Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Lifitegrast

Proprietary Product Name: Xiidra

Sponsor: Shire Australia Pty Ltd

November 2019

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

Common abbreviations

Abbreviation	Meaning
ACM	Advisory Committee on Medicines
AE	Adverse event
ANOVA	Analysis of variance
ARTG	Australian Register of Therapeutic Goods
ASA	Australian Specific Annex
AST	Aspartate transaminase
AT	Artificial tears
AUC	Area under the curve
$AUC_{0-24\,h}$	Area under the curve from dosing to 24 hours
BCVA	Best corrected visual acuity
CAE	Controlled adverse environment
CIC	Conjunctival impression cytology
C_{max}	Maximum concentration occurring at T_{max}
CYP	Cytochrome P450
DED	Dry eye disease
DLP	Data lock point
EDS	Eye dryness score
ECG	Electrocardiograph
EU	European Union
FDA	Food and Drug Administration (USA)
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
hERG	Human ether-à-go-go related gene
HPLC	High performance liquid chromatography
IC_{50}	Half maximal inhibitory concentration

Abbreviation	Meaning
ICAM	Intercellular adhesion molecule-1
ICH	International Council on Harmonisation
ICSS	Inferior corneal staining score
IFN γ	Interferon gamma
IL	Interleukin
IOP	Intraocular pressure
ISE	Integrated Summary of Efficacy
ISS	Integrated Summary of Safety
ITT	Intent to treat
IV	Intravenous
KCS	Keratoconjunctivitis sicca
Ki	Inhibition constant
LASIK	Laser-assisted in situ keratomileusis
LDPE	Low density polyethylene
LFA-1	Lymphocyte function associated antigen-1
LIF	Lifitegrast (also SAR1118, SPD606, SHP606)
LOCF	Last observation carried forward
MIP-1α	Macrophage inhibitory protein 1 alpha
NS-KCS	Non Sjorgren's syndrome keratoconjunctivitis sicca
NSP	National Sales perspectives (in USA)
OATP	Organic anion transport protein
OSDI	Ocular Surface Disease Index (Allergan, Inc)
PBRER	Periodic Benefit-Risk Evaluation Report
PSUR	Periodic Safety Update Report
RMP	Risk management plan
SAE	Serious adverse event

Abbreviation	Meaning
SAR1118	Lifitegrast (also SSP-005493, SPD606 and SHP606)
SD	Standard deviation
SE	Standard error
SOC	System Organ Class
SS-KCS	Sjögren's syndrome keratoconjunctivitis sicca
STT	Schirmer Tear Test
TCSS	Total corneal staining score
TFBUT	Tear film break up time
T_{max}	Time of maximum observed concentration during a dosing interval
TNFα	Tumour necrosis factor alpha
UK	United Kingdom
UV	Ultra violet
VAS	Visual analogue scale
VR	Vision related
VR-OSDI	Visual related function subscale of Ocular Surface Disease Index
w/v	Weight/volume

I. Introduction to product submission

Submission details

Type of submission:	New chemical entity
Decision:	Approved
Date of decision:	18 January 2019
Date of entry onto ARTG:	21 January 2019
ARTG number:	293589
, *Black Triangle Scheme*	Yes This product will remain in the scheme for 5 years, starting on the date the product is first supplied in Australia.
Active ingredient:	Lifitegrast
Product name:	Xiidra
Sponsor's name and address:	Shire Australia Pty. Ltd. Level 39 225 George Street, Sydney, NSW
Dose form:	Eye drops
Strength:	50 mg/mL
Container:	Ampoule
Pack sizes:	20 and 60 ampoules
Approved therapeutic use:	*Xiidra is indicated for the treatment of moderate to severe dry eye disease in adults for whom prior use of artificial tears has not been sufficient.*
Route of administration:	Ophthalmic
Dosage:	One drop in each eye, twice daily

Product background

This AusPAR describes the application by Shire Australia Pty Ltd (the sponsor);[1] to register Xiidra for the following indication:

Treatment of the signs and symptoms of dry eye disease in adults.

Dry eye disease is common; the estimated prevalence in the USA and Europe is between 4.3 to 21.9%. Although not life threatening, dry eye disease can cause distressing symptoms and result in loss of work productivity and quality of life. In rare situations it can lead to corneal ulcers and scarring.

The prevalence of dry eye disease increases with age. There are a number of environmental factors (such as exposure to medications (anti-histamine, diuretics), contact lens use, and dry environment) and diseases (such as connective tissue disease, post laser) that contribute to its development.

There are currently limited treatment options available for dry eye disease. Avoiding environmental triggers is important. Artificial tears and eye lubricants may provide some relief but require frequent application. There are lubricants available which do not contain a preservative that are suitable for long term use, however those which do contain a preservative may be associated with ocular surface damage. Punctate plugs (tiny devices inserted into tear ducts to block drainage) are occasionally used for persistent symptoms or due to dry eye associated with surgery.

Ciclosporin 0.05% (Restasis) eye drops are registered in USA for the treatment of dry eye disease. Restasis is thought to work by modulating the immune system, increasing the production of tear cells from lacrimal glands. Interestingly, tear production does not occur immediately but may be noticed 3 to 6 months after starting treatment. Ciclosporin eye drops are not approved, however are used off label for this indication in Australia.

