or LOCF. Other data collected, including missing dates, were, in general, not imputed and were displayed as observed.

For imputation of derived variables for LOCF, missing derived variables at a visit were carried forward rather than carrying forward individual items and then calculating the derived variable. This ensured that all components for a derived variable reflected data collected at the same visit.

Sensitivity Analyses for the Co-primary and Secondary Endpoints

The planned sensitivity analyses consisted of repeating the primary analysis using observed data, a stratified rank-based test (i.e., Wilcoxon) with LOCF, and repeated measures ANOVA (no imputation). The stratified rank-based test consisted of repeating the primary analysis (LOCF) using the overall ranks rather than the observed data. The repeated measures analysis modelled the outcome as a function of the randomisation strata, treatment, and time. In this model, all the model terms were treated as categorical variates with a common treatment effect assumed over time and the randomisation strata (i.e., main effects model). An unstructured covariance matrix was used for this analysis.

Some subjects were assigned to the incorrect strata at randomisation. Subjects assigned to the incorrect strata during randomisation were analysed using the stratification used for the randomisation. The co-primary efficacy endpoints were analysed using the strata that would have been the correct strata based on the baseline characteristics of the subjects.

OPUS 3

Primary Efficacy endpoint

The primary efficacy endpoint was defined as the mean change from baseline to Day 84 in EDS. The null hypothesis to be tested was that there was no difference in the mean change from baseline to Day 84 in EDS between lifitegrast and placebo with the alternative of a non-zero difference between them. The primary analysis was performed using a stratified 2-sample t-test (i.e., analysis of variance [ANOVA]). The stratification factors used for randomisation were used for this analysis. The individual strata contributed to the overall analysis proportionate to their size. The ANOVA model used to conduct the protocol-specified primary treatment comparison included treatment, strata, and the interaction between treatment and strata.

Key secondary endpoints

The 2 key secondary efficacy endpoints were defined as the mean change from baseline to Day 42 in EDS and mean change from baseline to Day 14 in EDS.

The 2 key secondary efficacy endpoints were analysed similarly to the primary efficacy endpoint by the stratified 2-sample t-test using the ANOVA model. Using a hierarchical approach, multiplicity adjustments were done on the key secondary efficacy endpoints.

Type I error control of the key secondary endpoints

Using a hierarchical approach, multiplicity adjustments were done on the primary and key secondary efficacy endpoints testing. No adjustment for multiplicity was done for other secondary endpoints.

Handling of dropouts or missing data

Missing post-baseline efficacy assessments were imputed from post-baseline values using the last observation carried forward (LOCF) method. All efficacy analyses were performed using LOCF, unless stated otherwise. If a subject had no post-baseline efficacy assessment, the subject was not included in analysis of the ITT population with LOCF.

Sensitivity analyses for the primary and secondary endpoints

Sensitivity analyses were done on the primary efficacy endpoint using additional statistical methods, particularly, a nonparametric Wilcoxon rank sum test (LOCF) and mixed model for repeated measures ANOVA (no imputation). The stratified rank-based test consisted of repeating the primary analysis (ANOVA model using LOCF) using the overall ranks (Wilcoxon) rather than the observed data. The repeated measures analysis modelled the outcome as a function of the randomisation strata, treatment, visit, and interaction between treatment and visit. In this model, all the model terms were treated as categorical covariates. All analysis visits were included in the model. An unstructured covariance matrix was used for this analysis. Least squares means were estimated for each treatment group at each visit. The difference between the least squares mean of the treatment groups was provided with the CI for the primary efficacy endpoint.

Subjects assigned to the incorrect stratum during randomisation were analysed using 1) the stratification used for the randomisation, and 2) the stratum that would have been the correct stratum based on the baseline characteristics of the subjects.

Sensitivity analyses were done on the key secondary efficacy endpoints similar to the primary efficacy endpoint.

Results

The results are presented separately for the OPUS-1, OPUS-2, and OPUS-3 studies. The primary endpoints are presented for each study (for secondary and tertiary endpoints please refer to the AR). The OPUS-1 and OPUS-2 studies both a primary 'sign'-endpoint and a primary 'symptom'-endpoint. The OPUS-3 employed a single primary 'symptom'-endpoint.

Results for OPUS-1

Though this study due to the CAE-inclusion criteria should be considered supportive more than pivotal, the results are presented in the following.

Conduct of the study OPUS-1

During a masked review of the data prior to database lock and unmasking, the sponsor reviewed the protocol deviations captured on the eCRF. Most of the reported deviations (e.g., failure to return a minimal number of used vials, visit window deviations) were determined to be minor, i.e., not affecting the efficacy or safety assessments of study subjects.

The following categories of deviations were determined to be important with the potential to affect the efficacy or safety assessments.

- Overall treatment compliance outside the protocol-specified range: A total of 5.7% of subjects (placebo: 4.5%; lifitegrast: 7.0%) had an overall treatment compliance <80% or >120% (see Table 6).

Table 6: Treatment Compliance (Safety Population)

	Placebo N=359 n (%)	Lifitegrast N=359 n (%)	Total N=718 n (%)
Treatment compliance (%), mean (SD) [a]	96.15 (8.205)	93.42 (13.258)	94.79 (11.101)
Treatment compliance (80-120%), n (%)			
Yes	343 (95.5)	334 (93.0)	677 (94.3)
No	16 (4.5)	25 (7.0)	41 (5.7)

[a] Calculated as (total number of used vials returned, including the vials used for on-site administration) / (2 × [number of days of double-masked treatment for all days between the first and last day of dosing + 1 dose for both the first and last day of dosing where only 1 dose was to be administered]).
SD=standard deviation
Source: Section 14, Table 1.4.2

- Incorrect stratification of subjects during randomisation: Some subjects were assigned to the incorrect strata at randomisation (see Table 7). A sensitivity analysis utilizing the corrected strata was performed to investigate the impact of incorrect stratification on the efficacy analyses.

Table 7: Incorrect Strata for Randomization (Randomized Population)				
	Randomization Strata	Value at Randomization	Placebo N=360 n (%)	Lifitegrast N=358 n (%)
Inferior corneal score	≤1.5	>1.5	11 (3.1)	13 (3.6)
	>1.5	≤1.5	6 (1.7)	5 (1.4)
Eye dryness	<60	≥60	5 (1.4)	6 (1.7)
	≥60	<60	2 (0.6)	2 (0.6)

Source: Section 14, Table 1.5.3

- Failure to meet inclusion/exclusion criteria: A total of 27 subjects (placebo: 13 subjects; lifitegrast: 14 subjects) were randomised in the study, but did not meet all inclusion/exclusion criteria. Two of these subjects (placebo: 1 subject; lifitegrast: 1 subject) were granted exemptions to be included in the study at or prior to randomisation by the sponsor. The other 25 subjects were identified after randomisation and assessed by the sponsor as able to continue participation in the study.
- Used prohibited medication: Overall, 5.0% of subjects (placebo: 5.6%; lifitegrast: 4.5%) used a prohibited concomitant medication during the study.

Baseline data (OPUS-1)

Table 4: Subject Demographics (Randomized Population)

	Placebo N=360	Lifitegrast N=358	Total N=718
Age (years)			
Mean (SD)	58.9 (14.26)	58.7 (13.93)	58.8 (14.09)
≥65 years, n (%)	135 (37.5)	122 (34.1)	257 (35.8)
≥75 years, n (%)	42 (11.7)	39 (10.9)	81 (11.3)
Sex, n (%)			
Male	95 (26.4)	73 (20.4)	168 (23.4)
Female	265 (73.6)	285 (79.6)	550 (76.6)
Ethnicity, n (%)			
Hispanic or Latino	64 (17.8)	79 (22.1)	143 (19.9)
Not Hispanic or Latino	296 (82.2)	279 (77.9)	575 (80.1)
Race, n (%)			
American Indian or Alaskan Native	2 (0.6)	4 (1.1)	6 (0.8)
Asian	14 (3.9)	19 (5.3)	33 (4.6)
Black or African American	34 (9.4)	30 (8.4)	64 (8.9)
Native Hawaiian or other Pacific Islander	3 (0.8)	2 (0.6)	5 (0.7)
White	305 (84.7)	303 (84.6)	608 (84.7)
Other	2 (0.6)	0	2 (0.3)
Iris color (study eye), n (%)			
Black	0	1 (0.3)	1 (0.1)
Blue	86 (23.9)	80 (22.3)	166 (23.1)
Brown	189 (52.5)	193 (53.9)	382 (53.2)
Hazel	49 (13.6)	56 (15.6)	105 (14.6)
Green	35 (9.7)	27 (7.5)	62 (8.6)
Gray	1 (0.3)	1 (0.3)	2 (0.3)

SD=standard deviation
Source: Section 14, Table 1.2.1

Summary of main efficacy results OPUS 1

Sign

The lifitegrast treatment group had a statistically significant mean decrease (improvement) from baseline to Day 84 (Visit 5) in ICSS (-0.07) as compared to the placebo treatment group (+0.17) (p=0.0007; see Table 7).

Table 7: Inferior Corneal Fluorescein Staining Score (ITT Population with LOCF)

	Placebo N=295	Lifitegrast N=293
Change from baseline to Day 84 (Visit 5), mean (SD)	0.17 (0.819)	-0.07 (0.868)
Treatment difference (95% CI)	0.24 (0.10, 0.38)	
t-test p-value (primary analysis)	0.0007	
Wilcoxon p-value	0.0006	

Note: Corneal staining scoring is as follows: 0=no staining/none; 1=occasional/trace; 2=countable/mild; 3=uncountable, but not confluent/moderate; 4=confluent/severe.
Note: Results presented in this table are from the study eye only.
CI=confidence interval; ITT=intent-to-treat; LOCF=last observation carried forward; SD=standard deviation
Source: Section 14, Table 3.1.1.1

The results of WOCF, ANCOVA repeated measures, and the Per-protocol Population analyses were consistent with the results of the primary ICSS analysis. Table 3.1.2.2. shows the ICSS at Visit 3, 4 and 5 (ITT population).

Table 3.1.2.2: Inferior Corneal Fluorescein Staining Score – Mean Change from Baseline (Repeated Measures) ITT Population Visits 3, 4 and 5 Observed Data – Study Eye

	Placebo (N=295)	LIF 5.0% (N=293)
Change from Baseline to Visit		
Visit 3 : n, Mean (SD)	290, 0.08 (0.776)	287, 0.04 (0.742)
Visit 4 : n, Mean (SD)	287, -0.02 (0.888)	281, -0.15 (0.872)
Visit 5 : n, Mean (SD)	283, 0.17 (0.813)	281, -0.08 (0.880)
ANCOVA - Repeated Measures [a]		
LS Means Difference (SE)	0.11 (0.044)	
95% Confidence Interval	0.02, 0.20	
p-value	0.0133	

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[a] Mixed model repeated measures analysis of change with terms for treatment, site, visit and baseline with an unstructured covariance matrix.
Data: ADEF Program: csr\prod\programs\tfl\t-mixed.sas, 3-1-2-2-t-mixed-inffl-itt.rtf (30SEP2013:12:41)

Symptom

An overall numeric decline (improvement) in VR-OSDI was observed in both treatment groups. The placebo and lifitegrast treatment groups had 0.12 and 0.11 mean decreases in VR-OSDI score from baseline to Day 84 (Visit 5), respectively. The difference between treatment groups was not statistically significant (p=0.7860; see Table 8).

Table 8: Visual-related Function Ocular Surface Disease Index Subscale Score (ITT Population with LOCF)

	Placebo N=295	Lifitegrast N=293
Change from baseline to Day 84 (Visit 5), mean (SD)	-0.12 (0.762)	-0.11 (0.829)
Treatment difference (95% CI)	-0.02 (-0.15, 0.11)	
t-test p-value (primary analysis)	0.7860	
Wilcoxon p-value	0.9065	

Note: Higher Ocular Surface Disease Index scores indicate greater ocular impairment.
CI=confidence interval; ITT=intent-to-treat; LOCF=last observation carried forward; SD=standard deviation
Source: Section 14, Table 3.1.1.2

OPUS 2

Subject disposition (OPUS-2)

Table 3: Subject Disposition

	Placebo N=360 n (%)	Lifitegrast N=358 n (%)	Total N=718 n (%)
Screened subjects [a]			1455
Number of subjects not starting Placebo Run-in Period			557
Number of subjects not randomized after Placebo Run-in Period			178
Number of subjects randomized			720
Excluded from data analysis because records represent second randomization for a subject			2
Included in data analysis			718
Randomized Population	360	358	718
Safety Population [b, c]	359 (99.7)	359 (100.3) [c]	718 (100.0)
ITT Population [b]	360 (100.0)	358 (100.0)	718 (100.0)
Subjects who completed study [b]	348 (96.7)	321 (89.7)	669 (93.2)
Subjects who withdrew from study [b]	12 (3.3)	37 (10.3)	49 (6.8)
Reason for withdrawal [b]			
Adverse event [b]	3 (0.8)	26 (7.3)	29 (4.0)
Lost to follow-up [b]	0	2 (0.6)	2 (0.3)
Non-compliance [b]	0	1 (0.3)	1 (0.1)
Other [b]	9 (2.5)	8 (2.2)	17 (2.4)

[a] The total screening count of 1455 subjects includes 1450 unique subjects.
[b] Percentages based on Randomized Population.
[c] Subjects are categorized by actual treatment received, even if randomized to the other treatment. Subject 78-006 was assigned to the placebo group, but received lifitegrast via an incorrect kit at Day 14 (Week 2, Visit 3) and was discontinued from the study. This subject was included in the lifitegrast group for the Safety Population, but in the placebo group for the Randomized and ITT Populations.
ITT=intent-to-treat
Source: Section 14, Table 1.1.1 and Table 1.1.2

Baseline data (OPUS-2)

Table 4: Subject Demographics (Randomized Population)

	Placebo N=360	Lifitegrast N=358	Total N=718
Age (years)			
Mean (SD)	58.9 (14.26)	58.7 (13.93)	58.8 (14.09)
≥65 years, n (%)	135 (37.5)	122 (34.1)	257 (35.8)
≥75 years, n (%)	42 (11.7)	39 (10.9)	81 (11.3)
Sex, n (%)			
Male	95 (26.4)	73 (20.4)	168 (23.4)
Female	265 (73.6)	285 (79.6)	550 (76.6)
Ethnicity, n (%)			
Hispanic or Latino	64 (17.8)	79 (22.1)	143 (19.9)
Not Hispanic or Latino	296 (82.2)	279 (77.9)	575 (80.1)
Race, n (%)			
American Indian or Alaskan Native	2 (0.6)	4 (1.1)	6 (0.8)
Asian	14 (3.9)	19 (5.3)	33 (4.6)
Black or African American	34 (9.4)	30 (8.4)	64 (8.9)
Native Hawaiian or other Pacific Islander	3 (0.8)	2 (0.6)	5 (0.7)
White	305 (84.7)	303 (84.6)	608 (84.7)
Other	2 (0.6)	0	2 (0.3)
Iris color (study eye), n (%)			
Black	0	1 (0.3)	1 (0.1)
Blue	86 (23.9)	80 (22.3)	166 (23.1)
Brown	189 (52.5)	193 (53.9)	382 (53.2)
Hazel	49 (13.6)	56 (15.6)	105 (14.6)
Green	35 (9.7)	27 (7.5)	62 (8.6)
Gray	1 (0.3)	1 (0.3)	2 (0.3)

SD=standard deviation
Source: Section 14, Table 1.2.1

Conduct of the study (OPUS-2)

During a masked review of the data prior to database lock and unmasking, the sponsor reviewed the protocol deviations captured on the eCRF. Most of the reported deviations (e.g., failure to return a minimal number of used vials, visit window deviations) were determined to be minor, i.e., not affecting the efficacy or safety assessments of study subjects.

The following categories of deviations were determined to be important with the potential to affect the efficacy or safety assessments.

- Overall treatment compliance outside the protocol-specified range: A total of 5.7% of subjects (placebo: 4.5%; lifitegrast: 7.0%) had an overall treatment compliance <80% or >120% (see Table 6).

Table 6: Treatment Compliance (Safety Population)

	Placebo N=359 n (%)	Lifitegrast N=359 n (%)	Total N=718 n (%)
Treatment compliance (%), mean (SD) [a]	96.15 (8.205)	93.42 (13.258)	94.79 (11.101)
Treatment compliance (80-120%), n (%)			
Yes	343 (95.5)	334 (93.0)	677 (94.3)
No	16 (4.5)	25 (7.0)	41 (5.7)

[a] Calculated as (total number of used vials returned, including the vials used for on-site administration) / (2 × [number of days of double-masked treatment for all days between the first and last day of dosing + 1 dose for both the first and last day of dosing where only 1 dose was to be administered]).
SD=standard deviation
Source: Section 14, Table 1.4.2

- Incorrect stratification of subjects during randomisation: Some subjects were assigned to the incorrect strata at randomisation (see Table 7). A sensitivity analysis utilizing the corrected strata was performed to investigate the impact of incorrect stratification on the efficacy analyses.

Table 7: Incorrect Strata for Randomization (Randomized Population)

	Randomization Strata	Value at Randomization	Placebo N=360 n (%)	Lifitegrast N=358 n (%)
Inferior corneal score	≤1.5	>1.5	11 (3.1)	13 (3.6)
	>1.5	≤1.5	6 (1.7)	5 (1.4)
Eye dryness	<60	≥60	5 (1.4)	6 (1.7)
	≥60	<60	2 (0.6)	2 (0.6)

Source: Section 14, Table 1.5.3

- Failure to meet inclusion/exclusion criteria: A total of 27 subjects (placebo: 13 subjects; lifitegrast: 14 subjects) were randomised in the study, but did not meet all inclusion/exclusion criteria. Two of these subjects (placebo: 1 subject; lifitegrast: 1 subject) were granted exemptions to be included in the study at or prior to randomisation by the sponsor. The other 25 subjects were identified after randomisation and assessed by the sponsor as able to continue participation in the study.
- Used prohibited medication: Overall, 5.0% of subjects (placebo: 5.6%; lifitegrast: 4.5%) used a prohibited concomitant medication during the study.

Summary of main efficacy results OPUS 2

Sign

Primary endpoint – Inferior Corneal Fluorescein Staining Score (Sign)

The lifitegrast group did not have a statistically significant difference (p=0.6186; see Table 9) from the placebo group for the co-primary endpoint of change from baseline to Day 84 (Week 12, Visit 5) in ICSS. An overall numeric decline (improvement) from baseline to Day 84 (Week 12, Visit 5) in ICSS was observed in both treatment groups. The placebo and lifitegrast groups had -0.71 and -0.73 mean changes in ICSS from baseline to Day 84 (Week 12, Visit 5), respectively.