Lifitegrast is the first in its pharmacological class. It acts as an antagonist of lymphocyte function-associated antigen 1 (LFA-1), inhibiting the interaction of LFA-1 with intracellular adhesion molecule-1 (ICAM-1) to prevent the formation of immunological synapses between T cells and antigen-presenting cells, which mediate inflammatory cell activation, recruitment and migration. Increased ICAM-1 expression in conjunctival and lacrimal tissues in patients with dry eye disease is reported in the literature.

Regulatory status

At the time the TGA considered this application; a similar application had been approved or was under consideration in the countries or regions as shown in Table 1 below.

Table 1: International regulatory status

Country/Region	Submission date	Status	Approved indications
USA	25 February 2015	Approved (11 July 2016)	Treatment of the signs and symptoms of dry eye disease
Canada	27 October 2016	Approved	Treatment of the signs

[1] Post registration the sponsorship has changed to Novartis Pharmaceuticals Australia Pty Ltd., 54 Waterloo Road, Macquarie Park NSW 2113.

Country/Region	Submission date	Status	Approved indications
		(22 December 2017)	and symptoms of dry eye disease
European Union (via Centralised procedure)	14 November 2018	Pending	
Switzerland	23 August 2017	Pending	
United Arab Emirates	2 May 2018	Approved (20 September 2018)	Treatment of signs and symptoms of dry eye disease (DED)

Submissions were also under consideration in Israel, South Korea, Taiwan, Kuwait, Saudi Arabia, Brazil, Colombia and Mexico.

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Registration time line

The following table captures the key steps and dates for this application and which are detailed and discussed in this AusPAR.

Table 2: Timeline for Submission PM-2017-03384-1-5

Description	Date
Submission dossier accepted and first round evaluation commenced	31 October 2017
First round evaluation completed	11 April 2018
Sponsor provides responses on questions raised in first round evaluation	8 June 2018
Second round evaluation completed	18 July 2018
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	6 November 2018
Sponsor's pre-Advisory Committee response	20 November 2018
Advisory Committee meeting	6 December 2018
Registration decision (Outcome)	18 January 2019

Description	Date
Completion of administrative activities and registration on ARTG	21 January 2019
Number of working days from submission dossier acceptance to registration decision*	216

*Statutory timeframe for standard applications is 255 working days

Evaluations included under Quality findings and Nonclinical findings incorporate both the first and second round evaluations.

III. Quality findings

Introduction

Lifitegrast is a first-in-class small molecule inhibitor of the interaction between lymphocyte function-associated antigen 1 (LFA-1) and intercellular adhesion molecule-1 (ICAM-1).

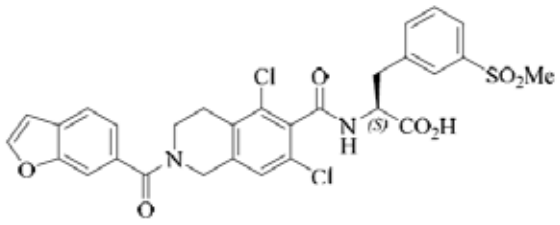
The product dose form is eye drops, solution, and a single strength of 50 mg/mL (5% weight/volume (w/v)) is proposed. The product is to be packed in single use low density polyethylene (LDPE) ampoules with 5 ampoules sealed in an aluminium foil laminate pouch in packs of 20 (starter pack) and 60 ampoules. Lifitegrast is not currently included in any registered medicines in Australia. Lifitegrast is not subject to British or European Pharmacopoeia nor United States Pharmacopeia monographs.

Drug substance (active ingredient)

Lifitegrast is a white to off-white powder. Its solubility increases with increasing pH up to > 1000 µg/mL at pH 6.0 to 8.0.

Lifitegrast is made by chemical synthesis. The active pharmaceutical ingredient contains 1 chiral centre and is the isomer with S configuration as proven by single crystal X-ray crystallography. Six polymorphic forms of lifitegrast are known, with Form 1 synthesised consistently by the drug substance manufacturer and is confirmed in the specification by powder X-ray diffraction.

Figure 1: Schematic structure of lifitegrast



The drug substance is appropriately controlled by acceptable tests and limits for appearance, identity (infra red and high performance liquid chromatography (HPLC)), assay, related substances, residual solvents, palladium content, powder X-ray diffraction and microbial limits. Related substances, residual solvents and heavy metal impurities have been controlled according to the International Council on Harmonisation (ICH) guidelines.

Drug product

Lifitegrast eye drops are a clear, colourless to slightly coloured ophthalmic solution. The only strength is 50 mg/mL (5% w/w). The formulation includes sodium thiosulfate as an antioxidant.

The product is to be packed in single use LDPE ampoules with 5 ampoules sealed in an aluminium foil laminate pouch in packs of 20 (starter pack) and 60 ampoules.

The manufacturing process for lifitegrast eye drops involves mixing the ingredients together under nitrogen and ensuring the pH is between 7.2 and 7.5.

The finished product is appropriately controlled using the finished product specifications. The specifications include acceptable tests and limits for appearance, identity (ultra violet (UV) and HPLC), colour, pH, osmolality, assay, related substances, minimum fill volume, sodium thiosulfate assay, particulate matter, sterility and endotoxin limits. No degradation impurities have been identified in the finished product and all individual degradation products are controlled according to the ICH identification threshold.

A shelf-life of 12 months and the label 'Store below 25°C. Protect from light' is recommended in the proposed container closure.

Quality summary and conclusions

Chemistry and quality control aspects are considered acceptable.

IV. Nonclinical findings

Introduction

The sponsor has applied to register a new chemical entity, lifitegrast (Xiidra eye drops). The product is proposed to be used for the treatment of the signs and symptoms of dry eye disease in adults. The proposed dosing regimen involves instillation of one drop of Xiidra (50 µL x 50 mg/mL (5% w/v) lifitegrast) twice a day into each eye. This yields a maximum recommended clinical dose of 10 mg lifitegrast per day (5 mg/eye).

Pharmacology

Primary pharmacology

Lifitegrast is the first in its pharmacological class. It acts as an antagonist of LFA-1, inhibiting the interaction of LFA-1 with ICAM-1 to prevent the formation of immunological synapses between T cells and antigen-presenting cells, which mediate inflammatory cell activation, recruitment and migration. Increased ICAM-1 expression in conjunctival and lacrimal tissues in patients with dry eye disease is reported in the literature.[2]

In vitro, lifitegrast was shown to inhibit adhesion of a human T cell line (Jurkat cells) to ICAM-1 with nanomolar potency (half maximal inhibitory concentration (IC_{50}), 3.7 nM), and to inhibit the secretion of various cytokines in human peripheral blood mononuclear cells, including several that are recognised to be increased in dry eye disease: interferon

[2] Gao J., et al (2004) ICAM-1 expression predisposes ocular tissues to immune-based inflammation in dry eye patients and Sjögrens syndrome-like MRL/lpr mice. *Exp. Eye Res*. 78: 823–835

gamma (IFN γ), interleukin (IL) 2, macrophage inhibitory protein 1 alpha (MIP-1α), tumour necrosis factor alpha (TNFα), IL 4, IL 10, IL 1α and IL 1β (presented in descending order of sensitivity; IC_{50} values, 1.6 to 360 nM).

In vivo, repeat topical ocular administration of lifitegrast:

- increased rather than decreased lacrimal gland inflammation in an autoimmune-prone mouse model (0.1 to 10% strengths; administered three times daily);
- had no effect or only slightly reduced conjunctival inflammation in dogs with spontaneous keratoconjunctivitis sicca (1% strength; three times daily); but
- significantly reduced corneal inflammation (neutrophil infiltration) when administered 3 and 15 h prior to the induction of inflammation in mice, although not when given 1 h before and 1 h after induction of inflammation (0.1 to 5% strengths tested, with greatest efficacy seen with the 1% strength).

Secondary pharmacodynamics and safety pharmacology

Screening assays revealed no significant secondary pharmacological targets for lifitegrast (tested at 10 μM) among a large panel of receptors, ion channels, transporters and enzymes.

Safety pharmacology studies with lifitegrast covered the central nervous, cardiovascular and respiratory systems. Central nervous system function was unaffected in rats at intravenous (IV) bolus doses up to 1 mg/kg (yielding peak plasma concentrations > 45 times higher than in patients at the maximum recommended clinical dose), while altered pupillary status (miosis) was observed at 10 mg/kg IV. Lifitegrast inhibited the hERG K+ channel;[3] but with very weak potency (IC_{50}, 478 μM; > 170,000 times greater than the clinical plasma maximum concentration (C_{max})). Blood pressure, heart rate and electrocardiograph (ECG) parameters were unaffected by lifitegrast in dogs, and respiration was unaffected in rats (tested up to 10 mg/kg IV in each species).

Pharmacokinetics

Systemic absorption following ocular administration was rapid in rats, rabbits and dogs, as in humans. Bioavailability by the ocular route was around 3% in rats and less than that in dogs. Ocular distribution studies in rats, rabbits and dogs showed highest levels of lifitegrast (or ^{14}C lifitegrast-derived radioactivity) in anterior tissues (conjunctiva and cornea), with levels in posterior tissues and the aqueous and vitreous humour markedly lower. Clearance was rapid.

Plasma protein binding was high in humans (98.9%) and in laboratory animal species (96.1 to 99.5% in rat, rabbit, dog and monkey). There was strong binding to human serum albumin and moderate binding to α1 acid glycoprotein. Moderate (but no preferential) binding to melanin was seen.

Lifitegrast was minimally metabolised by rat, dog, monkey and human hepatocytes in *in vitro* incubations. Unchanged lifitegrast was the major circulating species in rats and dogs after ocular and IV administration. Rather than metabolism, clearance of lifitegrast was primarily through biliary/faecal excretion. Excretion in urine was minor.

The pharmacokinetic profiles in the laboratory animal species (particularly those used in the pivotal repeat-dose toxicity studies) are seen to be sufficiently similar to humans to

[3] hERG = Human ether-à-go-go related gene

allow them to serve as appropriate models for the assessment of lifitegrast toxicity in humans.