Table 9: Inferior Corneal Fluorescein Staining Score – Mean Change from Baseline to Day 84 (Week 12, Visit 5) (ITT Population with LOCF)

	Placebo N=360	Lifitegrast N=358
Baseline (Day 0, Week 0, Visit 2), mean (SD)	2.40 (0.722)	2.39 (0.763)
Change from baseline to Day 84 (Week 12, Visit 5), mean (SD)	-0.71 (0.943)	-0.73 (0.926)
Treatment Effect (SE) [a]	0.03 (0.067)	
95% CI for Treatment Effect	-0.10, 0.17	
p-value	0.6186	

[a] ANCOVA model of change with treatment, stratum, and treatment by stratum interaction; weights set to stratum size.
Note: Corneal fluorescein staining scoring is as follows with 0.5 increments: 0=no staining; 1=few/rare punctate lesions; 2=discrete and countable lesions; 3=lesions too numerous to count, but not coalescent; 4=coalescent.
Note: Results presented in this table are from the study eye only.
ANCOVA=analysis of covariance; CI=confidence interval; ITT=intent-to-treat; LOCF=last observation carried forward; SD=standard deviation; SE=standard error
Source: Section 14, Table 3.1.1.1

Symptom

Primary endpoint – Eye Dryness Score (Visual Analogue Scale; Symptom)

The lifitegrast group had a statistically significant mean decrease (improvement) in the co-primary efficacy endpoint of the change from baseline to Day 84 (Week 12, Visit 5) in EDS (-35.30) as compared to the placebo group (-22.75) ($p<0.0001$; see Table 10).

Table 10: Eye Dryness Score (Visual Analogue Scale) – Mean Change from Baseline to Day 84 (Week 12, Visit 5) (ITT Population with LOCF)

	Placebo N=360	Lifitegrast N=358
Baseline (Day 0, Week 0, Visit 2), mean (SD)	69.22 (16.761)	69.68 (16.954)
Change from baseline to Day 84 (Week 12, Visit 5), mean (SD)	-22.75 (28.600)	-35.30 (28.400)
Treatment Effect (SE) [a]	12.61 (2.085)	
95% CI for Treatment Effect	8.51, 16.70	
p-value	<0.0001	

[a] ANCOVA model of change with treatment, stratum, and treatment by stratum interaction; weights set to stratum size.
Note: Eye dryness score (VAS) uses 0-100 point scale (0=no discomfort; 100=maximal discomfort).
ANCOVA=analysis of covariance; CI=confidence interval; ITT=intent-to-treat; LOCF=last observation carried forward; SD=standard deviation; SE=standard error; VAS=visual analogue scale
Source: Section 14, Table 3.1.1.2

The results of all sensitivity analyses for the primary efficacy results were consistent with the results of the primary analyses.

OPUS-3

Baseline data (OPUS-3)

Demographic and Other Baseline Characteristics

Demographic data are summarised by treatment group in Table 5. Baseline characteristics were similar between treatment groups. Subjects' age ranged from 18 to 93 years, with the mean (SD) being 58.7 (14.47) years. The majority of subjects was female (75.5%), not Hispanic or Latino (83.4%), and white (76.5%). The most common iris colours were brown (55.3%) and blue (19.7%).

Table 5: Subject Demographics (Randomized Population)

	Placebo N=356	Lifitegrast N=355	Total N=711
Age (years)			
Mean (SD)	58.6 (14.84)	58.8 (14.10)	58.7 (14.47)
≥65 years, n (%)	137 (38.5)	128 (36.1)	265 (37.3)
≥75 years, n (%)	44 (12.4)	48 (13.5)	92 (12.9)
Sex, n (%)			
Male	87 (24.4)	87 (24.5)	174 (24.5)
Female	269 (75.6)	268 (75.5)	537 (75.5)
Ethnicity, n (%)			
Hispanic or Latino	58 (16.3)	60 (16.9)	118 (16.6)
Not Hispanic or Latino	298 (83.7)	295 (83.1)	593 (83.4)
Race, n (%)			
American Indian or Alaskan Native	0	2 (0.6)	2 (0.3)
Asian	24 (6.7)	24 (6.8)	48 (6.8)
Black or African American	47 (13.2)	48 (13.5)	95 (13.4)
Native Hawaiian or other Pacific Islander	1 (0.3)	2 (0.6)	3 (0.4)
White	279 (78.4)	265 (74.6)	544 (76.5)
Other	5 (1.4)	14 (3.9)	19 (2.7)

SD=standard deviation
Source: Section 14, Table 1.2.1

To promote balance of treatment assignment across baseline sign and symptom severity, randomisation was stratified by ICSS (≤1.5 or >1.5) and EDS (<60 or ≥60) in the study eye. Most subjects had an ICSS >1.5 and an EDS ≥60 at randomisation (placebo: 54.8%; lifitegrast: 54.9%; see Table 6). A summary of subjects incorrectly stratified at randomisation is presented in Table 8.

Table 6: Randomization Strata (Randomized Population)

	Placebo N=356 n (%)	Lifitegrast N=355 n (%)
Inferior corneal staining score ≤1.5, EDS <60	20 (5.6)	19 (5.4)
Inferior corneal staining score ≤1.5, EDS ≥60	33 (9.3)	32 (9.0)
Inferior corneal staining score >1.5, EDS <60	108 (30.3)	109 (30.7)
Inferior corneal staining score >1.5, EDS ≥60	195 (54.8)	195 (54.9)

EDS=eye dryness score
Source: Section 14, Table 1.5.3.

Table 4: Subject Disposition

	Placebo N=356 n (%)	Lifitegrast N=355 n (%)	Total N=711 n (%)
Screened subjects[a]	NA	NA	1542
Number of subjects not starting placebo run-in period	NA	NA	558
Number of subjects not randomized after placebo run-in period	NA	NA	273
Number of subjects randomized			711
Randomized without placebo run-in	NA	NA	2
Included in data analysis	NA	NA	711
Randomized population	356	355	711
Safety population[b]	354 (99.4)	357 (100.6)	711 (100.0)
ITT population	356 (100.0)	355 (100.0)	711 (100.0)
Subjects who completed study	318 (89.3)	319 (89.9)	637 (89.6)
Subjects who withdrew from study	38 (10.7)	36 (10.1)	74 (10.4)
Reason for withdrawal			
Adverse event	9 (2.5)	22 (6.2)	31 (4.4)
Lost to follow-up	4 (1.1)	2 (0.6)	6 (0.8)
Non-compliance	5 (1.4)	2 (0.6)	7 (1.0)
Erroneously Admitted	7 (2.0)	4 (1.1)	11 (1.5)
Other	13 (3.7)	6 (1.7)	19 (2.7)

ITT=intent-to-treat; NA=not applicable

Percentages based on number of subjects randomized.

[a] Number may reflect multiple screenings for the same person.

[b] Subjects are categorized by actual treatment received, even if randomized to the other treatment group. Subjects 01-011 and 38-013 were randomized to the placebo grout but received lifitegrast by incorrectly dispensed kit at Visit 2. These subjects were included in the lifitegrast group for the safety population, but in the placebo group for the randomized and ITT populations.

Source: Section 14 , Table 1.1.1, and Table 1.1.2

Conduct of the study (OPUS-3)

During a masked review of the data prior to database lock and unmasking, the sponsor reviewed the protocol deviations. Most of the reported deviations (e.g., failure to return a minimal number of used vials, visit window deviations) were determined to be minor, i.e., not affecting the efficacy or safety assessments of study subjects.

The following categories of deviations were determined to be important with the potential to affect the efficacy or safety assessments.

- Overall treatment compliance outside the protocol-specified range: A total of 28 (2.9%) subjects (placebo: 4.2%; lifitegrast 3.6%) had an overall treatment compliance <80% or >120%.
- Incorrect stratification of subjects during randomisation: Some subjects were assigned to the incorrect strata at randomisation (see Table 8). A sensitivity analysis using the corrected strata was performed to investigate the impact of incorrect stratification on the efficacy analyses.

Table 8: Randomization to Incorrect Strata (Randomized Population)				
	Randomization Strata	Value at Randomization	Placebo N=356 n (%)	Lifitegrast N=355 n (%)
Inferior corneal score	≤1.5	>1.5	16 (4.5)	20 (5.6)
	>1.5	≤1.5	9 (2.5)	6 (1.7)
Eye dryness	<60	≥60	6 (1.7)	8 (2.3)
	≥60	<60	7 (2.0)	5 (1.4)

SD=standard deviation
Source: Section 14, Table 1.5.2.

- Used prohibited medication: Overall, 3.5% of subjects (placebo: 3.1%; lifitegrast 3.9%) used a prohibited concomitant medication during the study.
- Failure to meet inclusion/exclusion criteria: A total of 23 subjects (3.2%; placebo: 10 subjects; lifitegrast: 13 subjects) were randomised in the study, but did not meet all inclusion/exclusion criteria.

As described, Subjects 01-011 and 38-013 were randomised to placebo but incorrectly received lifitegrast at Day 0/Visit 2. These subjects were included in the lifitegrast group of the safety population and in the placebo groups of the randomised and ITT populations. Footnotes have been included in the Listings and Tables to identify these 2 subjects.

Summary of main efficacy results (OPUS-3)

There was only one primary endpoint, which was Eye dryness score (EDS).

Symptom

Primary efficacy results – Eye Dryness Score at Day 84 (Visual Analogue Scale)

A statistically significant difference in the mean change from baseline to Day 84 in subject-reported EDS was observed between the lifitegrast (-37.9) and the placebo (-30.7) groups; p-value=0.0007. Presented in Table 9 are mean EDS at baseline, the mean change from baseline to Day 84, and treatment effect.

Table 9: Eye Dryness Score (VAS) – Mean Change from Baseline to Day 84 (Week 12, Visit 5) (ITT Population with LOCF)		
	Placebo N=356	Lifitegrast N=355
Baseline, Day 0/Visit 2		
n	356	355
Mean (SD)	69.0 (17.08)	68.3 (16.88)
Change from baseline to Day 84/Visit 5		
n	353	353
Mean (SD)	-30.7 (28.01)	-37.9 (28.85)
Treatment Effect (SE)	7.16 (2.096)	
95% CI for Treatment Effect	3.04, 11.28	
P-value	0.0007	

CI = confidence interval; ITT=intent-to-treat; LOCF = last observation carried forward; SD=standard deviation; SE=standard error; VAS=visual analogue scale
Note: Eye dryness was scored on a VAS from 0-100 (0=no discomfort; 100=maximal discomfort).
Source: Section 14, Table 3.1.1.1

Summary of results – all OPUS studies

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

Table 1. Summary of efficacy for trial SPD606-301 – OPUS-1

Title: A Phase 3, Multicenter, Randomized, Double-Masked and Placebo-Controlled Study Evaluating the Efficacy of a 5.0% Concentration of SAR 1118 Ophthalmic Solution compared to Placebo in Subjects with Dry Eye		
Study identifier	OPUS-1 (SPD606-301; 1118-KCS-200)	
Design	Phase 3, multicenter, randomised, prospective, double - masked, placebo-controlled, parallel-arm study conducted in the United States. Randomization was stratified by active use of artificial tears, prior to start of the study. NOTE: No concomitant use of artificial tears during the study was permitted.	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	12 Weeks 2 Weeks not applicable
Hypothesis	Superiority: The null hypothesis to be tested was that there was no difference in the mean change from baseline to Day 84 in visual-related function Ocular Surface Disease Index subscale (VR-OSDI) score and inferior corneal fluorescein staining score (ICSS) between lifitegrast and placebo with the alternative of a nonzero difference between them.	

Treatment groups	PBO		Placebo-treated Screening period (14 days)-subjects received twice daily open-label vehicle administered to the ocular surface as a single eye drop to both eyes. Treatment period (84 days) subjects received twice daily double-masked vehicle administered to the ocular surface as a single eye drop to both eyes. 295 randomised subjects.
	LIF		Lifitegrast -treated During the Screening period (14 days)-subjects received twice daily open-label vehicle administered to the ocular surface as a single eye drop to both eyes. Treatment period (84 days) subjects received twice daily double-masked 5.0% lifitegrast ophthalmic solution administered to the ocular surface as a single eye drop to both eyes. 293 randomised subjects.
Endpoints and definitions	Co-Primary endpoints Symptom: Sign:	VR-OSDI ICSS 84	Mean change from baseline to Day 84 (Week 12, visit 5) in the visual-related function Ocular Surface Disease Index subscale (VR-OSDI) score Mean change from baseline to Day 84 (Week 12, visit 5) in Inferior Corneal Fluorescein Staining Score (ICSS) in the designated study eye
	Secondary **Sign** endpoints	STT 14	Mean change from baseline to Day 14 (visit 3) in Schirmer Tear Test (STT) in the designated study eye
		STT 84	Mean change from baseline to Day 84 (Week 12, visit 5) in STT in the designated study eye
	Secondary **Symptom** endpoints	OSDI 14	Mean change from baseline to Day 14 (visit 3) in the total OSDI score
		OSDI 84	Mean change from baseline to Day 84 (Week 12, visit 5) in the total OSDI score

	Additional **Sign** endpoints	TCSS 84	Mean change from baseline to Day 84 (Week 12, visit 5) in total corneal staining score (TCSS) in the designated study eye
	Additional **Symptom** endpoints	EDS-VAS 84	Mean change from baseline to Day 84 (Week 12, visit 5) in the Eye Dryness Score (using Visual Analogue Scale)
Study Completion	28Apr2012		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat (ITT) population was the primary efficacy analysis population using last observation carried forward (LOCF). The ITT population included all randomised subjects who received at least 1 dose of investigational product. Day 84 was the time point of the primary efficacy analyses, and occurred after 12 weeks of twice daily administration of investigational product.		
Descriptive statistics and estimate variability	Treatment group	PBO	LIF
	Number of subjects	295	293
	VR-OSDI Mean change from baseline	-0.12	-0.11
	Standard Deviation	0.762	0.829
	ICSS 84 Mean change from baseline	0.17	-0.07
	Standard Deviation	0.819	0.868

Effect estimate per comparison	Co-Primary Symptom endpoint VR-OSDI 84	Comparison groups	PBO, LIF
		Treatment Effect	-0.02
		95% Confidence interval	-0.15, 0.11
		P-value (t-test)	0.7860
	Co-Primary Sign endpoint ICSS 84	Comparison groups	PBO, LIF
		Treatment Effect	0.24
		95% Confidence interval	0.10, 0.38
		P-value (t-test)	0.0007
Notes	The primary analysis of the co-primary endpoints was performed using a 2-sample t-test comparing lifitegrast to placebo in the ITT Population with LOCF.		
Analysis description	**Secondary endpoint analysis**		

Analysis population and time point description	Intent to treat (ITT) population was the primary efficacy analysis population, using last observation carried forward (LOCF). The ITT population included all randomised subjects who received at least 1 dose of investigational product. Day 14 was a secondary efficacy analysis time point and occurred after 2 weeks of twice daily administration of investigational product. Day 84 was a secondary efficacy analysis time point, and occurred after 12 weeks of twice daily administration of investigational product.		
Descriptive statistics and estimate variability	Treatment group	PBO	LIF
	Number of subjects	295	293
	STT 14 Mean change from baseline Standard deviation	0.97 4.620	1.00 4.754
	STT 84 Mean change from baseline Standard deviation	1.57 5.072	1.73 5.445
	OSDI 14 Mean change from baseline Standard deviation	-2.34 14.000	-1.33 13.405
	OSDI 84 Mean change from baseline Standard deviation	-3.84 14.949	-2.98 15.250

Effect estimate per comparison	**STT 14**	Comparison groups	PBO, LIF
		Treatment Effect	-0.03
		95% Confidence interval	-0.79, 0.73
		P-value (nominal)	0.9440
	STT 84	Comparison groups	PBO, LIF
		Treatment Effect	-0.16
		95% Confidence interval	-1.02, 0.69
		P-value (nominal)	0.7087
	OSDI 14	Comparison groups	PBO, LIF
		Treatment Effect	-1.01
		95% Confidence interval	-3.23, 1.21
		P-value (nominal)	0.3731
	OSDI 84	Comparison groups	PBO, LIF
		Treatment Effect	-0.86
		95% Confidence interval	-3.31, 1.59
		P-value (nominal)	0.4904

Notes	The analysis was performed using a 2-sample t-test comparing lifitegrast to placebo in the ITT Population with LOCF. As statistical significance was not achieved for the symptom co-primary endpoint, nominal p-values are presented as descriptive statistics not corrected for multiplicity for the subsequent secondary and tertiary endpoints

Analysis description	**Additional analysis of sign endpoints**		
Analysis population and time point description	Analysis population: Intent to treat (ITT) population using last observation carried forward (LOCF). The ITT population included all randomised subjects who received at least 1 dose of investigational product. Day 84 was the time point of the primary efficacy analyses, and occurred after 12 weeks of twice daily administration of investigational product.		
Descriptive statistics and estimate variability	Treatment group	PBO	LIF
	Number of subjects	294	293
	TCSS 84 Mean change from baseline Standard deviation	 -0.14 1.923	 -0.55 1.989

Effect estimate per comparison	**TCSS 84**	Comparison groups	PBO, LIF
		Treatment Effect	0.41
		95% Confidence interval	0.09, 0.73
		P-value (nominal)	0.0117

Notes	The analysis was performed using a 2-sample t-test comparing lifitegrast to placebo in the ITT Population with LOCF.
Analysis description	**Additional analysis of symptom endpoints and subgroup analyses based on randomisation stratification factor (AT use) and symptom severity (EDS-VAS ≥40)**
Analysis population and time point description	Analysis populations: (1) Intent to treat (ITT) population using last observation carried forward (LOCF) (2) Intent to treat (ITT) population with history of artificial tear use (LOCF) (3) Intent to treat (ITT) population with history of artificial tear use and baseline EDS≥40 (LOCF) The ITT population included all randomised subjects who received at least 1 dose of investigational product. Day 84 was the time point of the primary efficacy analyses, and occurred after 12 weeks of twice daily administration of investigational product.

Descriptive statistics and estimate variability	Treatment group	PBO	LIF
	EDS-VAS 84 (ITT population) Number of subjects Mean change from baseline Standard deviation	 295 -11.23 28.783	 293 -15.17 31.482

	EDS-VAS 84 (AT users only) Number of subjects Mean change from baseline Standard deviation	129 -9.92 30.381	128 -16.88 32.700
	EDS-VAS 84 (AT users with Baseline EDS≥40) Number of subjects Mean change from baseline Standard deviation	67 -22.06 31.591	63 -35.40 31.722

Effect estimate per comparison	**EDS-VAS 84 (ITT population)**	Comparison groups	PBO, LIF
		Treatment Effect	3.94
		95% Confidence interval	-0.95, 8.83
		P-value (nominal)	0.1137
	EDS-VAS 84 (AT users only)	Comparison groups	PBO, LIF
		Treatment Effect	6.96
		95% Confidence interval	-0.79, 14.71
		P-value (nominal)	0.0783
	EDS-VAS 84 (AT users with Baseline EDS≥40)	Comparison groups	PBO, LIF
		Treatment Effect	13.34
		95% Confidence interval	2.35, 24.33
		P-value (nominal)	0.0178
Notes	The analysis was performed using a 2-sample t-test comparing lifitegrast to placebo in the ITT Population with LOCF.		