Pharmacokinetic drug interactions

Lifitegrast was found to be a direct inhibitor of cytochrome P450 (CYP) enzyme 2C9 (IC_{50}, 4.1 μM) and an irreversible (time-dependent) inhibitor of CYP 3A4 (inhibition constant (Ki), 107 μM; kinact,[4] 0.16 min^{-1}) in experiments with human liver microsomes. With low systemic exposure, no clinically significant inhibition of these enzymes (to give rise to pharmacokinetic interactions) is expected. Lifitegrast (10 μM) produced no notable inhibition of CYPs 1A2, 2B6, 2C8, 2C19 or 2D6.

Transport experiments with transfected cells indicated that lifitegrast is a substrate of human organic anion transport protein (OATP) 1A2 and OATP2B1, but not of OATP2A1, P glycoprotein or breast cancer resistance protein. OATP1A1 and OATP1B2 transporters were seen to be involved in the hepatic uptake and biliary excretion of lifitegrast in the rat; the human counterparts of these are considered to be OATP1A2 and OATP1B1.[5]

Toxicology

Acute toxicity

Single dose toxicity studies involving IV administration to rats at up to 10 mg/kg and topical ocular administration to rabbits at up to 3.5 mg/eye, showed lifitegrast to have a low order of acute toxicity. Notable effects were limited to squinting immediately after ocular instillation (resolving within four minutes) in the rabbit study.

Repeat dose toxicity

Repeat-dose toxicity studies by the topical ocular route of up to 9 months duration were conducted in rabbits and dogs; additional studies by the IV route were performed in rats (13 weeks duration) and dogs (up to 4 weeks) to maximise systemic exposure. The pivotal (9 month) studies were adequately conducted in terms of the species used, duration, dose selection, and the monitoring and analyses performed. All of the ocular studies involved three times daily dosing to both eyes, exceeding the twice daily regimen proposed clinically.

Relative exposure

Exposure ratios at the highest dose levels in key repeat-dose toxicity studies have been calculated below based on animal: human plasma area under the curve from dosing (time zero) to 24 hours ($AUC_{0-24\,h}$). High (dog) or very high (rabbit) multiples of the clinical systemic exposure were obtained with ocular administration, and IV administration yielded massive exposure multiples (rats and dogs).

[4] Kinact is the maximum potential rate of inactivation
[5] OATP = Organic anion transporting related gene

Table 3: Relative systemic exposure at the high-dose levels in key repeat-dose toxicity studies

Species	Study		Dose	$AUC_{0-24\,h}$^a (ng·h/mL)	Exposure ratio#
Rat (SD)	R6337M-SPD606	13 weeks	30 mg/kg/day; IV	7472	5414
Rabbit (NZW)	L6329M-SPD606	39 weeks	5.25 mg/eye/day	67.2	49
Dog (Beagle)	D6336M-SPD606	39 weeks	5.25 mg/eye/day	22.5	16
	D6338M-SPD606	4 weeks	30 mg/kg/day; IV	27786	20135
Human (healthy volunteers)	SAR1118-001		1 drop x 5% strength to both eyes twice daily	1.38b	–

= animal:human plasma $AUC_{0-24\,h}$; ^ = values are for the sexes combined at the last sampling occasion; a = animal AUC_{0-t} value for a single dosing interval tripled to reflect three times daily dosing; b = clinical AUC_{0-t} value for a single dosing interval doubled to reflect twice daily dosing. SAR1118 = Lifitegrast

Major findings

There were no toxicologically significant adverse effects in any of the repeat-dose toxicity studies.

Treatment-related ocular findings were limited to transient blinking and squinting, signs of mild ocular irritation. This was seen immediately after ocular instillation of strengths of lifitegrast matching (5%) and below (1% and 3%) that in the clinical formulation, with the incidence and duration dose-dependent; there were no accompanying microscopic lesions in ocular tissues.

The tongue was identified as a potential target for lifitegrast, with a modest increase in the incidence/grade of myofibre regeneration in the tongue [as a response to prior degeneration] compared with controls observed at all doses in the 9 month rabbit study (≥ 0.315 mg/eye/day; relative exposure, ≥ 7) and findings of minimal granulomatous inflammation observed in dogs treated topically at 5.25 mg/eye/day for 9 months (relative exposure 16). Effects on the tongue were not seen with IV administration in rats and dogs (consistent with ocular administration resulting in significant oral exposure through nasolacrimal drainage). These findings are not considered to be toxicologically significant based on their nature/severity. Dysgeusia was reported to be commonly observed in clinical trial subjects, but it is unclear whether the tongue findings in animals are related.

Xiidra contains sodium thiosulfate pentahydrate, a novel excipient by the ocular route in Australia. This excipient was included in the eye drop formulation tested in the 9 month study in dogs (present at the proposed clinical strength, and given at a dose exceeding the human dose), with no ocular toxicity due to its presence evident. Systemic exposure to this excipient with Xiidra therapy does not exceed that already approved.

Genotoxicity

The genotoxic potential of lifitegrast was investigated in the standard battery of tests: a bacterial reverse mutation assay, an *in vitro* clastogenicity assay (using Chinese hamster ovary cells) and a bone marrow micronucleus test (in mice). Negative results were obtained in the bacterial mutagenicity assay and *in vivo* in the bone marrow micronucleus test, both appropriately conducted. A significant increase in the frequency of structural

chromosomal aberrations was evident, though, in the *in vitro* clastogenicity assay, but only at the highest concentration (3500 µg/mL) in assays without metabolic activation. This concentration was notably cytotoxic (suppressing the mitotic index by > 50%). No clastogenic activity was evident at the next lower concentration, 2450 µg/mL (which itself exceeds the maximum recommended concentration for testing (500 µg/mL) in ICH S2 (R1));[6] or at 3500 µg/mL with metabolic activation (where exposure to lifitegrast will only be marginally reduced). The weight of evidence supports that lifitegrast is not genotoxic.

Carcinogenicity

No carcinogenicity studies with lifitegrast were submitted. This is acceptable in accordance with ICH S1A;[7] given the low systemic exposure with topical ocular administration in patients, and with no cause for concern for carcinogenic potential having been identified from the studies on genotoxicity or repeat-dose toxicity (for example, findings of pre neoplastic lesions).

Reproductive toxicity

Reproductive toxicity studies submitted by the sponsor covered fertility (in rats) and embryofoetal development (rats and rabbits). The studies were appropriately designed and conducted, and involved IV administration. Massive multiples of the clinical exposure were obtained at the highest dose levels tested.

Table 4: Relative systemic exposure at the high-dose levels in the pivotal reproductive toxicity studies

Species	Study	Dose	$AUC_{0-24\,h}$ ng·h/mL	Exposure ratio#
Rat (SD)	Fertility and embryofetal development [R6341M-SPD606]	30 mg/kg/day; IV	7472a	5414
Rabbit (NZ White)	Embryofetal development [L6340M-SPD606]	30 mg/kg/day; IV	47874	34691
Human (healthy volunteers)	SAR1118-001	1 drop x 5% strength to both eyes twice daily	1.38b	–

Human (healthy volunteers) SAR1118-001; 1 drop x 5% strength to both eyes twice daily 1.38b;
= animal: human plasma $AUC_{0-24\,h}$; a = based on toxicokinetic data obtained in a 13 week general repeat-dose toxicity study (R6337M-SPD606); b = clinical AUC_{0-t} value for a single dosing interval doubled to reflect twice daily dosing

Male and female fertility were unaffected in rats, and no adverse effects on embryofetal development were observed in rats or rabbits (≤ 30 mg/kg/day IV; relative exposure, > 5400 in rats and > 34000 in rabbits). No pre /postnatal development study was submitted. This is considered acceptable given the low systemic exposure in patients and the absence of cause for concern from the other reproductive toxicity studies. No data on placental transfer or excretion in milk were provided.

[6] ICH guideline S2 (R1): Genotoxicity testing and data interpretation for pharmaceuticals intended for human use.
[7] ICH guideline S1A: Need for carcinogenicity studies of pharmaceuticals.

Pregnancy classification

The sponsor has proposed Pregnancy Category B1.[8] This is considered appropriate; being consistent with the absence of adverse effects on embryofetal development observed in adequately conducted animal studies.

Local tolerance

Ocular tolerance was investigated in the general repeat-dose toxicity program, with the 9 month dog study utilising the proposed commercial formulation. Dermal irritation studies in rats and minipigs showed no skin irritation specifically attributable to lifitegrast (1% strength) after single or repeated skin application.

Cytotoxicity

Cytotoxicity to human corneal epithelial cells was seen with lifitegrast *in vitro* following incubation at strengths ≥ 1% for ≥ 1 hour; cell viability was not reduced with strengths ≤ 0.3%. While the strength at which cytotoxicity was evident is below the clinical strength (5%), the *in vitro* conditions exaggerate sensitivity. *In vivo*, the cornea is not exposed to such high concentrations for a prolonged period, being rapidly diluted in tears. Accordingly, the *in vitro* finding is not considered to be clinically relevant; this is supported by the absence of ophthalmological changes in rabbits and dogs in the repeat-dose toxicity studies.

Phototoxicity

Lifitegrast absorbs UV light with a molar extinction coefficient of 2765 L/mol/cm at 290 nm, above the 1000 L/mol/cm threshold for absorption of light within the range of natural sunlight (290 to 700 nm) as a prerequisite for phototoxicity, as described in ICH guideline S10.[9] No phototoxic potential was found for lifitegrast in an adequately conducted *in vitro* study in mouse 3T3 fibroblast cells.

Impurities

The sponsor provided data on genotoxicity and general safety for a number of impurities requiring qualification. Proposed limits for specified impurities in the drug substance and drug product are considered to be toxicologically acceptable.

Paediatric use

Lifitegrast is not proposed for paediatric use and no specific studies in juvenile animals were submitted. Developing systems were not identified as targets for lifitegrast toxicity in general repeat-dose toxicity studies, conducted in young adult animals.

Comments on the nonclinical safety specification of the risk management plan

Key safety concerns arising from nonclinical data are adequately identified in the safety specification of the risk management plan.

[8] Category B1: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. Studies in animals have not shown evidence of an increased occurrence of foetal damage.
[9] ICH guideline S10: Photosafety evaluation of pharmaceuticals.