Table 2. Summary of efficacy for trial SPD606-302 - OPUS-2

Title: A Phase 3, Multicenter, Randomized, Double-Masked and Placebo-Controlled Study Evaluating the Efficacy of a 5.0% Concentration of Lifitegrast Ophthalmic Solution compared to Placebo in Subjects with Dry Eye Currently Using Artificial Tears		
Study identifier	OPUS-2 (SPD606-302; 1118-DRY-300)	
Design	Phase 3, multicenter, randomised, prospective, double – masked, placebo-controlled, parallel-arm study conducted in the United States. Subjects were stratified by baseline inferior corneal staining score (≤1.5 or >1.5) and eye dryness score (<60 or ≥60).	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	12 Weeks 2 Weeks not applicable
Hypothesis	Superiority: The null hypothesis to be tested was that there was no difference in the mean change from baseline to Day 84 in Eye Dryness Score (EDS) and inferior corneal fluorescein staining score (ICSS) between lifitegrast and placebo with the alternative of a nonzero difference between them.	

Treatment groups	PBO		Placebo-treated Screening period (14 days)-subjects received twice daily open-label vehicle administered to the ocular surface as a single eye drop to both eyes. Treatment period (84 days) subjects received twice daily double-masked vehicle administered to the ocular surface as a single eye drop to both eyes. 360 randomised subjects.
	LIF		Lifitegrast -treated During the Screening period (14 days)-subjects received twice daily open-label vehicle administered to the ocular surface as a single eye drop to both eyes. Treatment period (84 days) subjects received twice daily double-masked 5.0% lifitegrast ophthalmic solution administered to the ocular surface as a single eye drop to both eyes. 358 randomised subjects.
Endpoints and definitions	Co-Primary endpoints		
	Symptom:	EDS-VAS 84	Mean change from baseline to Day 84 (Week 12, visit 5) in the Eye Dryness Score (using Visual Analogue Scale)
	Sign:	ICSS 84	Mean change from baseline to Day 84 (Week 12, visit 5) in Inferior Corneal Fluorescein Staining Score (ICSS) in the designated study eye
	Response endpoints by baseline severity		
	Symptom:	EDS-VAS 84 resp	Percentage of subjects in each of 4 subgroups (based on baseline ICSS ≤/> 1.5 and EDS-VAS </≥60) who experienced an improvement from baseline to Day 84 in EDS-VAS of ≥30%
	Sign:	ICSS 84 resp	Percentage of subjects in each of 4 subgroups (based on baseline ICSS ≤/> 1.5 and EDS-VAS </≥60) who experienced an improvement from baseline to Day 84 in ICSS of ≥1point

	Composite	COMP 84 resp	Percentage of subjects in each of 4 subgroups (based on baseline ICSS ≤/> 1.5 and EDS-VAS </≥60) who experienced improvement from baseline to Day 84 of both EDS-VAS of ≥30% and ICSS of ≥1point
	Secondary **Sign** endpoints	TCSS 84	Mean change from baseline to Day 84 (Week 12, visit 5) in Total Corneal Fluorescein Staining Score in the designated study eye
		NConjSS 84	Mean change from baseline to Day 84 (Week 12, visit 5) in Nasal Conjunctival lissamine green Staining Score in the designated study eye
	Secondary **Symptom** Endpoints	ODS 84	Mean change from baseline to Day 84 (Week 12, visit 5) in ocular discomfort score in the designated study eye
		Eye discomfort score (VAS) 84	Mean change from baseline to Day 84 (Week 12, visit 5) in eye discomfort score in the designated study eye
Database lock	27Nov2013		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat (ITT) population was the primary efficacy analysis population using last observation carried forward (LOCF). The ITT population included all randomised subjects who received at least 1 dose of investigational product. Day 84 was the time point of the primary efficacy analyses, and occurred after 12 weeks of twice daily administration of investigational product.		
Descriptive statistics and estimate variability	Treatment group	PBO	LIF
	Number of subjects	360	358
	EDS-VAS 84 Mean change from baseline	-22.75	-35.30
	Standard Deviation	28.600	28.400
	ICSS 84 Mean change from baseline	-0.71	-0.73
	Standard Deviation	0.943	0.926

Effect estimate per comparison	Co-Primary Symptom endpoint EDS-VAS 84	Comparison groups	PBO, LIF
		Treatment Effect	12.61
		95% Confidence interval	8.51, 16.70
		P-value (ANOVA)	<0.0001
	Co-Primary Sign endpoint ICSS 84	Comparison groups	PBO, LIF
		Treatment Effect	0.03

		95% Confidence interval	-0.10, 0.17
		P-value (ANOVA)	0.6186
Notes	The p-value and treatment effect from OPUS-2 were calculated from ANOVA model of change with treatment, stratum, and treatment by stratum interaction; weights set to stratum size.		
Analysis description	**Subgroup Analyses based on Randomisation Stratification Factors**		
Analysis population and time point description	Intent to treat (ITT) population was the primary efficacy analysis population, using last observation carried forward (LOCF). The ITT population included all randomised subjects who received at least 1 dose of investigational product. Day 84 was the time point of the primary efficacy analyses, and occurred after 12 weeks of twice daily administration of investigational product.		
Responder proportions and comparisons by baseline severity subgroups: (ICSS ≤1.5 or >1.5 and EDS-VAS <60 or ≥60)	EDS-VAS 84 Subgroup: **ICSS≤1.5 and EDS-VAS<60**	Comparison group	PBO (N=23) LIF (N=23)
		Percentage with pre-defined response	PBO: 60.9% LIF: 69.6%
		P-value (nominal)	0.5358
	EDS-VAS 84 resp Subgroup: **ICSS≤1.5 and EDS-VAS≥60**	Comparison group	PBO (N=29) LIF (N=31)
		Percentage with pre-defined response	PBO: 51.7% LIF: 71.0%
		P-value (nominal)	0.1255
	EDS-VAS 84 resp Subgroup: **ICSS>1.5 and EDS-VAS<60**	Comparison group	PBO (N=99) LIF (N=100)
		Percentage with pre-defined response	PBO: 51.5% LIF: 68.0%
		P-value (nominal)	0.0177
	EDS-VAS 84 resp Subgroup: **ICSS>1.5 and EDS-VAS≥60**	Comparison group	PBO (N=209) LIF (N=204)
		Percentage with pre-defined response	PBO: 45.9% LIF: 68.6%
		P-value (nominal)	<0.0001
	ICSS 84 resp Subgroup: **ICSS≤1.5 and EDS-VAS<60**	Comparison group	PBO (N=23) LIF (N=23)
		Percentage with pre-defined response	PBO:17.4% LIF: 17.4%
		P-value (nominal)	1.000
	ICSS 84 resp Subgroup: **ICSS≤1.5 and EDS-VAS≥60**	Comparison group	PBO (N=29) LIF (N=31)
		Percentage with pre-defined response	PBO: 20.7% LIF: 22.6%
		P-value (nominal)	0.8590
	ICSS 84 resp Subgroup: **ICSS>1.5 and EDS-VAS<60**	Comparison group	PBO (N=99) LIF (N=100)
		Percentage with pre-defined response	PBO:46.5% LIF:50.0%
		P-value (nominal)	0.6178
	ICSS 84 resp Subgroup: **ICSS>1.5 and**	Comparison group	PBO (N=209) LIF (N=204)
		Percentage with pre-defined response	PBO:51.2% LIF:56.9%

	EDS-VAS≥60	P-value (nominal)	0.2480
	COMP 84 resp Subgroup: **ICSS≤1.5 and EDS-VAS<60**	Comparison group	PBO (N=23) LIF (N=23)
		Percentage with pre-defined responses	PBO: 13.0% LIF:13.0%
		P-value (nominal)	1.000
	COMP 84 resp Subgroup: **ICSS≤1.5 and EDS-VAS≥60**	Comparison group	PBO (N=29) LIF (N=31)
		Percentage with pre-defined response	PBO:10.3% LIF: 12.9%
		P-value (nominal)	0.7577
	COMP 84 resp Subgroup: **ICSS>1.5 and EDS-VAS<60**	Comparison group	PBO (N=99) LIF (N=100)
		Percentage with pre-defined responses	PBO: 27.3% LIF: 33.0%
		P-value (nominal)	0.3787
	COMP 84 resp Subgroup: **ICSS>1.5 and EDS-VAS≥60**	Comparison group	PBO (N=209) LIF (N=204)
		Percentage with pre-defined responses	PBO: 25.8% LIF: 40.7%
		P-value (nominal)	0.0014

Analysis description Analysis population and time point description	**Secondary endpoint analysis** Intent to treat (ITT) population was the primary efficacy analysis population, using last observation carried forward (LOCF). The ITT population included all randomised subjects who received at least 1 dose of investigational product. Day 84 was the time point of the primary efficacy analyses, and occurred after 12 weeks of twice daily administration of investigational product.		
Descriptive statistics and estimate variability	Treatment group	PBO	LIF
	Number of subjects	360	358
	TCSS 84 Mean change from baseline Standard deviation	-1.49 2.097	-1.62 2.043
	NConjSS 84 Mean change from baseline Standard deviation	-0.27 0.805	-0.25 0.850
	ODS 84 Mean change from baseline Standard deviation	-0.57 1.354	-0.91 1.280
	Eye discomfort score (VAS) 84 Mean change from baseline Standard deviation	-16.73 31.207	-26.46 31.238
Effect estimate per comparison	**TCSS 84**	Comparison groups	PBO, LIF
		Treatment Effect	0.14

		95% Confidence interval	-0.16, 0.44
		P-value (nominal)	0.3711
	NConjSS 84	Comparison groups	PBO, LIF
		Treatment Effect	-0.02
		95% Confidence interval	-0.14, 0.10
		P-value (nominal)	0.6982
	ODS 84	Comparison groups	PBO, LIF
		Treatment Effect	0.34
		95% Confidence interval	0.15, 0.53
		P-value (nominal)	0.0005
	Eye discomfort score (VAS) 84	Comparison groups	PBO, LIF
		Treatment Effect	9.77
		95% Confidence interval	5.27, 14.28
		P-value (nominal)	<0.0001
Notes	The p-value and treatment effect from OPUS-2 were calculated from ANOVA model of change with treatment, stratum, and treatment by stratum interaction; weights set to stratum size. As statistical significance was not achieved for the sign co-primary endpoint, nominal p-values are presented as descriptive statistics not corrected for multiplicity for the subsequent secondary and tertiary endpoints		

Table 3. Summary of efficacy for trial SHP606-304 - OPUS-3

Title: A Phase 3, Multicenter, Randomized, Double-masked, and Placebo-controlled Study Evaluating the Efficacy and Safety of a 5.0% Concentration of Lifitegrast Ophthalmic Solution Compared to Placebo in Subjects with Dry Eye Disease and History of Recent Artificial Tear use (OPUS-3)		
Study identifier	OPUS-3 (SHP606-304)	
Design	Phase 3, randomised, multicenter, double-masked, placebo-controlled study conducted in the United States (US). Subjects were stratified by baseline inferior corneal staining score (≤1.5 or >1.5) and eye dryness score (<60 or ≥60). The study was designed, with input from regulatory agencies, to replicate the symptom co-primary endpoint (EDS-VAS 84) evaluation of the OPUS-2 (SPD606-302) study.	
	Duration of main phase:	12 weeks
	Duration of Run-in phase:	2 Weeks
	Duration of Extension phase:	not applicable
Hypothesis	Superiority: The null hypothesis to be tested was that there was no difference in the mean change from baseline to Day 84 in EDS between lifitegrast and placebo with the alternative of a nonzero difference between them.	

Treatment groups	PBO		Placebo -treated Screening period (14 days)-subjects received twice daily open-label vehicle administered to the ocular surface as a single eye drop to both eyes. Treatment period (84 days)- subjects received twice daily double-masked vehicle administered to the ocular surface as a single eye drop to both eyes. 356 randomised subjects.
	LIF		Lifitegrast -treated Screening period (14 days)-subjects received twice daily open-label vehicle administered to the ocular surface as a single eye drop to both eyes Treatment period (84 days) subjects received twice daily double-masked 5.0% lifitegrast ophthalmic solution administered to the ocular surface as a single eye drop to both eyes. 355 randomised subjects.
Endpoints and definitions	Primary endpoint	EDS-VAS 84	Mean change from baseline to Day 84 (Week 12, visit 5) in the Eye Dryness Score (using Visual Analogue Scale)
	Ad hoc sign endpoints	ICSS 84	Mean change from baseline to Day 84 (Week 12, visit 5) in Inferior Corneal Fluorescein Staining Score (ICSS) in the designated study eye
		TCSS 84	Mean change from baseline to Day 84 (Week 12, visit 5) in Total Corneal Fluorescein Staining Score (TCSS) in the designated study eye

	Response endpoints by baseline severity		
	Symptom:	EDS-VAS resp	Percentage of subjects in each of 4 subgroups (based on baseline ICSS ≤/> 1.5 and EDS-VAS </≥60) who experienced an improvement from baseline to Day 84 in EDS-VAS of ≥30%
	Sign:	ICSS resp	Percentage of subjects in each of 4 subgroups (based on baseline ICSS ≤/> 1.5 and EDS-VAS </≥60) who experienced an improvement from baseline to Day 84 in ICSS of ≥1point
	Composite:	COMP resp	Percentage of subjects in each of 4 subgroups (based on baseline ICSS ≤/> 1.5 and EDS-VAS </≥60) who experienced improvement from baseline to Day 84 of both EDS-VAS of ≥30% and ICSS of ≥1point
	Key secondary endpoints	EDS-VAS 42 EDS-VAS 14	Mean change from baseline to Days 42 (Week 6) and 14 (Week 2) in the Eye Dryness Score (using Visual Analogue Scale)
	Other secondary endpoints	ODS 84; Additional VAS items: ●Burning/ stinging ●Itching ●Foreign body sensation ●Eye discomfort ●Photophobia ●Pain	Mean change from baseline to Day 84 (Week 12, visit 5) in each item using Visual Analogue Scale
Database lock	22Oct2015		

<u>Results and Analysis</u>

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat (ITT) population was the primary efficacy analysis population using last observation carried forward (LOCF). The ITT population included all randomised subjects who received at least 1 dose of investigational product. Day 84 was the time point of the primary efficacy analysis, and occurred after 12 weeks of twice daily administration of investigational product.		
Descriptive statistics and estimate variability	Treatment group	PBO	LIF
	Number of subjects	356	355
	EDS-VAS 84 Mean change from baseline	-30.73	-37.87
	Standard Deviation	28.006	28.847

Effect estimate per comparison	Primary endpoint EDS-VAS 84	Comparison groups Treatment Effect 95% Confidence Interval P-value (ANOVA)	PBO, LIF 7.16 3.04, 11.28 0.0007
Notes	The p-value and treatment effect from OPUS-2 were calculated from ANOVA model of change with treatment, stratum, and treatment by stratum interaction; weights set to stratum size.		
Analysis description	**Ad hoc Sign Endpoint Analyses (to match co-primary sign endpoint of OPUS-2):**		
Analysis population and time point description	Intent to treat (ITT) population was the primary efficacy analysis population using last observation carried forward (LOCF). The ITT population included all randomised subjects who received at least 1 dose of investigational product. Day 84 was the time point of the primary efficacy analysis, and occurred after 12 weeks of daily administration of investigational product.		

Descriptive statistics and estimate variability	Treatment group	PBO	LIF
	Number of subjects	356	355
	ICSS 84 Mean change from baseline Standard Deviation	 -0.64 0.915	 -0.81 0.941
	TCSS 84 Mean change from baseline Standard Deviation	 -1.36 2.063	 -1.68 2.284

Effect estimate per comparison	ICSS 84	Comparison groups Treatment Effect 95% Confidence Interval P-value (nominal)	PBO, LIF 0.17 0.03, 0.30 0.0144
	TCSS 84	Comparison groups Treatment Effect 95% Confidence Interval P-value (nominal) ANOVA	PBO, LIF 0.32 -0.00, 0.64 0.0520
Notes	The p-value and treatment effect from OPUS-3 were calculated from ANOVA model of change with treatment, stratum and treatment by stratum interaction; weights were set to stratum size. Because OPUS-3 was designed to replicate the symptom effect observed in OPUS-2, the sign assessments were analysed as safety endpoints; however, in response to FDA comments received on 08 December 2015 regarding the End of Review meeting, ad hoc analyses were conducted for ICSS and total corneal staining score on the ITT population using LOCF. No multiplicity adjustment was conducted on these endpoints. Summary statistics including nominal p-values are reported.		
Analysis description	**Subgroup Analyses based on Randomisation Stratification Factors**		
Analysis population and time point description	Intent to treat (ITT) population was the primary efficacy analysis population using last observation carried forward (LOCF). The ITT population included all randomised subjects who received at least 1 dose of investigational product.		

	Day 84 was the time point of the primary efficacy analyses, and occurred after 12 weeks of daily administration of investigational product.		
Responder proportions and comparisons by baseline severity subgroups: (ICSS ≤1.5 or >1.5 and EDS-VAS <60 or ≥60).	EDS-VAS 84 resp Subgroup: **ICSS≤1.5 and EDS-VAS<60**	Comparison groups	PBO (N=20) LIF (N=19)
		Percentage with pre-defined response	PBO: 65.0% LIF: 73.7%
		P-value (nominal)	0.5570
	EDS-VAS 84 resp Subgroup: **ICSS≤1.5 and EDS-VAS≥60**	Comparison groups	PBO (N=33) LIF (N=32)
		Percentage with pre-defined response	PBO: 48.5% LIF: 78.1%
		P-value (nominal)	0.0133
	EDS-VAS 84 resp Subgroup: **ICSS>1.5 and EDS-VAS<60**	Comparison groups	PBO (N=108) LIF(N=109)
		Percentage with pre-defined response	PBO: 72.2% LIF: 72.5%
		P-value (nominal)	0.9665
	EDS-VAS 84 resp Subgroup: **ICSS>1.5 and EDS-VAS≥60**	Comparison groups	PBO (N=195) LIF (N=195)
		Percentage with pre-defined response	PBO: 53.8% LIF: 73.8%
		P-value (nominal)	<0.0001
	ICSS 84 resp Subgroup: **ICSS≤1.5 and EDS-VAS<60**	Comparison groups	PBO (N=20) LIF (N=19)
		Percentage with pre-defined response	PBO: 25.0% LIF: 36.8%
		P-value (nominal)	0.4232
	ICSS 84 resp Subgroup: **ICSS≤1.5 and EDS-VAS≥60**	Comparison groups	PBO (N=33) LIF (N=32)
		Percentage with pre-defined response	PBO: 18.2% LIF: 31.3%
		P-value (nominal)	0.2214
	ICSS 84 resp Subgroup: **ICSS>1.5 and EDS-VAS<60**	Comparison groups	PBO (N=108) LIF (N=109)
		Percentage with pre-defined response	PBO: 42.6% LIF: 52.3%
		P-value (nominal)	0.1525
	ICSS 84 resp Subgroup: **ICSS>1.5 and EDS-VAS≥60**	Comparison groups	PBO (N=195) LIF (N=195)
		Percentage with pre-defined response	PBO: 47.7% LIF: 53.8%
		P-value (nominal)	0.2242
	COMP 84 resp Subgroup: **ICSS≤1.5 and EDS-VAS<60**	Comparison groups	PBO (N=20) LIF (N=19)
		Percentage with pre-defined responses	PBO: 25.0% LIF: 15.8%
		P-value (nominal)	0.4765
	COMP 84 resp Subgroup: **ICSS≤1.5 and EDS-VAS≥60**	Comparison groups	PBO (N=33) LIF (N=32)
		Percentage with pre-defined response	PBO: 12.1% LIF: 31.3%
		P-value (nominal)	0.0607