Nonclinical summary and conclusions

Key safety concerns arising from nonclinical data are adequately identified in the safety specification of the risk management plan.

- Nonclinical submission was of good overall quality and adequate in scope. All pivotal safety-related studies were Good Laboratory Practice (GLP) compliant.
- Lifitegrast acts an antagonist of LFA-1, inhibiting the interaction of LFA-1 with ICAM-1, which mediates inflammatory cell activation, recruitment and migration.
- *In vitro*, lifitegrast was shown to inhibit human T-cell adhesion to ICAM-1 with nanomolar potency, and to inhibit inflammatory cytokine release from human peripheral blood mononuclear cells.
- *In vivo* pharmacology studies did not offer compelling evidence in support of efficacy. While reduced corneal inflammation following topical ocular administration of lifitegrast was shown in one study in mice, increased lacrimal gland inflammation was seen in another study in mice and no effect or only a slight reduction in conjunctival inflammation was observed in dogs.
- No significant secondary pharmacological targets for lifitegrast were identified in screening assays. Safety pharmacology studies indicated no clinically relevant effects on the central nervous system, cardiovascular or respiratory systems.
- Systemic absorption of lifitegrast after topical ocular administration was shown to be rapid but low in laboratory animal species, as in humans. Ocular distribution studies in rats, rabbits and dogs showed highest exposure in anterior tissues (conjunctiva and cornea), with drug levels in posterior ocular tissues and the aqueous and vitreous humour markedly lower. Clearance was rapid. Lifitegrast was shown to be minimally metabolised by CYP enzymes *in vitro* in experiments with rat, dog, monkey and human hepatocytes. Excretion in rats and dogs was predominantly via bile/faeces.
- Lifitegrast did not inhibit key CYP enzymes at therapeutically relevant concentrations. Systemically absorbed lifitegrast is subject to hepatic uptake, with the drug identified as a substrate for the human OATP1A2 and OATP2B1 transporters, and potentially OATP1B1 (based on analogy with rat OATP1B2/OATP4).
- Lifitegrast had a low order of acute toxicity in single-dose toxicity studies performed by the IV route (to maximise systemic exposure) in rats and by the topical ocular route in rabbits.
- Repeat-dose toxicity studies by the ocular route were performed in rabbits and dogs (up to 9 months duration in both species), and by the IV route in rats and dogs (13 and 4 weeks duration, respectively). No toxicologically significant adverse effects were observed. Treatment-related findings were limited to transient signs of mild ocular irritation, and minor histological changes in the tongue.
- The weight of evidence supports that lifitegrast is not genotoxic. Carcinogenicity studies have not been performed; this is considered acceptable under ICH S1A.[7]
- Lifitegrast did not affect male or female fertility (in rats) or embryofetal development (in rats and rabbits) at IV doses yielding systemic exposure levels vastly in excess of that in patients at the maximum recommended human dose. Assignment to Pregnancy Category B1;[8] as proposed by the sponsor, is supported.
- Lifitegrast was shown to not be phototoxic in an *in vitro* assay. Cytotoxicity to human corneal epithelial cells was observed with lifitegrast *in vitro*, but under conditions that exaggerate sensitivity; the finding is not considered to predict ocular cytotoxicity *in vivo* in patients.
- There are no nonclinical objections to the registration of Xiidra.

V. Clinical findings

A summary of the clinical findings is presented in this section.

Introduction

Lifitegrast is a first in class, selective anti-inflammatory small molecule, antagonist of lymphocyte function antigen-1 (LFA-1). LFA-1 is also known as CD11a/CD18 or αLβ2).

Information on the condition being treated

Dry eye disease (DED) is one of the most frequent reasons for seeking eye care. It is a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface. It is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface. Subjective symptoms are the most striking feature of the disease and often are the only factor upon which the diagnosis in based. Dry eye symptoms affect activities of daily living and can lead to despair, depression, decreased productivity, and adversely impact tasks such as driving and job functionality. Left untreated, the chronic nature of DED can progress to corneal scarring, ulcers and ultimately vision loss.

Key risk factors of DED include age > 50 years, female gender, use of certain medications, (for example, antihistamines, diuretics), connective tissue disease, post-laser assisted in situ keratomileusis status, contact lens usage, androgen deficiency and environmental factors (for example, low humidity, high air speed).

Global prevalence estimates of DED range from 5 to 30% of people over the age of 50 years. Overall, the US prevalence by self-reported dry eye symptoms has been estimated to be 7.8% of females aged 50 years and older and 4.3% of males aged 50 years and older. DED prevalence and incidence between the US and the European Union (EU) are similar. Among adults, the prevalence estimate of DED was 9.6% in the UK for adult women, 11.0% in Spain, and 21.9% in France. There has not been any reported geographic disparity between affected patients in the US versus those in Europe.

Similar results have been found in Asian countries (Japan: prevalence of clinically diagnosed DED to be 2.1% in men and 7.9% in women; Taiwan: a population-based survey of eye diseases in the elderly (≥ 65 years), 33.7% of participants (30.2% males, 39.1% females) reported DED symptoms; South Korea, the prevalence of clinically diagnosed DED was 10.4% among 17,542 adult (>18 years) participants.

The submission did not include information about the natural history of DED which is probably more correctly described as a syndrome (as it is in ICD-9 and 10);[10] rather than a disease as it is multifactorial and heterogeneous with no single test that can be used to accurately assess disease progression or response to treatment.[11] One publication included in the submission;[12] states that '*most studies have concluded that dry eye undergoing treatment is relatively stable condition(s), with severe disease tending to worsen and moderate disease tending to improve*.'

[10] ICD-9; and ICD-10: International Classification of Diseases, Ninth Revision and Tenth Revision respectively. The ICD is the international standard diagnostic tool for epidemiology, health management and clinical purposes and is maintained by the World Health Organization (WHO).
[11] Bartlett JD, et al. 2015 Associations between signs and symptoms of dry eye disease: a systematic review. *Clinical Ophthalmology* 9: 1719-1930
[12] Johnson ME 2009. The association between symptoms of discomfort and signs in dry eye. *Ocul Surf* 2009; 7: 199-211.

Current treatment options

There are currently limited options that can treat the underlying inflammation and improve the symptoms of DED.

Current treatments include artificial tears (AT) and punctal plugs (a tear duct plug which is a small medical device that is inserted into the tear duct (puncta) of the eye to block the duct) but these treatments may offer only temporary relief and do not address the pathobiology of the process.

In the EU and the US, cyclosporin is the only approved pharmacologic agent for the treatment of moderate to moderately severe aqueous deficient dry eye disease, characterised by moderate to moderately severe: ocular staining, reduction in tear production and fluctuating visual symptoms, such as blurred vision. Cyclosporin is, however, associated with high numbers of patient discontinuations due to the delayed onset of action (24 weeks), and frequently it requires adjunct topical corticosteroid therapy.

The sponsor states that despite the increasing understanding of the chronic inflammatory nature of ocular surface disease over the past two decades, there remains a serious unmet need for approved pharmacologic agents with faster onset of action that are well tolerated and that can improve both the signs and symptoms of dry eye.

Clinical rationale

Dry eye disease is one of the most challenging ocular diseases to investigate and consequently, the number of efficacious therapies is limited. Historically, it has been misunderstood that dry eye signs and symptoms are well-correlated, when in fact a low and inconsistent correlation between signs and subjective symptoms in dry eye disease has been well established in the literature.[13,14] In any DED treatment trial, it is difficult to document a significant change in both aspects because of the multifactorial aetiology of the disease, the variability of the disease state, subjects' exposure to variable environments prior to the visit for testing, the inherent variability of subjects' response to subjective questionnaires, and the inherent variability in the testing for the disease state. All of these challenges have resulted in a series of failed studies across multiple compounds based on co-primary endpoints in the treatment of dry eye disease.

In a disease state that lacks standardised endpoints and diagnostic criteria, the sponsor believes that registration definition of a clinically meaningful response in dry eye disease is demonstration of statistical significance in improving a sign (objective) and a symptom (subjective) in adequate and well-controlled studies. Designing studies with co-primary endpoints assumes there exists an interdependent relationship between the objective and subjective variables. The eye dryness score (EDS) of the visual analogue score (VAS) accurately captures the symptom measurements. It is easily understood by patients and also represents a spontaneous assessment, which avoids any recall bias, especially in the elderly population. Corneal fluorescein staining is a practical clinical method for assessing the sign severity of DED. The fluorescein stains devitalised corneal epithelial cells, indicative of ocular surface insult.

Throughout the clinical development of lifitegrast, studies were conducted in a sequential manner to leverage study findings and apply the learnings to the next study. Hence, in the initial study, observations were made that history of artificial tear use could be used as a

[13] Report of the Clinical Trials Subcommittee of the International Dry Eye Workshop. 2007 Design and Conduct of Clinical Trials. *The Ocular Surface* 5(2): 153-162

[14] Hay EM, et al. 1998 Weak Association between Subjective Symptoms of and Objective Testing for Dry Eyes and Dry Mouth: Results from a Population Based Study. *Ann. Rheum. Dis.* 57: 20-24

proxy for symptomatology at Baseline and that visual-related function subscale of the Ocular Surface Disease Index (VR-OSDI), as well as eye dryness score, could serve as symptom endpoints since treatment effect was seen for both of these endpoints.

Lifitegrast targets the interaction between, a cell surface protein found on leukocytes, and ICAM-1, its cognate ligand.

LFA-1 is a heterodimer integrin protein that mediates cell-to-cell interactions essential to immune and inflammatory response mechanisms. Its expression is restricted to leukocytes (neutrophil, eosinophil, basophil, monocyte, T and B lymphocyte), where it functions both as a key adhesion receptor and as a signal-transducing molecule. ICAM-1 is a member of the immunoglobulin superfamily and is normally expressed in low levels on leukocytes, endothelium and epithelium. Its expression level can greatly increase in response to the presence of inflammatory cytokines. Among the ICAMs, ICAM-1 is the principle ligand for LFA-1. Notably, conjunctival biopsies from patients with DED exhibit significant expression of ICAM-1 compared with normal controls.