	COMP 84 resp Subgroup: **ICSS>1.5 and EDS-VAS<60**	Comparison groups	PBO (N=108) LIF (N=109)
		Percentage with pre-defined responses	PBO: 33.3% LIF: 39.4%
		P-value (nominal)	0.3492
	COMP 84 resp Subgroup: **ICSS>1.5 and EDS-VAS≥60**	Comparison groups	PBO (N=195) LIF (N=195)
		Percentage with pre-defined responses	PBO: 29.2% LIF: 42.6%
		P-value (nominal)	0.0061

Analysis description	**Key Secondary Endpoint Analysis**			
Analysis population and time point description	Intent to treat (ITT) population was the primary efficacy analysis population using last observation carried forward (LOCF). The ITT population included all randomised subjects who received at least 1 dose of investigational product. Day 42 (Week 6, Visit 4) and Day 14 (Week 2, Visit 3) were the time points of the key secondary efficacy analyses.			
Descriptive statistics and estimate variability	Treatment group		PBO	LIF
	Number of subjects (Baseline)		356	355
	EDS-VAS 42 Mean change from baseline		-23.92	-33.21
	Standard Deviation		25.994	27.425
	EDS-VAS 14 Mean change from baseline		-15.02	-22.86
	Standard Deviation		22.397	25.435
Effect estimate per comparison	EDS-VAS 42	Comparison groups		PBO, LIF
		Treatment Effect		9.32
		95% Confidence Interval		5.44, 13.20
		P-value (nominal)		<0.0001
	EDS-VAS 14	Comparison groups		PBO, LIF
		Treatment Effect		7.85
		95% Confidence Interval		4.33, 11.37
		P-value (nominal)		<0.0001
Notes	The p-value and treatment effect from OPUS-3 were calculated from ANOVA model of change with treatment, stratum and treatment by stratum interaction; weights were set to stratum size. In order to maintain study-wide Type I error control at 2-sided 5% level, the hypothesis testing for the primary and the 2 key secondary efficacy endpoints was done sequentially. Since the primary was statistically significant, the first key secondary was tested. Subsequently, since the first key secondary (Day 42) was statistically significant, then the second key secondary (Day 14) was tested.			
Analysis description	**Other Secondary Endpoint Analyses :**			

Analysis population and time point description	Intent to treat (ITT) population was the primary efficacy analysis population. The ITT population included all randomised subjects who received at least 1 dose of investigational product. Day 84 was the time point of the secondary efficacy analyses, and occurred after 12 weeks of daily administration of investigational product.		
Descriptive statistics and estimate variability	Treatment group	PBO	LIF
	Number of subjects	356	355
	ODS 84 Mean change from baseline Standard Deviation	 -0.9 1.19	 -0.9 1.33
	Other VAS Items **Burning/stinging** Mean change from baseline Standard Deviation **Itching** Mean change from baseline Standard Deviation **Foreign body sensation** Mean change from baseline Standard Deviation **Eye discomfort** Mean change from baseline Standard Deviation **Photophobia** Mean change from baseline Standard Deviation **Pain** Mean change from baseline Standard Deviation	 -18.4 29.07 -18.5 27.68 -18.5 31.16 -23.0 29.46 -18.9 27.21 -14.6 26.55	 -19.0 30.82 -19.6 28.32 -19.8 30.65 -26.4 31.84 -19.6 29.04 -16.1 27.89
Effect estimate per comparison	**ODS 84**	Comparison groups Treatment Effect 95% Confidence Interval P-value (nominal)	PBO, LIF 0.04 -0.15, 0.23 0.6655
	Other VAS Items Burning/stinging	Comparison groups Treatment Effect 95% Confidence Interval P-value (nominal)	PBO, LIF 0.62 -3.71, 4.96 0.7777
	Itching	Treatment Effect 95% Confidence Interval P-value (nominal)	1.10 -2.96, 5.16 0.5948

	Foreign body sensation	Treatment Effect 95% Confidence Interval P-value (nominal)	1.36 -3.16, 5.88 0.5539
	Eye discomfort	Treatment Effect 95% Confidence Interval P-value (nominal)	3.43 -1.00, 7.87 0.1292
	Photophobia	Treatment Effect 95% Confidence Interval P-value (nominal)	0.71 -3.39, 4.82 0.7335
	Pain	Treatment Effect 95% Confidence Interval P-value (nominal)	1.57 -2.39, 5.52 0.4367
Notes	The p-value and treatment effect from OPUS-3 were calculated from ANOVA model of change with treatment, stratum and treatment by stratum interaction; weights were set to stratum size. No multiplicity adjustment was done on the secondary efficacy endpoints. Summary statistics including nominal p-values are reported.		

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

N/A

Clinical studies in special populations

The phase 2, the OPUS-1, OPUS-2, OPUS-3, and the one-year SONATA study all included elderly patients. Hence, no specific studies of patients aged above 65 years are presented.

Supportive study(ies)

The Phase 2 and the OPUS-1 studies have been described above.

The 1-year Sonata Study was a study conducted to evaluate long term safety. Principal eligibility criteria included evidence of aqueous deficient dry eye disease (STT ≥1 and ≤10mm), corneal staining score ≥2.0 in at least 1 region of either eye, and visual analogue scale eye dryness or eye discomfort score ≥40.

Subjects were treated with lifitegrast or placebo twice daily and permitted to use contact lenses, topical ophthalmic/nasal antihistamines and mast cell stabilizers, loteprednol, and artificial tears after the Day 14 assessments.

Description of the study population including demographics is given in the Safety section of this overview.

Summary of efficacy-related results from the SONATA-study

In the Sonata study, tests of corneal fluorescein staining score were conducted. As corneal fluorescein staining score was the primary endpoint in the phase 2 study and the primary 'sign'-endpoint in the OPUS-1 Study, the results of corneal fluorescein staining score are included as supportive efficacy results.

Otherwise, the SONATA-study mainly contributes safety data; please refer to the safety section of this overview.

Table 24: Corneal Fluorescein Staining Score by Region – Mean Change from Baseline (Safety Population)

	Placebo N=111			Lifitegrast N=220		
	n	Right Eye Mean (SD)	Left Eye Mean (SD)	n	Right Eye Mean (SD)	Left Eye Mean (SD)
Total corneal staining						
Day 0 (Month 0, Visit 2, baseline)	111	4.72 (2.254)	5.03 (2.421)	219	4.74 (2.184)	4.88 (2.171)
Change from baseline to Day 14 (Week 2, Visit 3)	109	-0.70 (1.926)	-0.85 (1.754)	217	-0.93 (2.059)	-0.88 (1.660)
Change from baseline to Day 90 (Month 3, Visit 4)	100	-1.41 (2.177)	-1.65 (2.275)	204	-1.62 (2.429)	-1.63 (2.221)
Change from baseline to Day 180 (Month 6, Visit 5)	95	-1.84 (2.248)	-1.97 (2.401)	190	-2.05 (2.473)	-1.97 (2.278)
Change from baseline to Day 270 (Month 9, Visit 6)	94	-1.86 (2.112)	-2.07 (2.377)	174	-2.08 (2.426)	-1.99 (2.201)
Change from baseline to Day 360 (Month 12, Visit 7)	92	-2.17 (2.085)	-2.16 (2.096)	172	-2.09 (2.159)	-2.07 (2.314)
Inferior corneal region						
Day 0 (Month 0, Visit 2, baseline)	111	2.26 (0.762)	2.32 (0.785)	219	2.28 (0.813)	2.29 (0.821)
Change from baseline to Day 14 (Week 2, Visit 3)	109	-0.39 (0.997)	-0.42 (0.798)	217	-0.40 (0.910)	-0.36 (0.778)
Change from baseline to Day 90 (Month 3, Visit 4)	100	-0.69 (0.997)	-0.69 (0.884)	204	-0.71 (1.063)	-0.69 (1.011)
Change from baseline to Day 180 (Month 6, Visit 5)	95	-0.83 (0.994)	-0.82 (1.032)	190	-0.91 (1.164)	-0.84 (1.045)
Change from baseline to Day 270 (Month 9, Visit 6)	94	-0.82 (1.069)	-0.93 (1.015)	174	-0.93 (1.098)	-0.93 (1.071)
Change from baseline to Day 360 (Month 12, Visit 7)	92	-1.00 (1.046)	-0.92 (0.979)	172	-0.97 (1.038)	-0.92 (1.096)

Central corneal region						
Day 0 (Month 0, Visit 2, baseline)	111	0.98 (0.935)	1.11 (1.028)	219	0.91 (0.910)	0.98 (0.919)
Change from baseline to Day 14 (Week 2, Visit 3)	109	-0.13 (0.771)	-0.25 (0.912)	217	-0.20 (0.822)	-0.20 (0.747)
Change from baseline to Day 90 (Month 3, Visit 4)	100	-0.26 (0.830)	-0.38 (0.946)	204	-0.36 (0.970)	-0.40 (0.953)
Change from baseline to Day 180 (Month 6, Visit 5)	95	-0.45 (0.884)	-0.49 (1.059)	190	-0.43 (0.930)	-0.42 (1.008)
Change from baseline to Day 270 (Month 9, Visit 6)	94	-0.39 (0.895)	-0.46 (1.001)	174	-0.45 (0.945)	-0.40 (0.882)
Change from baseline to Day 360 (Month 12, Visit 7)	92	-0.47 (0.891)	-0.56 (0.808)	172	-0.41 (0.886)	-0.39 (0.932)
Superior corneal region						
Day 0 (Month 0, Visit 2, baseline)	111	1.48 (1.054)	1.59 (1.108)	219	1.54 (1.053)	1.61 (1.035)
Change from baseline to Day 14 (Week 2, Visit 3)	109	-0.19 (0.810)	-0.19 (0.813)	217	-0.34 (0.987)	-0.32 (0.823)
Change from baseline to Day 90 (Month 3, Visit 4)	100	-0.46 (0.958)	-0.59 (0.962)	204	-0.56 (1.078)	-0.54 (1.011)
Change from baseline to Day 180 (Month 6, Visit 5)	95	-0.56 (1.011)	-0.66 (0.966)	190	-0.72 (1.014)	-0.71 (1.057)
Change from baseline to Day 270 (Month 9, Visit 6)	94	-0.64 (0.944)	-0.68 (0.978)	174	-0.69 (1.132)	-0.67 (0.981)
Change from baseline to Day 360 (Month 12, Visit 7)	92	-0.70 (0.932)	-0.68 (1.050)	172	-0.72 (1.053)	-0.76 (1.020)

Note: Corneal fluorescein staining scoring of each region (inferior, central, superior) is as follows with 0.5 increments: 0=no staining; 1=few/rare punctate lesions; 2=discrete and countable lesions; 3=lesions too numerous to count, but not coalescent; 4=coalescent. Total score is derived from the sum of all regions (inferior, central, superior) (0-12 points).
SD=standard deviation
Source: Section 14, Table 4.9.5

3.3.6. Discussion on clinical efficacy

The present application is supported by one Phase II dose-finding study, one supportive phase III study (OPUS 1) and two pivotal Phase III studies (OPUS 2 and OPUS 3) as well as additional data from a 1-year safety study (SONATA).

Phase II study

The phase 2 study was a prospective, multi-center, randomised, double-masked, placebo-controlled parallel-arm studies conducted in the United States. CAE methodology was employed to refine the study population in order to include patients who had a worsening of DED-symptoms under adverse conditions. The population included was mainly Caucasian females. The overall study design is considered adequate for a Phase 2 study. However, it should be noted that several exclusion criteria were applied, hence, patients with previous or present ocular conditions including surgeries could participate upon the discretion of the investigator, as per the protocol. The Phase 2 study had one primary 'sign'-endpoint, ICSS, which did not show statistical significance between lifitegrast and placebo. No primary 'symptom'-endpoints were defined. Several secondary endpoints were included but not prioritized and no correction for multiplicity was made. Accordingly, the outcomes of these secondary endpoints are considered explorative.

Design and conduct of clinical phase 3 studies

The three Phase III studies (the supportive OPUS-1, and the pivotal OPUS-2 and OPUS-3 studies) were similar in design. They were prospective, multi-center, randomised, double-masked, placebo-controlled parallel-arm studies conducted in the United States. The Applicant has presented a justification for the extrapolation of from the US to the European population. It is agreed that the DED can be considered to be similar disease in both Europe and the US. Further, the characteristics of patients in the US are comparable with the European patient population (with regard to ethnicity, disease characteristics, age and gender). In the present studies, a large proportion of the included patients were Caucasian, post-menopausal women, which are similar to the demographic of the most frequently affected population also in Europe. Thus, taken together, as intrinsic and extrinsic factors are considered mostly similar, extrapolation from the US conducted studies to the EU population can be accepted.
The overall study design (prospective, multi-center, randomised, double-masked, parallel-arm studies) is endorsed, however, the study duration of 12 Weeks/3 months is questioned. For obtaining an indication for long-term treatment of a chronic disease, the Applicant is usually requested to provide efficacy data from at least one study of minimum 6 and preferable 12 months' duration. This should also be seen in the light that long-term efficacy is explored in the long-term safety study (the SONATA study) where corneal fluorescein staining score (measured at baseline, and Month 3, 6, 9 and 12) are included as supportive efficacy results. No statistics were applied but numeric the treatment difference to placebo was small (even favoured placebo at some time-points e.g. at Month 12) and no clinically relevant difference was observed. No symptomatic endpoints were included in the SONATA study. Thus, it is difficult to see how these results support a long-term (clinically relevant) effect, and therefore the major objection related to the indication text is maintained. **(MO)**.

With regards to the comparator, placebo may be considered acceptable, however, it could also be argued that treatment with eye gel or ointments which have a higher viscosity could be used as active comparators; especially in the pivotal OPUS-2 and OPUS-3 studies where the included patients seem to have more severe DED. Further, in the 'real-world setting', AT and other lubricant eye drops are used as needed and often more than twice daily. Therefore, it can be argued that the choice of vehicle/placebo as comparator in the pivotal studies is not mimicking real-world however, the Applicant has sufficiently justified the choice of comparator and the issue will not be pursued.

Inclusion criteria were mostly similar for the three OPUS studies. In the OPUS-1 trial, patients should demonstrate ≥1 point increase in the Ora scale for ICSS after exposure to the Controlled Adverse Environment (CAE) prior to inclusion into the study. Use of CAE results in an artificially enriched patient population which is not expected to reflect the target population and while this approach may be acceptable in the initial studies, it seems inappropriate in a pivotal Phase III study. Therefore, the OPUS-1 study is considered supportive rather than pivotal. In the OPUS-2 and -3 studies (but not in the OPUS-1 study), patients should have been treated with AT for symptoms of DED within 30 days prior to the screening visit and further, patients should have a EDS ≥40 (0-100 point VAS) in both eyes. Thus, more severe patients were included in the OPUS-2 and -3 studies. By changing the inclusion criteria and the target group to be included in the studies, the reproduction of the results (from OPUS-1 to OPUS -2 and OPUS-3) is difficult.

Exclusion criteria were numerous and included (but are not limited to) patients with lid margin disorders glaucoma, diabetic retinopathy as well as patients with chronic illness and patients with DED secondary to scarring, refractory surgery (within 12 months) or patients with DED due to medical treatment with e.g. antihistamines, anti-cholinergics etc. Indeed, these patients could potentially also benefit from the treatment and it is considered a limitation for extrapolation of the study results that these patients were mostly excluded from all pivotal studies. Also patients with secondary DED, i.e. patients with DED secondary to Sjögren's syndrome, rheumatoid arthritis, systemic lupus erythematosus and other

autoimmune diseases were only eligible for enrollment if they *"were not in a medical state – in the opinion of the principal investigator – that could interfere with study parameters, were not taking systemic/ocular steroids, and were not immunodeficient/immunosuppressed (e.g., receiving immunosuppressive drugs to manage their baseline medical state)."* It is endorsed that patients with secondary DED are also (potentially) included in the studies, as these represent an important group of patients with DED. However, the limitations for including patients with these disorders are not endorsed. Overall, the numerous exclusion criteria are considered problematic for the extrapolation of study results to the 'real world setting' and it is indeed likely, that these patients will be treated with lifitegrast if approved. Therefore, by the initial assessment, the Applicant was asked to present the rationale for excluding these patients from all pivotal Phase III studies, to discuss if the results from the Phase III studies can be extrapolated to these patients and to discuss whether treatment with lifitegrast should be offered to these patients. In their response, the Applicant justified the multiple exclusion criteria with an argumentation that these conditions *"could confound assessment of efficacy and safety"* and that patients with these conditions could *"require treatment for these conditions during the clinical trial"*. Another justification used for several of the conditions was according to the Applicant that *"The extra burden of using additional drops for the clinical trial could lead to missed IP doses, protocol deviations and confounding bias."* These arguments are acknowledged but it should be born in mind that part of the purpose with the Phase III trials is to investigate and establish the use of the product in the target population(s). Therefore, this should also include e.g. patients who are at risk of having a lower compliance due to concomitant treatments. Therefore, exclusion criteria clearly confounding evaluation of efficacy and/or safety are considered acceptable but those where it is speculated that it maybe could lead to impaired compliance should be thoroughly considered prior to the study initiation and are not fully endorsed though the issue will not be pursued.

Given that all participants in OPUS-2 and -3 were prior users of artificial tears and were recruited based on symptoms and signs not exacerbated by exposure to an adverse controlled environment, the populations recruited to OPUS 2 and 3 are likely to be more severe than those recruited to the earlier trials.

The objectives of the OPUS-1 and OPUS-2 studies were to evaluate the efficacy of lifitegrast compared to placebo in the treatment of DED as assessed by the co-primary endpoints of both a sign and a symptom of DED. While it is endorsed that the Applicant has chosen to evaluate both signs and symptoms of DED, the chosen endpoints are of a concern (see later). Further, the objective of the OPUS-3 study was to evaluate the efficacy of lifitegrast compared to placebo in the treatment of DED only by assessing the symptoms. It is not understood, why the Applicant chose not to evaluate effect of lifitegrast on signs, but this will not be specifically pursued though an insufficient response was presented from the Applicant.

With regard to the chosen endpoints; it is acknowledged that though several scales have been validated, it is discussable, to which degree they are able to measure changes in signs and symptoms of DED and overall the correlation is weak. There is no consensus with regard to which scale to use in clinical settings when testing treatments and there are no EMA guidelines to adhere to. In general, well-known and established signs (objective) and symptoms (subjective) of ocular changes have been assessed as single or composite endpoints. Corneal staining with fluorescein or lissamine green are widely used and accepted standardised methods to detect loss of epithelial cell membrane or junctional integrity. The sensitivity of these tests to detect actual differences is low. Nevertheless, the Applicant has sufficiently justified the choice of ICSS rather than e.g. total staining score or central staining score. It is acknowledged that the inferior corneal surface usually displays the most staining and therefore it may be easier to measure changes in this part of the ocular surface.

OPUS 2 and 3 used a visual analogue scale to assess the degree of symptom severity and change from baseline in symptom severity (primary endpoint) whereas in OPUS-1 a subscale of the Ocular Surface Disease Index Score (OSDI) items 6 to 9, incorporating reading, night driving, computer use and

watching television was used. In other words, the VAS allowed for measurement of change in symptoms whereas the OSDI was a quality of life type measure in that it measured change in activities of daily living related to the condition as a result of treatment. The Applicant submitted a psychometric validation of the eye dryness endpoint of the VAS. Data from the Phase 2 and OPUS-1 and -2 were used to validate the instrument. Criterion validity was demonstrated but not cross-sectional sensitivity. Eye dryness VAS concordance with the OSDI total was 66%-72%, and with the mean ODS was 64%-67%.

The OSDI can be considered a valid and reliable standardised instrument for measuring and evaluating the severity of symptoms of DED and it is an advantage that this scale is broad measuring different aspects of the DED symptomatology. Likewise, the 7-item VAS score measures both eye dryness, eye discomfort, itching, burning/stinging, pain, foreign body sensation and photophobia, is covering several aspects of the DED symptomatology. Therefore, it is endorsed that the OSDI scale was used as co-primary (symptomatic) endpoint for the OPUS-1 study. As mentioned above, in the OPUS-2 and OPUS-3 studies, the symptomatic endpoint was changed to EDS. The change in the primary endpoints strongly limits the reproducibility of the results. Furthermore, due to the heterogenicity and multi-symptomatic nature of the disease, it is considered crucial that when using a single endpoint as the primary endpoint it indeed needs to be supported by clinically relevant changes in other symptomatic endpoints. Despite several post hoc analyses, this has not convincingly been demonstrated and therefore, the Applicant is asked to justify lack of statistically significant and more importantly, clinically relevant effect on other symptomatic endpoints. **(MO)**

Efficacy data and additional analyses

Results

Approximately 600-700 patients were included in each of the OPUS-1 and OPUS-2 studies and OPUS-3 study. In all three studies, patients were randomised 1:1 to lifitegrast or placebo. In all three studies, demographics were comparable between treatment groups and in general, the majority of patients were female (76%), not Hispanic or Latino (83-98%), and white (77-93%). The most common (>30%) iris colour was brown. Mean age was approximately 60 years.

The frequency of major protocol violations was high (>10% in all studies). The most common reasons for non-compliance were use of prohibited medication and non-compliance with investigational product based on the return of (un)used vials. This was addressed by the initial assessment, and the Applicant clarified that there was no clinically relevant difference between the treatment groups and the frequency of protocol deviations did not lead to pre-approval inspections. The issue will not be pursued. There seemed to be a higher frequency of patients with AEs among patients with a low compliance (e.g. Compliance with study medication less than 80%). This indicates that in some patients the compliance is compromised due to adverse reactions. This is not unexpected.

Table 2 shows the changes from baseline for all primary and secondary endpoints in the OPUS-studies. Table 3 shows the treatment effects for all primary and secondary endpoints in the OPUS-studies.

Table 2

Change from baseline (SD)						
	Primary endpoint			**Secondary endpoint**		
Study	**OPUS-1**	**OPUS-2**	**OPUS-3**	**OPUS-1**	**OPUS-2**	**OPUS-3**
Signs						
ICSS (signs)	Placebo: 0.17 (0.819) Lifitegr. -0.07 (0.868)	Placebo: -0.71 (0.943) Lifitegr. -0.73 (0.926)				
STT (signs)				Placebo: 1,57 (5.072)		

				Lifitegr. 5.90 (4.815)		
Total corneal fluorescein staining score (signs)					Placebo: -1.49 (2.097) Lifitegr. -1.62 (2.043)	
Nasal conjuctival lissamine green staining score (signs)					Placebo: -0.27 (0.805) Lifitegr. -0.25 (0.850)	
Symptoms						
VR-OSDI (symptoms)	Placebo: -0.12 (0.762) Lifitegr. -0.11 (0.829)					
Total OSDI (symptoms)				Placebo: -3.84 (14.949) Lifitegr. -2.98 (15.250)		
EDS, Day 84 (symptoms)		Placebo: -22.75 (28.600) Lifitegr. -35.30 (28.400)	Placebo: -30.7 (28.01) Lifitegr. -37.9 (28.85)			
EDS, Day 42 (symptoms)						Placebo: -23.9 (25.99) Lifitegr. -33.2 (27.42)
EDS, Day 14 (symptoms)						Placebo: -15.0 (22.40) Lifitegr. -22.9 (25.44)
Eye discomfort scale (symptoms)					Placebo: -16.73 (31.207) Lifitegr. -26.46 (31.238)	
ODS (symptoms)					Placebo: 0.57 (1.354) Lifitegr. -0.91 (1.280)	Placebo: -0.9 (1.19) Lifitegr. -0.9 (1.33)
VAS by symptoms (symptoms)						See Table 13

Table 3

Treatment effect (95%CI)						
	Primary endpoint			**Secondary endpoint**		
Study	**OPUS-1**	**OPUS-2**	**OPUS-3**	**OPUS-1**	**OPUS-2**	**OPUS-3**
Signs						
ICSS (signs)	0.24 (0.10;0.38) p=0.0007	0.03 (-0.10;0.17) p=0.6186				
STT (signs)				-0.16 (-1.02;0.69) p=0.7087		
Total corneal fluorescein staining score (signs)					0.14 (-0.16;0.44) p=0.3711	
Nasal conjunctival					-0.02 (-0.14;0.10)	

lissamine green staining score (signs)					p=0.6982	
Symptoms						
VR-OSDI (symptoms)	-0.02 (-0.15;0.11) p=0.7860					
Total OSDI (symptoms)				-0.86 (-3.31;1.59) p=0.4904		
EDS, Day 84 (symptoms)		12.61 (8.51;16.70) p<0.0001	7.16 (3.04;11.28) p=0.0007			
EDS, Day 42 (symptoms)						9.32 (5.44;13.20) p<0.0001
EDS, Day 14 (symptoms)						7.85 (4.33;11.37) p<0.0001
Eye discomfort scale (symptoms)					9.77 (5.27;14.28) p<0.0001	
ODS (symptoms)					0.34 (0.15;0.53) p=0.0005	0.04 (SE: 0.095) p=0.6655
VAS by symptoms (symptoms)						See Table 13.

With regard to lifitegrast's effect on signs of DED, there are no consistent results. In the OPUS-1 study, a statistically significant treatment difference compared to placebo measured as the effect on ICSS was observed, but this could not be reproduced in the OPUS-2 study. Additionally, in the Phase 2 study, as mentioned above, and in the 1-year SONATA study, which provides additional efficacy data, no significant difference was observed in the ICSS between lifitegrast and placebo. Secondary endpoints measuring lifitegrast's effect on signs did not manage to find any statistically significant difference to placebo measured on the STT, Total corneal fluorescein staining score or the Nasal conjunctival lissamine green staining score. Thus overall, the OPUS-studies failed to demonstrate convincing effect as compared to placebo on signs related to DED. Therefore, as a major objection the Applicant was requested to further justify the indication of treatment of signs related to DED. In their initial response, the Applicant submitted a post hoc statistical analysis in the clinical overview showing a *"nominally statistically significant"* mean improvement from baseline in ICFSS at Day 84 (p=0.0144). However, the limitations of a post hoc analysis with no adjustments for multiplicity of testing should be borne in mind in this case. Of note, though meaningful clinical changes in corneal staining score have not been determined, the absolute differences from placebo of <0.25 in all staining scores (OPUS-1 and -2 studies primary and secondary sign-related endpoints) is not considered convincingly clinically relevant to the Rapporteurs. Therefore, the major objection related to the sign-related indication was maintained.

With regard to lifitegrast's effect on symptoms of DED, several different scores have been used. This has been addressed above but overall, it may be speculated that the choice of scales is data-driven. This issue will however, not be pursued. In the OPUS-1 study, the Applicant failed to demonstrate a statistically significant and a clinically relevant treatment effect compared to placebo when measured on the OSDI-scale. In the OPUS-2 study, the Applicant had changed the symptomatic scale to the narrower single-item EDS. While the treatment difference was statistically significant, the absolute difference of 12.6 points on a 0-100 score is not considered convincingly clinically relevant. The statistically significant result of the treatment effect on symptoms measured on the EDS-scale was reproduced in the OPUS-3 study. In the pivotal study OPUS-3 which had one primary endpoint related to change in EDS on a VAS,

a statistically significant improvement in the score at D84 from baseline was seen for lifitegrast compared to placebo. Both treatments were associated with substantial decreases in the EDS (-30.7 vs. -37.9) so the actual treatment effect in favour of lifitegrast at 7.16 (95%CI 3.04, 11.28) was small. It is unclear whether this difference is actually clinically significant. The study also met its key secondary endpoints which were the same as the primary endpoint but with EDS assessed at days 14 and 42 respectively. The Applicant has been requested to present subgroup analyses of OPUS-2 and OPUS-3 in patients with baseline EDS above and below 60 and ICSS above and below 1.5 as these were pre-specified factors used for randomisation in the two studies. The Applicant has presented results from responder analyses by baseline DED severity subgroups based on symptoms and signs. According to the Applicant, these show that lifitegrast has the most pronounced effect on elements of both signs and symptoms in subjects with baseline ICSS>1.5 and baseline ≥60 however, this is not agreed. Actually, in several of the presented Responder Analyses as well as in the analysis of Change from baseline in OSDI, the results across the different subgroups were comparable in the lifitegrast treatment group. Therefore, the statistically significant results in the subgroup of patients with ICSS>1.5 & EDS≥60 seem to be driven by the variability in the number of responders in the placebo group. This should be addressed by the Applicant **(MO).**

Changes in the symptomatic ODS score was also measured as a secondary endpoint in the OPUS-2 and -3 studies. The results were conflicting as in the OPUS-2 study, the difference of 0.34 (on a 0-4 point scale) was statistically significant but this was not reproduced in the OPUS-3 study, where the treatment effect on ODS was not significant. Both OPUS-2 and -3 evaluated changes in the ocular discomfort score (ODS) as a secondary endpoint. In OPUS-3 the ocular discomfort score had decreased equally (-0.9) at Day 84 in both treatment arms whereas in OPUS-2 there was a greater improvement for the lifitegrast arm (-0.57 for placebo, -0.91 for lifitegrast). This would suggest a stronger placebo effect in OPUS-3. Further, the absolute treatment effects of 0.34 (OPUS-2 study) and 0.04 (OPUS-3 study) are not considered clinically relevant. This is further supported by the observed changes in VAS. In OPUS-2, the changes for Itching (difference of 4.79, p=0.0253), Foreign body sensation (difference of 5.54, p=0.0164), Eye discomfort (difference of 9.77, p<0.0001) were nominally statistically significant in addition to eye dryness. However, in OPUS-3, only the changes for eye dryness were statistically significant. The changes in (1) Burning/stinging, (2) Itching, (3) Foreign body sensation, (4) Eye discomfort, (5) Photophobia and (6) Pain were not statistically significant different from placebo and numeric, the differences in change from baseline compared to placebo were all <6 on a 100 point scale thus not clinically relevant. In order to address this, the Applicant submitted additional Responder analyses as well as an analysis of Change from baseline in OSDI. With regard to the analyses of Change from baseline in OSDI, the patients were stratified on the above-mentioned subgroups, and it is noted that the absolute treatment effect of lifitegrast was comparable in all subgroups thus, claiming a better response in a single subgroup (ICSS>1.5 & EDS≥60) needs further justification. Furthermore, in this subgroup, the absolute treatment effect was 7.64. Considered that OSDI is a 0-100 scale, an improvement of 7.64 (in a single subgroup) is not considered clinically relevant and the Applicant needs to further justify the clinical relevance of the improvement seen in the lifitegrast population compared to the improvement seen in the placebo population. **(MO)**

The Applicant also submitted results from an O'Brien rank-sum type test. Of note, the O'Brien rank-sum type test is a global test and therefore, the Applicant should further justify the statement that the results *"demonstrate improvements across a variety of symptom endpoint"* (underlined by the Assessor) and also demonstrate that the claimed better improvement for lifitegrast is clinically relevant better compared to placebo. Taken together, the results of the pivotal studies are considered neither statistically nor clinically persuasive and despite the responses to the initial lists of questions, this still needs further discussion. **(MO)**

3.3.7. Conclusions on clinical efficacy

Despite the Applicant's responses to the initial lists of questions, there are several weaknesses related to the present dossier, and overall, most of the major objections are maintained. Several different endpoints have been used and the rationale for this is still not evident. It cannot be excluded that it is data-driven however, this issue will not be pursued. More importantly, the results are at the best inconclusive.

For lifitegrast's effect on DED signs, statistically significant better effect compared to placebo was only found for the co-primary endpoint (ICSS) in the OPUS-1 study which due to the use of CAE is considered supportive rather than pivotal, and not for any of the sign-related endpoints in the OPUS-2 study.

For lifitegrast's effect on DED symptoms, a statistically significant effect was found for the EDS endpoint (the (co-) primary endpoint in the OPUS-2 and OPUS-3 studies) and for the Ocular Discomfort Score in OPUS-2. The statistically significant treatment effect on ODS in the OPUS-2 study could not be reproduced in the OPUS-3 study. While an effect was found on itching, foreign body sensation, eye discomfort and eye dryness in OPUS-2, no effect was found in any other endpoints for the 7-point VAS scale in OPUS-3. Overall, none of the observed treatment effect on the symptomatic endpoints are convincingly clinically relevant. In EDS which was the only reproducible statistically significant results from the pivotal OPUS-studies, the actual difference was 12.6 and 7.2 in the OPUS-2 and OPUS-3 study, respectively. Measured on a 0-100 point scale, this is not considered being convincingly clinically relevant, especially also considered the inconsistent results throughout the studies. The subgroups analyses presented by the Applicant (as response to the major objections) are post-hoc analyses and are not controlled for multiplicity. Therefore, the credibility of the results is also compromised from a statistical point of view.

These issues all constitute major objections precluding a marketing authorisation unless these are satisfactorily addressed by the Applicant.

3.3.8. Clinical safety

Study populations

Data from 5 studies conducted in subjects with dry eye disease are presented for an integrated overall evaluation of safety:

- One Phase 2, double-masked, placebo-controlled, 12-week, efficacy and safety study (the Phase 2 dry eye study)
- Three Phase 3, double-masked, placebo-controlled, 12-week, efficacy and safety studies (OPUS-1, OPUS-2, and OPUS-3)
- One Phase 3, double-masked, placebo-controlled, 1-year, safety study (SONATA). The study designs, subject populations, and safety assessments for the Phase 2 dry eye, OPUS-1, OPUS-2, OPUS-3, and SONATA studies were similar in many important aspects (refer to Section 3 of the Phase 2 dry eye CSR, Section 3 of the OPUS-1 CSR, Section 3 of the OPUS-2 CSR, Section 3 of the OPUS-3 CSR, and Section 3 of the SONATA CSR), which allowed for pooling of these data for purposes of summarization and description. All studies were multicenter, randomised, double-masked, placebo-controlled, parallel-arm studies conducted in the United States. Only adult subjects with a self-reported history of dry eye disease were enrolled. All studies were completed and unmasked prior to the integrated analysis.

Controlled adverse environment (CAE) methodology

The CAE methodology used in the lifitegrast developmental program is a standardized environmental ocular stress (relative humidity <10%, temperature 76ºF ± 6, standardized air-exchange) for a fixed period of time (90 minutes).

Controlled adverse environment is an established "enrichment strategy" for ophthalmic drug development used worldwide that helps select subjects who develop worsening ocular surface signs and ocular discomfort in response to standardized desiccating environmental conditions.

- In the Phase 2 study CAE was used to refine patient selection before randomisation and was used at each study assessment visit. Statistical interaction between CAE and lifitegrast on endpoints was not assessed.
- In OPUS-1, a Phase 3 dry eye study, the CAE was used only at screening (Visit 1) and baseline (Visit 2) as a prognostic "enrichment strategy" to refine patient selection before randomisation. It was not used at each study assessment visit.
- In the Phase 3 studies OPUS-2, OPUS-3, and SONATA, the CAE was not used.

Patient exposure

The DED clinical development program involved 2578 subjects overall; 1401 subjects have been exposed to lifitegrast in the phase 2 and four phase 3 studies in the proposed indication, DED. Of these, 1287 patients were exposed to the proposed 5% formulation of lifitegrast consisting of 1067 patients in the 12-week studies (phase 2 + OPUS1-3) and 220 patients in the 1-year SONATA study. Exposure to the 5% formulation for more than a year was obtained for 170 patients.

Patient Exposure in Lifitegrast Clinical Studies

Placebo Controlled	Patients enrolled	Patients exposed	Patients exposed to the proposed dose range (5%)	Duration of treatment	Patients with long term safety data
SAR 1118-001 (Phase 1)	28	20	5	3 weeks	
1118-ACJ-100 (Phase 2 Allergic conjunctivitis)	60	45	15	2 weeks	
1118-KCS-100 (Phase 2 dry eye)	230	172	58	12 weeks*	
Formulation change					
1118-KCS-200 (SPD606-301; OPUS-1)	588	293	293	12 weeks*	
Final formulation change + Baseline severity inclusion criteria change					
1118-DRY-300 (SPD606-302; OPUS-2)	718	358	358**	12 weeks*	
SHP606-304 (OPUS-3)	711	355	355**	12 weeks*	
1118-DRY-400 (SPD606-303;SONATA)	332	221	221**	1 year	177> 6 months 170>12 months

Subjects exposed to lifitegrast 5% in all studies	1305	
*12 Week Dry Eye Studies Pool	1067[a]	
**Subjects exposed to final formulation lifitegrast	934	

Table 5: Summary of Treatment Exposure – All Dry Eye Studies Pool (Safety Population)

	Placebo N=1177	All LIF N=1401	All Subjects N=2578
Total duration of treatment exposure (days)[a]			
Mean (SD)	103.2 (76.80)	115.2 (94.38)	109.7 (86.98)
Standard error	2.24	2.53	1.72
Median	85.0	85.0	85.0
Min, max	1, 370	1, 377	1, 377
Subjects with duration of treatment exposure, n (%)[b]			
0-3 months	1036 (88.0)	1173 (83.7)	2209 (85.7)
>3 months	140 (11.9)	223 (15.9)	363 (14.1)
>6 months	94 (8.0)	177 (12.6)	271 (10.5)
>9 months	93 (7.9)	173 (12.3)	266 (10.3)
≥12 months	89 (7.6)	170 (12.1)	259 (10.0)

LIF=lifitegrast; max=maximum; min=minimum; SD=standard deviation

[a] Total treatment exposure is from first randomized masked study treatment to last.

[b] One month is 30.4375 (365.25/12) days. The last category of at least 12 months is defined as at least 355 days based on the planned visit at Day 360 with a visit window of 5 days for SONATA.

Source: Module 5.3.5.3, Table 1.2.1

The age distribution of the study participants is representative of the population with DED. There were more females than males and more White than Non-white participants included in the studies.

Table 16: Summary of Demographic and Baseline Characteristics – All Dry Eye Studies Pool (Safety Population)

	Placebo N=1177	All LIF N=1401	All Subjects N=2578
Age (years)			
Mean (SD)	59.6 (13.72)	59.6 (13.26)	59.6 (13.47)
<65 years, n (%)	731 (62.1)	902 (64.4)	1633 (63.3)
≥65 years, n (%)	446 (37.9)	499 (35.6)	945 (36.7)
<75 years, n (%)	1032 (87.7)	1217 (86.9)	2249 (87.2)
≥75 years, n (%)	145 (12.3)	184 (13.1)	329 (12.8)
Sex, n (%)			
Male	298 (25.3)	318 (22.7)	616 (23.9)
Female	879 (74.7)	1083 (77.3)	1962 (76.1)
Ethnicity, n (%)			
Hispanic or Latino	145 (12.3)	180 (12.8)	325 (12.6)
Not Hispanic or Latino	1032 (87.7)	1221 (87.2)	2253 (87.4)
Race, n (%)			
White	1003 (85.2)	1176 (83.9)	2179 (84.5)
Non-white	174 (14.8)	225 (16.1)	399 (15.5)

LIF=lifitegrast; SD=standard deviation
Source: Module 5.3.5.3, Table 1.1.4

Adverse events

Approximately 60% of the patients treated with lifitegrast experienced adverse events, which was almost 2-fold as many patients as in the placebo group. Most AEs were categorised as mild or moderate AEs.

Table 22: Summary of Subjects with Treatment-emergent Adverse Events – All Dry Eye Studies Pool (Safety Population)

	Placebo N=1177 n (%)	All LIF N=1401 n (%)	All Subjects N=2578 n (%)
Subjects with at least 1 TEAE	**393 (33.4)**	**816 (58.2)**	**1209 (46.9)**
Ocular TEAEs	250 (21.2)	634 (45.3)	884 (34.3)
Mild	201 (17.1)	502 (35.8)	703 (27.3)
Moderate	44 (3.7)	118 (8.4)	162 (6.3)
Severe	5 (0.4)	14 (1.0)	19 (0.7)
Non-ocular TEAEs	213 (18.1)	439 (31.3)	652 (25.3)
Mild	118 (10.0)	269 (19.2)	387 (15.0)
Moderate	81 (6.9)	142 (10.1)	223 (8.7)
Severe	14 (1.2)	28 (2.0)	42 (1.6)
Subjects with possibly or probably drug-related TEAEs	**183 (15.5)**	**626 (44.7)**	**809 (31.4)**
Ocular TEAEs	169 (14.4)	545 (38.9)	714 (27.7)
Mild	135 (11.5)	433 (30.9)	568 (22.0)
Moderate	32 (2.7)	100 (7.1)	132 (5.1)
Severe	2 (0.2)	12 (0.9)	14 (0.5)
Non-ocular TEAEs	23 (2.0)	223 (15.9)	246 (9.5)
Mild	17 (1.4)	170 (12.1)	187 (7.3)
Moderate	5 (0.4)	49 (3.5)	54 (2.1)
Severe	1 (0.1)	4 (0.3)	5 (0.2)
Subjects prematurely withdrawn due to TEAEs	**31 (2.6)**	**95 (6.8)**	**126 (4.9)**
Ocular TEAEs	18 (1.5)	73 (5.2)	91 (3.5)
Non-ocular TEAEs	13 (1.1)	27 (1.9)	40 (1.6)
Subjects with serious TEAEs	**17 (1.4)**	**24 (1.7)**	**41 (1.6)**
Ocular TEAEs	0	0	0
Non-ocular TEAEs	17 (1.4)	24 (1.7)	41 (1.6)
Subjects with a TEAE resulting in death	**1 (0.1)**	**1 (0.1)**	**2 (0.1)**

Table 50 Adverse Drug Reactions from Clinical Trials with Lifitegrast

SOC/Adverse Drug Reaction	Lifitegrast 5% (N=1287) n (%)	Placebo (N=1177) n (%)
Nervous System Disorders[a]		
Headache	(2.3)	8 (0.7)
Eye Disorders[a]		
Eye irritation	228 (17.7)	43 (3.7)
Eye pain	151 (11.7)	33 (2.8)
Eye pruritus	64 (5.0)	22 (1.9)
Lacrimation increased	47 (3.7)	8 (0.7)
Vision blurred	38 (3.0)	12 (1.0)
Gastrointestinal Disorders		
Dysgeusia[b]	186 (14.5)	4 (0.3)
General Disorders and Administration Site Conditions		
Instillation site reactions	158 (12.3)	27 (2.3)

N = number of subjects; SOC = System Organ Class
[a] Some preferred terms were combined to capture similar medical concepts (ie, eye irritation and instillation site irritation; eye pain and instillation site pain; eye pruritus and instillation site pruritus; lacrimation increased and instillation site lacrimation; and headache and tension headache).
[b] Dysgeusia was reported under the SOC 'Nervous System Disorders' in the clinical studies. The SOC 'Gastrointestinal Disorders' is used for the Reference Safety Information, since the dysgeusia is due to the eye drop running down the tear duct into the mouth, so is more informative for the physician.
Source: Module 5.3.5.3 Table 1.3.1.3; Table 1.3.1.4

Common adverse events

The most common adverse events were related to installation of the ocular drops. Dysgeusia was the most common non-ocular adverse event.

Table 1: Summary of Subjects with Common (>5% of Subjects in Either Treatment Group) Treatment-emergent Adverse Events – All Dry Eye Studies Pool (Safety Population)

Preferred Term	**Placebo N=1177 n (%)**	**All LIF N=1401 n (%)**	**All Subjects N=2578 n (%)**
Ocular TEAEs			
Subjects with ≥1 ocular TEAE	250 (21.2)	634 (45.3)	884 (34.3)
Instillation site irritation	33 (2.8)	195 (13.9)	228 (8.8)
Instillation site reaction	27 (2.3)	158 (11.3)	185 (7.2)
Instillation site pain	25 (2.1)	147 (10.5)	172 (6.7)
Non-ocular TEAEs			
Subjects with ≥1 non-ocular TEAE	213 (18.1)	439 (31.3)	652 (25.3)
Dysgeusia	4 (0.3)	189 (13.5)	193 (7.5)

Table 1: Summary of Subjects with Common (>5% of Subjects in Either Treatment Group) Treatment-emergent Adverse Events – All Dry Eye Studies Pool (Safety Population)

Preferred Term	Placebo N=1177 n (%)	All LIF N=1401 n (%)	All Subjects N=2578 n (%)

AE=adverse event; LIF=lifitegrast; TEAE=treatment-emergent adverse event

Note: TEAEs are defined as AEs that occur after the start of randomised treatment or that worsen in severity compared to the pre-treatment state if the first onset of the AE is before the first treatment administration. Subjects are counted once per system organ class and once per preferred term; worst severity is used if a subject has multiple AEs of the same preferred term.

Source: Module 5.3.5.3, Table 1.3.1.1 and Table 1.3.1.2

Among all lifitegrast treated patients, 18% experienced at least one event of Eye or Installation site pain:

Table 53: Summary of Subjects with at Least 1 Event of Eye Irritation and/or Instillation Site Irritation – All Dry Eye Studies Pool, CAE Studies Pool, Non-CAE Studies Pool, 12-Week Dry Eye Studies Pool, and SONATA (Safety Population)

	Placebo		LIF 5.0%		LIF All Doses[a]	
	n	Eye Irritation/ Instillation Site Irritation n (%)	n	Eye Irritation / Instillation Site Irritation n (%)	n	Eye Irritation / Instillation Site Irritation n (%)
All Dry Eye Studies Pool	1177	42 (3.6)	1287	227 (17.6)	1401	229 (16.3)[a]
CAE Studies Pool	353	15 (4.2)	351	73 (20.8)	465	75 (16.1)
Non-CAE Studies Pool	713	21 (2.9)	716[b]	113 (15.8)	-	-
12-Week Dry Eye Studies Pool	1066	36 (3.4)	1067	186 (17.4)	1181	188 (15.9)
SONATA	111	6 (5.4)	220[b]	41 (18.6)	-	-

CAE=controlled adverse environment; LIF=lifitegrast
[a] All lifitegrast doses (0.1%, 1.0%, and 5.0%).
[b] Lifitegrast dose used was only 5.0%.
Source: Module 5.3.5.3, Table 1.5.1, Table 1.5.2, Table 1.5.3, Table 1.5.4, and Table 1.5.5

Other ocular-AEs were increased pruritus (5%) lacrimation (4%) and blurred vision (%):

Table 54: Summary of Subjects with at Least 1 Event of Eye Pruritus and/or Instillation Site Pruritus – All Dry Eye Studies Pool, CAE Studies Pool, Non-CAE Studies Pool, 12-Week Dry Eye Studies Pool, and SONATA (Safety Population)

	Placebo		LIF 5.0%		LIF All Doses[a]	
	n	Eye Pruritus/ Instillation Site Pruritus n (%)	n	Eye Pruritus / Instillation Site Pruritus n (%)	n	Eye Pruritus / Instillation Site Pruritus n (%)
All Dry Eye Studies Pool	1177	21 (1.8)	1287	64 (5.0)	1401	66 (4.7)[a]
CAE Studies Pool	353	8 (2.3)	351	26 (7.4)	465	28 (6.0)
Non-CAE Studies Pool	713	10 (1.4)	716[b]	25 (3.5)	-	-
12-Week Dry Eye Studies Pool	1066	18 (1.7)	1067	51 (4.8)	1181	53 (4.5)
SONATA	111	3 (2.7)	220[b]	13 (5.9)	-	-

CAE=controlled adverse environment; LIF=lifitegrast

[a] All lifitegrast doses (0.1%, 1.0%, and 5.0%).

[b] Lifitegrast dose used was only 5.0%.

Source: Module 5.3.5.3, Table 1.5.1, Table 1.5.2, Table 1.5.3, Table 1.5.4, and Table 1.5.5

Table 51: Summary of Subjects with at Least 1 Event of Vision Blurred – All Dry Eye Studies Pool, CAE Studies Pool, Non-CAE Studies Pool, 12-Week Dry Eye Studies Pool, and SONATA (Safety Population)

	Placebo		LIF 5.0%		LIF All Doses[a]	
	n	Vision Blurred n (%)	n	Vision Blurred n (%)	n	Vision Blurred n (%)
All Dry Eye Studies Pool	1177	12 (1.0)	1287	38 (3.0)	1401	41 (2.9)[a]
CAE Studies Pool	353	4 (1.1)	351	11 (3.1)	465	14 (3.0)
Non-CAE Studies Pool	713	4 (0.6)	716[b]	18 (2.5)	-	-
12-Week Dry Eye Studies Pool	1066	8 (0.8)	1067	29 (2.7)	1181	32 (2.7)
SONATA	111	4 (3.6)	220[b]	9 (4.1)	-	-

CAE=controlled adverse environment; LIF=lifitegrast

[a] All lifitegrast doses (0.1%, 1.0%, and 5.0%).

[b] Lifitegrast dose used was only 5.0%.

Source: Module 5.3.5.3, Table 1.5.1, Table 1.5.2, Table 1.5.3, Table 1.5.4, and Table 1.5.5

Table 55: Summary of Subjects with at Least 1 Event of Lacrimation Increased and/or Instillation Site Lacrimation – All Dry Eye Studies Pool, CAE Studies Pool, Non-CAE Studies Pool, 12-Week Dry Eye Studies Pool, and SONATA (Safety Population)

	Placebo		LIF 5.0%		LIF All Doses[a]	
	n	Lacrimation Increased/ Instillation Site Lacrimation n (%)	n	Lacrimation Increased/ Instillation Site Lacrimation n (%)	n	Lacrimation Increased/ Instillation Site Lacrimation n (%)
All Dry Eye Studies Pool	1177	8 (0.7)	1287	46 (3.6)	1401	48 (3.4)[a]
CAE Studies Pool	353	2 (0.6)	351	16 (4.6)	465	18 (3.9)
Non-CAE Studies Pool	713	3 (0.4)	716[b]	19 (2.7)	-	-
12-Week Dry Eye Studies Pool	1066	5 (0.5)	1067	35 (3.3)	1181	37 (3.1)
SONATA	111	3 (2.7)	220[b]	11 (5.0)	-	-

CAE=controlled adverse environment; LIF=lifitegrast
[a] All lifitegrast doses (0.1%, 1.0%, and 5.0%).
[b] Lifitegrast dose used was only 5.0%.
Source: Module 5.3.5.3, Table 1.5.1, Table 1.5.2, Table 1.5.3, Table 1.5.4, and Table 1.5.5

Controlled adverse environment (CAE) vs. Non-CAE pool

Controlled adverse environment is an established "enrichment strategy" used worldwide for ophthalmic drug development that helps select subjects who develop worsening ocular surface signs and ocular discomfort in response to standardized desiccating environmental conditions. Overall, a higher percentage of subjects had ocular TEAEs in the CAE Studies Pool (43.2%) than the Non-CAE Studies Pool (26.9%), likely due to the CAE.

CAE Studies (Phase 2 and OPUS-1):

Ocular: As noted above, CAE studies intentionally exacerbate the signs and symptoms of DED. The most common (>5% of subjects in either treatment group) ocular TEAEs in the CAE Studies Pool were related to instillation (instillation site irritation [placebo: 3.4%; lifitegrast 5.0%:19.7%], instillation site pain [placebo: 5.7%; lifitegrast 5.0%:28.5%], instillation site pruritus [placebo: 1.7%; lifitegrast 5.0%:6.0%], and instillation site reaction [placebo: 0.6%; lifitegrast 5.0%:16.8%]). The common instillation site TEAEs occurred at a higher frequency in the CAE Studies Pool than in the non-CAE Studies Pool. Reduced visual acuity (placebo: 5.1%; lifitegrast 5%: 4.3%), which was defined per protocol as change from baseline in visual acuity of ≥0.22 logMAR, was also a common ocular TEAE in CAE studies.

Non-ocular: In the CAE Studies Pool, the most common (>5% of subjects in either treatment group) non-ocular TEAEs were nasopharyngitis and dysgeusia. Nasopharyngitis occurred at a similar percentage in both treatment groups (placebo: 7.9%; lifitegrast 5.0%: 6.0%), whereas dysgeusia occurred at a higher percentage in the lifitegrast 5.0% group (13.1%) than the placebo group (0%).

The non-CAE studies represent a naturalistic environment.

Ocular: The most common (>5% of subjects in either treatment group) ocular TEAEs in the Non-CAE Studies Pool were mostly related to instillation (instillation site irritation [placebo: 2.2%; lifitegrast 5%: 13.0%] and instillation site reaction [placebo: 3.2%; lifitegrast 5%: 9.8%]).

Non-ocular: In the Non-CAE Studies Pool, the most common (>5% of subjects in either treatment group) non-ocular TEAE was dysgeusia. Similar to the CAE Studies Pool, dysgeusia occurred at a higher

percentage in the lifitegrast 5.0% group (14.5%) than the placebo group (0.3%). In the lifitegrast 5.0% group, dysgeusia occurred at a similar percentage in the CAE Studies Pool (13.1%) and Non-CAE Studies Pool (14.5%). Each of the events that were considered to be common in the CAE Studies Pool and Non-CAE Studies Pool, occurred at a greater frequency in the lifitegrast 5.0% group than in the placebo group, with the exception of visual acuity reduced, which had a greater frequency in the placebo group.

Adverse events specifically related to ocular inflammation

The frequency of infectious ocular AEs was similar between lifitegrast- and placebo-treated.subjects across the development program, with even a small trend to a higher rate in placebo treated patients (Table 7-2). However, ocular AEs of a non-infectious nature were generally higher in lifitegrast-treated versus placebo-treated subjects.

Table 7-2 Summary of Subjects with ocular inflammations differentiated between infectious and non-infectious

	Infectious				Non-infectious			
	Placebo		LIF 5%		Placebo		LIF 5%	
	n	HLGT n (%)	n	HLGT n (%)	n	HLGT n (%)	n	HLGT n (%)
Phase 2, OPUS-1, OPUS-2, OPUS-3	1066	7 (0.7)	1067	4 (0.4)	1066	44 (4.1)	1067	95 (8.9)
SONATA	111	3 (2.7)	220	1 (0.5)	111	14 (12.6)	220	32 (14.5)
Pooled All Safety	1177	10 (0.8)	1287	5 (0.4)	1177	58 (4.9)	1287	127 (9.9)

The difference in non-infectious ocular AEs was driven by eye irritations, eye pruritus and Hyperemia.

Serious adverse events and deaths

Deaths

There were 2 deaths reported during the clinical studies with lifitegrast. One death (cardiac arrest) occurred in the lifitegrast 1.0% group of the Phase 2 dry eye and another death (arrhythmia) in the placebo group of the SONATA study. Both death were not regarded related to the study group.

Serious adverse events

Whilst the incidence of serious TEAE in the lifitegrast group is higher in the long-term SONATA study compared to the 12 week studies pool (4.1% v 1.1%) the incidence is comparatively increased in the placebo group (5.4% v 1.0%). Review of the SOC and PT listing reflected serious, non-ocular AE consistent with the medical profile of the age group studied, as did the 2 deaths reported. No ocular serious TEAE were reported in either 12 week or 1 year studies. No serious TEAEs in SONATA were considered causally related to lifitegrast.

The serious adverse events are summarised for the 12-weeks studies (12-Week Dry Eye Studies Pool) and for the long term (SONATA) study below:

Table 41: Summary of Subjects with Serious Treatment-emergent Adverse Events – 12-Week Dry Eye Studies Pool (Safety Population)

System Organ Class Preferred Term	Placebo N=1066 n (%)	LIF 5.0% N=1067 n (%)	All Subjects N=2133 n (%)
Subjects with at least 1 serious TEAE	11 (1.0)	12 (1.1)	23 (1.1)
Ear and labyrinth disorder	0	1 (<0.1)	1 (<0.1)
Vertigo	0	1 (<0.1)	1 (<0.1)
Endocrine disorder	0	1 (<0.1)	1 (<0.1)
Thyrotoxic crisis	0	1 (<0.1)	1 (<0.1)
Gastrointestinal disorders	1 (<0.1)	1 (<0.1)	2 (<0.1)
Abdominal pain upper	0	1 (<0.1)	1 (<0.1)
Colitis ischaemic	1 (<0.1)	0	1 (<0.1)
General disorders and administration site conditions	0	1 (<0.1)	1 (<0.1)
Non-cardiac chest pain	0	1 (<0.1)	1 (<0.1)
Infections and infestations	0	2 (0.2)	2 (<0.1)
Infectious peritonitis	0	1 (<0.1)	1 (<0.1)
Pneumonia	0	1 (<0.1)	1 (<0.1)
Injury, poisoning, and procedural complications	1 (<0.1)	1 (<0.1)	2 (<0.1)
Humerus fracture	0	1 (<0.1)	1 (<0.1)
Periprosthetic fracture	1 (<0.1)	0	1 (<0.1)
Musculoskeletal and connective tissue disorders	3 (0.3)	0	3 (0.1)
Intervertebral disc protrusion	1 (<0.1)	0	1 (<0.1)
Lower limb fracture	1 (<0.1)	0	1 (<0.1)
Osteoarthritis	1 (<0.1)	0	1 (<0.1)
Neoplasms benign, malignant, and unspecified (includes cysts and polyps)	3 (0.3)	1 (<0.1)	4 (0.2)
Renal cancer	0	1 (<0.1)	1 (<0.1)
Basal cell carcinoma	1 (<0.1)	0	1 (<0.1)
Bladder cancer	1 (<0.1)	0	1 (<0.1)
Prostate cancer	1 (<0.1)	0	1 (<0.1)
Nervous system disorders	1 (<0.1)	3 (0.3)	4 (0.2)
Cerebrovascular accident	1 (<0.1)	1 (<0.1)	2 (<0.1)
Presyncope	0	1 (<0.1)	1 (<0.1)
Transient ischaemic attack	0	1 (<0.1)	1 (<0.1)
Respiratory, thoracic, and mediastinal disorders	1 (<0.1)	1 (<0.1)	2 (<0.1)
Lung neoplasm malignant	0	1 (<0.1)	1 (<0.1)
Asthma	1 (<0.1)	0	1 (<0.1)
Vascular disorders	1 (<0.1)	0	1 (<0.1)
Accelerated hypertension	1 (<0.1)	0	1 (<0.1)

AE=adverse event; LIF=lifitegrast; TEAE=treatment-emergent adverse event

Note: TEAEs are defined as AEs that occur after the start of randomized treatment or that worsen in severity compared to the pre-treatment state if the first onset of the AE is before the first treatment administration. Subjects are counted once per system organ class and once per preferred term; worst severity is used if a subject has multiple AEs of the same preferred term.

Source: Module 5.3.5.3, Table 1.3.5

Table 2: Subjects with Serious Treatment-emergent Adverse Events – SONATA Study (Safety Population)

Preferred Term	Placebo N=111 n (%)	LIF 5.0% N=220 n (%)	All Subjects N=331 n (%)
Subjects with at least 1 serious TEAE	6 (5.4)	9 (4.1)	15 (4.5)
Back pain	0	1 (0.5)	1 (0.3)
Intervertebral disc protrusion	1 (0.9)	0	1 (0.3)
Osteoarthritis	0	1 (0.5)	1 (0.3)
Rheumatoid arthritis	0	1 (0.5)	1 (0.3)
Arrhythmia	1 (0.9)	0	1 (0.3)
Atrioventricular block	0	1 (0.5)	1 (0.3)
Myocardial infarction	0	1 (0.5)	1 (0.3)
Hip fracture	0	1 (0.5)	1 (0.3)
Spinal fracture	1 (0.9)	0	1 (0.3)
Chronic obstructive pulmonary disease	2 (1.8)	0	2 (0.6)
Chest pain	1 (0.9)	0	1 (0.3)
Pneumonia	0	1 (0.5)	1 (0.3)
Urinary tract infection	0	1 (0.5)	1 (0.3)
Colonic polyp	0	1 (0.5)	1 (0.3)
Syncope	0	1 (0.5)	1 (0.3)
Dysmenorrhoea	0	1 (0.5)	1 (0.3)
Transient ischaemic attack	0	1 (0.5)	1 (0.3)

LIF=lifitegrast; TEAE=treatment-emergent adverse event

Source: SONATA Clinical Study Report, Table 4.4.2

Laboratory findings

Clinical laboratory evaluations were conducted only in the Phase 1 study and as part of a sub-study in the SONATA study. During the Phase 1 (healthy volunteer) and SONATA studies, the changes in clinical chemistry, haematology, and urinalysis results, lymphocyte counts, and corneal endothelial cell counts (SONATA only) were minimal and similar between treatment groups. There was no evidence of lymphocyte or neutrophil suppression (refer to Section 10.4 of the Phase 1 CSR and to Section 10.6, Section 10.8.7, and Section 10.8.8 of the SONATA CSR).

Vital Signs

Vital signs were only collected during the Phase 1 study. There were no clinically meaningful changes from baseline in vital signs during the study. Refer to Section 10.5.1 of the Phase 1 CSR for a full summary of vital sign results.

Physical Examination Findings

Physical examination findings were only collected during the Phase 1 study. No clinically meaningful changes from baseline in physical examination findings were observed during the study. Refer to Appendix 16.2.4.2.1, Appendix 16.2.4.2.2, and Appendix 16.2.4.2.3 of the Phase 1 CSR for a full summary of physical examination results.

Electrocardiograms

Electrocardiograms were only performed in the Phase 1 study. No clinically meaningful changes from baseline in electrocardiogram results were observed during the study. Refer to Section 10.5.2 of the Phase 1 CSR for a full summary of electrocardiogram results.

Slit Lamp Biomicroscopy

Slit lamp biomicroscopy results were graded as normal or abnormal (clinically significant or not clinically significant) in the Phase 2 allergic conjunctivitis, Phase 2 dry eye, OPUS-1, OPUS-2, OPUS-3, and SONATA studies.

In the Phase 2 allergic conjunctivitis study, 2 subjects (both lifitegrast 5.0% group) had clinically significant slit lamp biomicroscopy results. In the Phase 2 dry eye study, no subject had clinically significant slit lamp biomicroscopy results. In the OPUS-1 study, 3 subjects (lifitegrast 5.0%: 1 subject; placebo: 2 subjects) had clinically significant slit lamp biomicroscopy results. In the OPUS-2 study, 17 subjects (lifitegrast 5.0%: 11 subjects; placebo: 6 subjects) had clinically significant slit lamp biomicroscopy results. In the OPUS-3 study, 15 subjects (lifitegrast 5.0%: 9 subjects; placebo: 6 subjects) had clinically significant slit lamp biomicroscopy results, per the investigator's discretion. In the SONATA study, 23 subjects (lifitegrast 5.0%: 15/220 subjects [6.8%]; placebo: 9/111 subjects [8.1%]) had clinically significant slit lamp biomicroscopy results.

Safety in special populations

Safety was not assessed in all special populations. The safety population contained predominantly older, female, white subjects. Analysis of safety by age-group, gender and race has raised other concerns. Pregnant and breast-feeding females and children were excluded from the studies. There was one pregnancy in the clinical studies (in a subject allocated to placebo).

Below, the exposure according to age, gender, and race is summarised:

Age and Gender

Table 8. Summary of Exposure by Age and Sex for All Dry Eye Studies (Safety Population)			
Total Exposure in Person Years[1]	**Vehicle (N=1177) n (years)**	**All Lifitegrast* (N=1401) n (years)**	**All Subjects (N=2578) n (years)**
<65 Years			
All	731 (203.49)	901 (294.21)	1632 (497.70)
Male	172 (45.00)	183 (62.57)	355 (107.56)
Female	559 (158.50)	718 (231.64)	1277 (390.14)
≥65 Years			
All	445 (128.66)	495 (146.21)	940 (274.87)
Male	125 (35.69)	133 (40.33)	258 (76.02)
Female	320 (92.97)	362 (105.88)	682 (198.85)
<75 Years			
All	1031 (288.94)	1213 (392.50)	2244 (681.44)
Male	259 (69.98)	260 (87.63)	519 (157.62)
Female	772 (218.96)	953 (304.86)	1725 (523.82)
≥75 Years			
All	145 (43.21)	183 (47.92)	328 (91.13)
Male	38 (10.70)	56 (15.26)	94 (25.96)
Female	107 (32.51)	127 (32.66)	234 (65.17)

Race

Table 10. Summary of Exposure to lifitegrast by Race for All Dry Eye Studies (Safety Population)			
Total Exposure in Person Years[1]	**Vehicle (N=1177) n (years)**	**All Lifitegrast (N=1401) n (years)**	**All Subjects (N=2578) n (years)**
Ethnic/Racial Origin			
White	1002 (282.64)	1176 (367.78)	2173 (650.42)
Black or African American	109 (30.81)	128 (42.88)	237 (73.69)
Native Hawaiian or Other Pacific Islander	4 (0.88)	6 (2.91)	10 (3.78)
Asian	46 (14.48)	64 (20.76)	110 (35.24)
American Indian or Alaskan Native	4 (0.94)	8 (1.88)	12 (2.81)
Other	11 (2.41)	19 (4.22)	30 (6.63)

[1] Total exposure in person years=sum of days of exposure across all subjects/365.25.

Renal or hepatic impairment, paediatric population

N/A

Immunological events

One case of hypersensitivity was identified during the RCTs. From post-marketing experience, the following was identified:

An analysis of post marketing case reports was performed of all worldwide safety data relating to hypersensitivity (using MedDRA version 19.1 for *Hypersensitivity* Standard MedDRA Query (SMQ) *Narrow*) in patients treated with lifitegrast through to 07 Feb 2017, within the Shire Global Safety System (SGSS) database. A total of 187 patients had case reports that were retrieved from the post-marketing database with this Hypersensitivity search. (One duplicate report for one patient was noted and reconciled). The 187 case reports from this Hypersensitivity search included 221 events. There were 8 case reports that were assessed as serious. Five of these 8 serious case reports contained sufficient information to assess causality as plausible to lifitegrast. These serious case reports were medically confirmed.

Safety related to drug-drug interactions and other interactions

No data have been presented. Please also refer to the PK/PD-section

Discontinuation due to AES

During the 12-week studies: A total of 2.6% of subjects in the placebo group and 6.8% of subjects in the lifitegrast group had TEAEs that led to treatment discontinuation.

During the 1-year SONATA study: A total of 8.1% of subjects in the placebo group and 12.2% of subjects in the lifitegrast group had TEAEs that led to treatment discontinuation.

Table 46: Summary of Subjects with Treatment-emergent Adverse Events Leading to Discontinuation of Investigational Product – 12-Week Dry Eye Studies Pool (Safety Population)

System Organ Class Preferred Term	Placebo N=1066 n (%)	LIF 5.0% N=1067 n (%)	All Subjects N=2133 n (%)
Subjects with ≥1 TEAE leading to discontinuation of investigational product	20 (1.9)	61 (5.7)	81 (3.8)
Eye disorders	10 (0.9)	33 (3.1)	43 (2.0)
Eye irritation	0	7 (0.7)	7 (0.3)
Eye pain	1 (<0.1)	6 (0.6)	7 (0.3)
Lacrimation increased	0	4 (0.4)	4 (0.2)
Ocular hyperaemia	1 (<0.1)	4 (0.4)	5 (0.2)
Photophobia	0	4 (0.4)	4 (0.2)
Visual acuity reduced	0	4 (0.4)	4 (0.2)
Blepharitis	0	3 (0.3)	3 (0.1)
Conjunctival hyperaemia	0	3 (0.3)	3 (0.1)
Vision blurred	0	3 (0.3)	3 (0.1)
Dry eye	1 (<0.1)	2 (0.2)	3 (0.1)
Conjunctivitis allergic	0	1 (<0.1)	1 (<0.1)
Corneal erosion	1 (<0.1)	1 (<0.1)	2 (<0.1)
Corneal infiltrates	1 (<0.1)	1 (<0.1)	2 (<0.1)
Corneal oedema	0	1 (<0.1)	1 (<0.1)
Erythema of eyelid	0	1 (<0.1)	1 (<0.1)
Eye pruritus	0	1 (<0.1)	1 (<0.1)
Eyelid irritation	0	1 (<0.1)	1 (<0.1)
Foreign body in eye	0	1 (<0.1)	1 (<0.1)
Punctate keratitis	1 (<0.1)	1 (<0.1)	2 (<0.1)
Retinal tear	0	1 (<0.1)	1 (<0.1)
Vitreous haemorrhage	0	1 (<0.1)	1 (<0.1)
Conjunctivitis	1 (<0.1)	0	1 (<0.1)
Herpes simplex ophthalmic	1 (<0.1)	0	1 (<0.1)
Retinal vein occlusion	1 (<0.1)	0	1 (<0.1)
Ulcerative keratitis	1 (<0.1)	0	1 (<0.1)
Gastrointestinal disorders	0	2 (0.2)	2 (<0.1)
Abdominal pain upper	0	1 (<0.1)	1 (<0.1)
Diarrhoea	0	1 (<0.1)	1 (<0.1)
General disorders and administration site conditions	2 (0.2)	22 (2.1)	24 (1.1)
Instillation site irritation	0	11 (1.0)	11 (0.5)
Instillation site reaction	2 (0.2)	8 (0.7)	10 (0.5)
Instillation site pain	0	6 (0.6)	6 (0.3)

Table 47: Subjects with Treatment-emergent Adverse Events Leading to Discontinuation – SONATA Study (Safety Population)

System Organ Class Preferred Term	Placebo N=111 n (%)	LIF 5.0% N=220 n (%)	All Subjects N=331 n (%)
Subjects with at least 1 TEAE leading to discontinuation	10 (9.0)	27 (12.3)	37 (11.2)
Ocular TEAEs			
Subjects with at least 1 ocular TEAE leading to discontinuation	6 (5.4)	18 (8.2)	24 (7.3)
Eye disorders	4 (3.6)	11 (5.0)	15 (4.5)
Lacrimation increased	1 (0.9)	3 (1.4)	4 (1.2)
Vision blurred	1 (0.9)	2 (0.9)	3 (0.9)
Visual acuity reduced	0	3 (1.4)	3 (0.9)
Amaurosis	1 (0.9)	0	1 (0.3)
Conjunctivitis allergic	0	1 (0.5)	1 (0.3)
Corneal dystrophy	0	1 (0.5)	1 (0.3)
Corneal erosion	0	1 (0.5)	1 (0.3)
Dry eye	1 (0.9)	0	1 (0.3)
Eye pruritus	0	1 (0.5)	1 (0.3)
Foreign body sensation in eyes	0	1 (0.5)	1 (0.3)
Ocular hyperaemia	0	1 (0.5)	1 (0.3)
Punctate keratitis	0	1 (0.5)	1 (0.3)
General disorders and administration site conditions	2 (1.8)	7 (3.2)	9 (2.7)
Instillation site irritation	2 (1.8)	2 (0.9)	4 (1.2)
Instillation site reaction	0	4 (1.8)	4 (1.2)
Instillation site pain	1 (0.9)	2 (0.9)	3 (0.9)
Instillation site lacrimation	1 (0.9)	0	1 (0.3)
Non-ocular TEAEs			
Subjects with at least 1 non-ocular TEAE leading to discontinuation	4 (3.6)	9 (4.1)	13 (3.9)
Nervous system disorders	0	6 (2.7)	6 (1.8)
Dysgeusia	0	4 (1.8)	4 (1.2)
Headache	0	1 (0.5)	1 (0.3)
Neuropathy peripheral	0	1 (0.5)	1 (0.3)
Musculoskeletal and connective tissue disorders	2 (1.8)	0	2 (0.6)
Back pain	1 (0.9)	0	1 (0.3)
Intervertebral disc protrusion	1 (0.9)	0	1 (0.3)
Respiratory, thoracic, and mediastinal disorders	1 (0.9)	1 (0.5)	2 (0.6)
Epistaxis	1 (0.9)	0	1 (0.3)
Pulmonary fibrosis	0	1 (0.5)	1 (0.3)

Dysgeusia

Dysgeusia occurred in a higher percentage of subjects in the lifitegrast 5.0% group (13.1-16.4%) than in the placebo group (0-1.8%) in the All Dry Eye Studies Pool, CAE Studies Pool, Non- CAE Studies Pool, 12-Week Dry Eye Studies Pool, and SONATA.

In the lifitegrast 5.0% group, 2 subjects (0.2%) and 4 subjects (1.8%) in the 12-Week Dry Eye Studies Pool and SONATA, respectively, were withdrawn from treatment due to a TEAE of dysgeusia.

Post marketing experience

Presented post-marketing experience relates to hypersensitivity reactions. Please refer to the section of immunological events.

3.3.9. Discussion on clinical safety

Overall, 1401 subjects have been exposed to lifitegrast in the phase 2 and 3 studies in the proposed indication, DED. Of these, 1287 patients were exposed to the proposed 5% formulation of lifitegrast consisting of 1067 patients in the 12-week studies (phase 2 + OPUS1-3) and 220 patients in the 1-year SONATA study. Exposure to the 5% formulation for more than a year was obtained for 170 patients.

The EMA guideline CHMP/ICH/375/95 recommend 300-600 patients to be exposed for six months and 100 patients to be exposed for 12 months. However, since the frequency of AEs was low, the AEs mainly occurred in relation to installation of the eye drops, and there were no differences in frequency of AEs between the 12-week studies and the 1-year study, the exposure of mainly 12-weeks appears sufficient. Further, a phase 1 study of healthy volunteers, 20 subjects, and a phase 2 study in allergic conjunctivitis, 45 subjects, provide supportive data. According to the fourth PSUR for XIIDRA, the estimated patient exposure to lifitegrast worldwide, based on marketing data was 154,295 person-years cumulatively since product launch up to 10 JUL 2018.

The safety population data presented fulfils requirements.

Discontinuations

In the 12-week studies, 6% of the patients in the lifitegrast group discontinued as compared to 2% in the placebo group. In the 1-year SONATA study, 12% of the patients in the lifitegrast group discontinued as compared to 9% in the placebo group. The causes of discontinuations were similar in 1-year study and the 12-week studies, thus, not indicating a deterioration of the safety profile. Patients younger than 65 years appeared to have a lower rate of discontinuations (4%) than patients in older age groups (7-12%)~~.~~. The majority of the patients discontinued due to 'Eye pain/irritation', while 'Installation site irritation/reaction/pain' accounted for most of the remaining discontinuations. Non-ocular reasons for discontinuation comprised dysgeusia and other concomitant diseases not related to DED or lifitegrast. Two patients died during the RTCs, one in the placebo group and one in the lifitegrast group, the deaths were not related to DED or lifitegrast.

Adverse events

Installation site irritation occurred in 14% of lifitegrast patients as compared to 3% of the placebo patients. Similarly, installation site reaction and installation site irritation both occurred in 11 % of lifitegrast patients as compared to 2% of the placebo patients. Less common ocular events comprised 'blurred vision', 3% lifitegrast group vs. 1% placebo group, and 'increased lacrimation', 4% lifitegrast group vs. 1% placebo group. The severity of the ocular adverse events was most often reported to be of mild to moderate severity, however, in 11 subjects severe ocular adverse events occurred. Noteworthy, the risk of ocular infections seemed not to be increased in the lifitegrast group as compared to the placebo group. However, as there are insufficient data on concomitant use of lifitegrast and other topical treatments with an immune-depressant effect, the Applicant is requested to convey this information to the treating physicians in section 4.4 of the SmPC (**OC**).

The most common non-ocular adverse event was Dysgeusia occurring in 14% of the lifitegrast patients as compared to 0% in the placebo patients. Dysgeusia mainly occurred in younger individuals; <65 years

s 17%, 65-74 years 9%, 75-84 years 6%, and 85+ years 0%. Other non-ocular adverse events comprised gastrointestinal events, which a more than double frequency in the lifitegrast group (3%) than in the placebo group (1%). The gastrointestinal events included nausea, vomiting, gastrooesophageal reflux, upper abdominal pain and discomfort, which together occurred in approx. 1% of the population but did not seem to influence the use of lifitegrast. The majority of the adverse events were intermittent in nature, i.e. they occurred only in relation to instillation of the study product and resolved shortly afterwards.

There were 11 post-marketing case reports with serious events clinically consistent with hypersensitivity that were plausibly related to lifitegrast. There were no cases of hypersensitivity to lifitegrast in the clinical development programme. However, the risk of hypersensitivity is addressed in section 4.4 of the SmPC.

Of note, the longest follow-up was 12 months in 170 patients during the SONATA-study, hence, not allowing for assessment of possible long-term risk of new malignancies. The LFA-ICAM binding is necessary for T-cell activation. Continuous Lifitegrast treatment is assumed to inhibit surveillance and possibly destruction of malignant cells in the eye. Therefore, peri-ocular skin cancer, conjunctival and corneal neoplasia were proposed by the Agency to be included as important potential risks in the RMP.

There were no age, gender, or race dependent patterns in the occurrence of adverse events. Further, there were no differences between the lifitegrast groups and the placebo group with respect to clinical laboratory evaluations, vital signs, or physical examination.

Important limitations

Noteworthy, the RCTs providing data for the current application excluded patients, who had had LASIK or similar types of surgery within the last year or YAG laser capsulotomy Therefore, the safety profile of lifitegrast in patients with 'recent' surgery remain unknown and is included as missing information in the RMP.

3.3.10. Conclusions on clinical safety

The was a sufficient exposure to lifitegrast to enable evaluation of the safety profile: Overall, 1401 subjects have been exposed to lifitegrast, of whom 1067 patients were exposed for 12 weeks and 170 patients were exposed for more than a year. The adverse events comprise mainly eye and installation site reactions/pain/pruritus, most being of mild to moderate severity. The most common non-ocular adverse event was dysgeusia. However, both ocular AEs and dysgeusia diminished over 3-9 months of treatment. Clinically significant hypersensitivity to lifitegrast is known from post-marketing experience and addressed in the SmPC.

In terms of safety, there are no major objections precluding a positive risk benefit assessment. However, two other concerns have to be adequately addressed before a final conclusion on the safety of lifitegrast can be reached.

3.4. Risk management plan

3.4.1. Safety Specification

Summary of safety concerns

The Applicant proposed the following summary of safety concerns in the RMP dated the 05 February 2020:

Table 9-1 Table Part II SVIII.1: Summary of safety concerns

Important identified risks	• None
Important potential risks	• Peri-ocular skin cancer, conjunctival or corneal neoplasia • Reactivation or increased severity of ocular infections
Missing information	• Use in patients with active ocular herpes or history of ocular herpes • Use in patients with YAG posterior capsulotomy within 6 months of starting lifitegrast • Use in patients with ocular surgery (other than YAG posterior capsulotomy), including LASIK, within 12 months of starting lifitegrast • Use in patients with an active ocular infection • Use in patients with immunodeficiency

3.4.2. Discussion on safety specification

During the RCTs patients with a number of previous or ongoing eye conditions as well as chronic illnesses were excluded. Among the exclusion criteria were previous LASIK or similar types of surgery within the last year, (2), previous YAG laser capsulotomy, (3) other 'active ocular conditions', (4) and ocular herpes or a history of ocular herpes, Hereby, the Applicant has excluded a considerable part of the expected target-population and the safety profile of lifitegrast in these subgroups is considered unknown. Therefore, it is understood that the Applicant has included previous LASIK or similar types of surgery within the last year and previous YAG laser capsulotomy as missing information.

The Applicant has included patients with active ocular herpes as missing information. This is disagreed, since active ocular infection, including herpes infection, is a contraindication for use. Therefore, the "active ocular infection" should be removed as missing information (**OC**). However, it is agreed to include "history of ocular herpes" in the RMP as missing information.

Since lifitegrast inhibits the LFA-ICAM binding, the recruitment and activation of T-cells are inhibited. This may decrease the clearance of new malignant cells in case such cells should evolve. The longest follow-up on lifitegrast treatment was 1 year for patients included in the 1-year SONATA study. A possibly increased risk of new malignancies would not be detected within this time frame. Therefore, it is agreed to include "risk of new malignancies, such as peri-ocular skin cancer, conjunctival or corneal neoplasia", as an important potential risk in the RMP. Patients with immunodeficiency were excluded from the clinical trials, therefore it is agreed to include 'use in patients with immunodeficiency' as missing information.

3.4.3. Conclusions on the safety specification

Having considered the data in the safety specification it is considered that the following issues should be addressed:

"Active ocular infection" should be removed as missing information. **(OC)**

3.4.4. Pharmacovigilance plan

Routine pharmacovigilance activities including a specific adverse events follow-up questionnaire for the important potential risk of 'Peri-ocular skin cancer, conjunctival or corneal neoplasia' are proposed by the Applicant.

The MAH does not propose any additional PhV activities for the medicinal product.

In the last round, the CHMP requested the Applicant to include peri-ocular skin cancer, conjunctival or corneal neoplasia in the RMP as an important potential risk and in this remit, the Applicant was requested to discuss capability and appropriateness of available data sources in the EU to further characterise peri-ocular skin cancer, conjunctival or corneal neoplasia. The Applicant was requested to submit a review of the available data sources and justify which of these databases are considered suitable. The Applicant was requested to submit within 3 months from the marketing authorisation, a feasibility study which should include: a review of all the available data sources together with its suitability for this study, the study design options (case-control study or other types of pharmacoepidemiological studies), a sample size estimation including the assumptions used to reach the study size estimation and the calculations conducted, duration or length of follow-up, analytical methods, and evaluate capabilities of linkage between data sources.

The assessment of the preliminary feasibility assessment report addressed at the evaluation of the risk of periocular / eye surface neoplasia lead to the conclusion that the study does not seem feasible in view of the results provided by Applicant. The expected low incidence of eyelid malignancy and eye surface neoplasia in Europe altogether with the long (many years) for follow-up in order to detect the risk lead to very large sample size estimation. In addition, it is acknowledged that the dry eye syndrome may share common risk factors with the ocular neoplasia, therefore leading to confusion by indication. The Applicant also discussed the use of the main data sources in Europe used for pharmacoepidemiological research and their conclusion was that even if the databases were linked to obtain the outcome of interest, it could lead to unavailable or incomplete results. The assessor agrees on the Applicant's conclusion that the issue can be further characterised with routine Pharmacovigilance activities, including specific follow-up questionnaires. A proposal has been included in the RMP (v1.2) Annex 4. The review of the proposed questionnaire seems to be appropriate to collect the information in order to assess the causality.

Overall conclusion:

The PRAC Rapporteur, having considered the data submitted, is of the opinion that the proposed post-authorisation PhV development plan is sufficient to identify and characterise the risks of the product, at this stage.

PhV activities are subject to final CHMP conclusions of the summary of safety concerns.

The PRAC Rapporteur also considered that routine PhV remain sufficient to monitor the effectiveness of the risk minimisation measures.

3.4.5. Risk minimisation measures

3.4.5.1. Routine Risk Minimisation Measures

Table Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimization measures	Pharmacovigilance activities
Important Identified Risks		
None		
Important Potential Risks		

Safety concern	Risk minimization measures	Pharmacovigilance activities
Peri-ocular skin cancer, conjunctival or corneal neoplasia	**Routine risk minimization measures:** None **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Targeted follow-up using targeted checklist. **Additional pharmacovigilance activities:** None
Reactivation or increased severity of ocular infections	**Routine risk minimization measures:** None **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Missing Information		
Use in patients with active ocular herpes or history of herpes	**Routine risk minimization measures:** SmPC: Section 4.4 PL: Section 2 **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Use in patients with YAG posterior capsulotomy within 6 months of starting lifitegrast	**Routine risk minimization measures:** None **Additional risk minimization measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Use in patients with ocular surgery (other than YAG posterior capsulotomy), including LASIK, within 12 months of starting lifitegrast.	**Routine risk minimization measures:** None **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Use in patients with an active ocular infection	**Routine risk minimization measures:** SmPC Section 4.3 and Section 4.4. PL Section 2 **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Use in patients with immunodeficiency	**Routine risk minimization measures:** None **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None

Safety concern	Risk minimization measures	Pharmacovigilance activities
		Additional pharmacovigilance activities: None

The Applicant has updated the risk minimization measures based on the proposed summary of safety concerns.

3.4.5.2. Additional Risk Minimisation Measures

There are no additional risk minimisation measures proposed by the MAH. This is acceptable at this stage.

Overall conclusions on risk minimisation measures

The PRAC Rapporteur having considered the data submitted was of the opinion that the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication.

3.4.6. Conclusion on the RMP

The CHMP and PRAC considered that the risk management plan version 1.2 could be acceptable if the Applicant implements the changes to the RMP as detailed in the endorsed Rapporteur assessment report and in the 2nd list of outstanding issues in section 5.4.

The relevant sections of the RMP may need to be amended in line with the final agreed list of safety concerns.

The public summary of the RMP may require revision.

3.5. Pharmacovigilance system

It is considered that the pharmacovigilance system summary submitted by the Applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The active substance is not included in the EURD list and a new entry will be required. The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The Applicant has requested an alignment of the PSUR cycle with the international birth date (IBD).

4. Benefit risk assessment

4.1. Therapeutic Context

4.1.1. Disease or condition

Lifitegrast is being developed for the treatment of dry eye disease (DED) and is to be administered locally in the eye.

The updated claimed indication is:

"Treatment of moderate to severe dry eye disease in adults for whom prior artificial tears has not been sufficient."

Dry eye disease is the result of an immune-mediated disorder that is initially limited to the ocular surface. The integrity of the ocular surface epithelium is disrupted, which manifests as fluorescein staining of the cornea and lissamine green staining of the conjunctiva. Loss of the barrier function of the corneal epithelium exposes the underlying cells to the hyperosmolar tear film, which damages them directly, and indirectly through propagation of inflammation (Bron et al., 2017).

The subjective symptoms in DED are often non-specific. They include redness, burning, stinging, foreign body sensation, pruritus, and photophobia.

In late stages or in severe forms of the disease, conjunctival scarring or corneal complications can occur. In addition to filamentary keratitis, persistent epithelial defects, ulceration, and even corneal perforation can complicate the course.

4.1.2. Available therapies and unmet medical need

Global prevalence estimates of DED range from 5 to 30% of people over the age of 50 years. The variation in prevalence may be attributable to differences in diagnostic and other criteria used between studies. Despite its marked prevalence, there are limited treatment options that can treat the underlying inflammation and improve the symptoms, which are the basis of DED treatment and diagnosis, respectively.

4.1.3. Main clinical studies

The lifitegrast DED clinical development program consists of 6 randomised, double-masked, placebo-controlled clinical studies involving 2607 subjects: 1 study in healthy subjects and 4 multicenter, prospective, randomised, double-masked, placebo-controlled safety and efficacy studies: 1 Phase 2 (1118-KCS-100) and 3 Phase 3 (1118-KCS-200, 1118-DRY-300, and SHP606-304, hereafter referred to as OPUS-1, OPUS-2, and OPUS-3, respectively), and 1 long-term multicenter, prospective, randomised, double-masked, placebo-controlled, parallel arm safety study (1118-DRY-400; hereafter referred to as SONATA). A total of 2,247 subjects with DED have participated in clinical efficacy studies, with 1,181 of these exposed to lifitegrast. A total of 177 subjects have been exposed to lifitegrast for >6 months and 170 subjects have been exposed to lifitegrast for ≥12 months (defined as ≥355 days).

All clinical studies were performed in the USA.

4.2. Favourable effects

Treatment with lifitegrast appears to improve the symptom of eye dryness as assessed by the improvements in the Eye Dryness Score (EDS), which is a 0-100 VAS point scale (0=no discomfort; 100=maximal discomfort). The mean change of EDS (SE) with [CI] from baseline to day 84 in the lifitegrast 5% as compared to placebo were: Phase 2; 7.95 (5.00) [-1.96, 17.85], OPUS-1; 3.94 (2.49) [-0.95, 8.83], OPUS-2; 12.62 (2.09) [8.51, 16.70], and OPUS-3; 7.16 (2.10) [3.04-11.28]. .

4.3. Uncertainties and limitations about favourable effects

The results on the EDS were obtained from the Phase 2 and OPUS-1-3 studies. In the Phase 2 study, the EDS outcome was one of several not hierarchically ordered secondary outcomes. In the OPUS-2, EDS was a co-primary endpoint along with ICSS, the latter not being significant in the study. The five studies (Phase 2, OPUS 1-3, and SONATA) tested a number of different 'sign' and 'symptom' endpoints. The results of the majority of the endpoints were not reproduced between the studies, the most consistent

result being the 'symptom'-endpoint of EDS, further emphasising the risk of the EDS results being chance findings. Lack of consistent findings is still of concern. In the OPUS-3 study, only the changes for eye dryness were statistically significant. For the sub-endpoints in the VAS, changes in (1) Burning/stinging, (2) Itching, (3) Foreign body sensation, (4) Eye discomfort, (5) Photophobia and (6) Pain were not statistically significant different from placebo and numeric, the differences in change from baseline compared to placebo were all <6 on a 100 point scale thus not to be considered clinically relevant. Importantly, due to the multi-symptomatic and heterogenic pattern of DED, it is considered essential that a clinically relevant effect on different symptomatic endpoints is obtained.

In addition, the clinical relevance of the presumed positive effect on EDS is doubtful as the treatment difference in EDS compared to placebo varied within the interval of 4-13 points on a 1-100 point VAS. Compared to placebo, lifitegrast would lead to a seven point improvement on the 1-100 point VAS in the OPUS-3 study.

The clinical relevance of the EDS improvement is further questioned by the choice of placebo. In the lifitegrast clinical trials, the lifitegrast vehicle was used as placebo. However, the standard treatment of DED is artificial tears and ointments, which, firstly, are more viscous (and hence, remain in the eyes for a longer period), and, secondly, are dosed several times a day. In comparison, the lifitegrast vehicle (placebo) was dosed twice a day. Taken together, the less efficient placebo may have overestimated the effect of lifitegrast as compared to the effect, which could have been obtained by artificial tears (with high viscosity) and ointments.

Post hoc responder analyses have shown that subjects with baseline ICSS>1.5 and baseline EDS ≥60 may have the most profound effect. However, it appears that the actual (numeric) effect of lifitegrast did not vary considerable among the subgroups and in fact, the statistically significant results in the subgroup of patients with ICSS>1.5 & EDS≥60 seem to be driven by the variability in the number of responders in the placebo. Furthermore, the use of LOCF for imputation of missing values is questioned and add to the uncertainty of results.

Finally, all pivotal studies (and all studies with efficacy endpoints) had a duration of 12 weeks/3 months, thus long-term efficacy data is lacking which is of concern as DED is often a chronic disease.

4.4. Unfavourable effects

Patients treated with Lifitegrast experienced installation site irritation/reaction/pain/pruritus as well as eye irritation/reaction/pain/pruritus. Other ocular events included increased lacrimation and blurred vision. The majority of the discontinuations in the 12-week studies (6% lifitegrast vs. 3% placebo group) and the 1-year study (12% lifitegrast vs. 9% placebo group) was due to one of these ocular adverse events.

Among non-ocular adverse events, dysgeusia was most common (14%) and led to a few discontinuations. Less common non-ocular events comprised gastro-intestinal adverse events, including gastro-oesophageal reflux, upper abdominal pain/discomfort, nausea and vomiting.

4.5. Uncertainties and limitations about unfavourable effects

Drug-drug interactions between lifitegrast and other topical medications have not been investigated. The combined effect of lifitegrast and e.g. corticosteroids or cyclosporine is unknown. The immunosuppressive effect may be enhanced possibly leading to more infections or other adverse reactions.

It should be noted that rare adverse events are unlikely to have been captured by the current safety database.

4.6. Effects Table

Table - Effects Table for Xiidra for DED

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
SIGN= ICSS	OPUS-1 Co-Primary endpoint Change from baseline in lifitegrast 5% group as compared to placebo (week 12)	Difference in Score (95% CI) Between groups	0.24 (0.10, 0.38)			SCE Table 35
SIGN= ICSS	OPUS-2 Co-Primary endpoint Change from baseline in lifitegrast 5% group as compared to placebo (week 12)	Difference in Score (95% CI) Between groups	0.03 (-0.10,0.17)			
SYMPTOM = VR-OSDI	OPUS-1 Co-Primary endpoint Change from baseline in lifitegrast 5% group as compared to placebo (week 12)	Difference in Score (95% CI) Between groups Difference in Score (95% CI) Between groups	-0.02 (-0.15, 0.11)			SCE Table 31

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
SYMPTOM = EDS	OPUS-2 Co-Primary endpoint Change from baseline in lifitegrast 5% group as compared to placebo (week 12)	Difference in Score (95% CI) Between groups	12.61 (8.51, 16.70)		Co-primary endpoint of OPUS-2 (ICSS, the other co-primary endpoint did not show significant difference between lifitegrast and placebo)	SCE Table 28
SYMPTOM = EDS	OPUS-3 Single Primary endpoint Change from baseline in lifitegrast 5% group as compared to placebo (week 12)	Difference in Score (95% CI) Between groups	7.16 (3.04, 11.28)			SCE Table 28
Unfavourable Effects						
Installation site irriation		%	14%	3%	Overlap between 'Eye pain/irritation' and 'Installation site irritation/reaction/pain' -> percentage of patients experiencing AEs is higher	SCS Table 28
Installation site reaction		%	11%	2%	As above	SCS Table 28
Installation site pain		%	11%	2%	As above	SCS Table 28
Vision blurred		%	3%	1%	As above	SCS Table 51
Lacrimation increased		%	4%	1%	As above	SCS Table 55
Dysgeusia		%	14%	0%		SCS Table 28
Hypersensitivity reactions	One report of anaphylaxia, other reports of oedema, urticarial etc.				Post-marketing experience reports	SCS, RMP

Abbreviations: ICSS, inferior corneal fluorescein staining. Corneal fluorescein staining scoring is as follows with 0.5 increments: 0=no staining; 1=few/rare punctate lesions; 2=discrete and countable lesions; 3=lesions too numerous to count, but not coalescent; 4=coalescent. Total score is derived sum of all regions (0-12 points). Total score is derived sum of all regions (0-12 points).
VROSD, visual-related function subscale of Ocular Surface Disease Index.
Eye dryness score (VAS) uses 0-100 point scale (0=no discomfort; 100=maximal discomfort).
Notes: The phase 3 studies employed a mixture of SIGN-endpoints and SYMPTOM-endpoints.

4.7. Benefit-risk assessment and discussion

4.7.1. Importance of favourable and unfavourable effects

There are uncertainties related to the clinically relevant effect of the product. Thus, an effect on signs has not been convincingly demonstrated and an effect on symptoms has not been unequivocally demonstrated either. There was an unjustified lack of consistency in term of the endpoints selected in the three phase 3 studies hampering reproduction of the study results. Furthermore, when an effect was demonstrated the effect size was of doubtful clinical relevance and there was a lack of demonstration of long term efficacy. Due to the strict exclusion criteria applied in the phase 3 studies, it is uncertain if any benefit demonstrated can be extrapolated to the general DED population.
The unfavourable effects of lifitegrast appears manageable. Local installation of lifitegrast in the eye was associated with toxicity in the form of irritation/pruritus/pain as well as non-ocular toxicity mainly in the form of dysgeusia. However, unfavourable effects did not lead to discontinuation in the majority of patients. The RCTs included a very selected study population, excluding patient with any of a long list of concomitant medications and eye conditions. Thus, it may be difficult to extrapolate results obtained in the clinical trials to the general DED population. Provided that the labelling is modified to reflect patients for whom risk benefit is known, this uncertainty is not considered to preclude a positive opinion

4.7.2. Balance of benefits and risks

The benefit risk is considered negative.

4.7.3. Additional considerations on the benefit-risk balance

N/A

4.8. Conclusions

The overall B/R of Xiidra is negative.