Studies indicate that T cells play a critical role in the development of dry eye disease. 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. ICAM-1/LFA-1 interaction supports the formation of an immunological synapse between T cells and antigen presenting cells (APC), such as dendritic cells; inducing T-cell activation and the release of cytokines that promote ocular inflammation, a substantial component of dry eye disease pathophysiology.

Lifitegrast selectively targets a unique T cell surface adhesion molecule, is not an immunosuppressant, and provides anti-inflammatory properties. It represents a new approach towards treating ocular surface inflammation and is the only agent that treats the signs and the symptoms of DED.

Guidance

The TGA has adopted the following Guidance documents relevant to this submission:

- Note for Guidance on Population Exposure: The Extent of Population Exposure to Assess Clinical Safety. ICH Topic E 1CPMP/ICH/375/95 Effective: 12 February 2002.
- Clinical Investigation of Medicinal Products for Long Term Use (pp. 127 - 132 of Rules 1998 (3C)) Effective: 12 February 2002.

Contents of the clinical dossier

The following clinical information was submitted to support this application:

- 1 clinical pharmacology study providing pharmacokinetic and safety data; Study SAR1118-001
- 2 dose-finding studies:
  - Study 1118-ACJ-100; and
  - Study 1118-KCS-100 (which also provided efficacy data).
- 3 pivotal efficacy/safety studies:
  - Study 1118-KCS-200 (also known as the OPUS-1 trial);
  - Study 1118-DRY-300 (or OPUS-2 trial); and
  - Study SHP606-304 (or OPUS-3 trial).

- 1 long term safety study; Study 1118-DRY-400 (or SONATA trial)
- 1 Periodic Safety Update Report (PSUR)
- 1 Integrated Summary of Efficacy (ISE); tables and figures only
- 1 Integrated Summary of Safety (ISS); tables only
- Literature references.

The submission also included a Clinical Overview, Summary of Biopharmaceutic Studies and Associates Analytical Methods, Summary of Clinical Pharmacology, Summary of Clinical Efficacy and Summary of Clinical Safety.

Paediatric data

The submission did not include paediatric data.

The sponsor was granted a waiver from having to present a Paediatric Investigation Plan in Europe (PDCO EMEA-001979-PIP01-16 (decision number P/0263/2016): 'a waiver was granted for the indication treatment of dry eye disease, in all subsets of the paediatric population from birth to less than 18 years of age, on the grounds that the specific medicinal product does not represent a significant therapeutic benefit as clinical studies are not feasible.'

The sponsor was granted a full waiver from having to submit a Paediatric Assessment in the USA on the basis that the necessary studies are 'impossible or highly impracticable to conduct.'

Good clinical practice

All the clinical studies were conducted in the USA. The sponsor states that all studies were conducted in accordance with the ICH Good Clinical Practice (GCP), the principles of the Declaration of Helsinki as well as local ethical and legal requirements. All subjects gave written informed consent and the relevant study documentation was submitted and approved by appropriate ethics committees and regulatory authorities.

Pharmacokinetics

Studies providing pharmacokinetic data

Table 5: Submitted pharmacokinetic studies

Pharmacokinetic topic	Subtopic(s)	Study ID	Primary aim
PK in healthy adults	General PK Single dose Multiple dose	SAR1118-001	pharmacokinetics dose escalation
PK in special populations	Target population § Single dose Multi-dose	1118-DRY-400 (SONATA)	Efficacy and safety

PK = pharmacokinetics; § Subjects who would be eligible to receive the drug if approved for the proposed indication. None of the pharmacokinetic studies had deficiencies that excluded their results from consideration.

Evaluator's conclusions on pharmacokinetics

The submission did not include a full range of pharmacokinetic studies. The sponsor has argued that as the product is a topical solution applied to the eye and has demonstrated that very little is absorbed systemically this is acceptable.

The lack of accumulation was demonstrated in the long term study (Study 1118-DRY-400, or the SONATA trial) in which the mean trough concentration of lifitegrast being below the lower limit of quantification (0.500 ng/mL) at Day 0, 180 and 360.

One concern is that all the clinical studies were conducted in the USA and the studies did not include sufficient non-Caucasian patients enrolled in the studies to enable any meaningful racial subgroup analysis. The sponsor has provided an argument that the US population is similar to the European population but does not really address the issue of non-White populations, particularly Asian populations who are very poorly represented in the dossier.

Pharmacodynamics

Studies providing pharmacodynamic data

No clinical pharmacodynamic studies were included in the submission.

Evaluator's conclusions on pharmacodynamics

The sponsor has provided no clinical data on the pharmacodynamics of the product beyond the dose finding studies and there is no discussion of any pharmacodynamic effects in the Clinical Overview or Summary of Clinical Pharmacology.

The sponsor has stated that plasma exposure-efficacy relationships were not explored because firstly, the drug is administered directly to the site of action, and secondly, any drug that is measured in the systemic circulation is not considered relevant to the efficacy of the product for the treatment of DED syndrome.

This lack of pharmacodynamic data is rare for a first in class new product. Although the limited systemic studies is justified, there were no studies examining the topical pharmacodynamic effects. The sponsor has failed to demonstrate that lifitegrast at the doses used in the clinical studies has produced the pharmacological action claimed by the sponsor.

It is also unclear from the clinical data provided what any potential consequences of systemic exposure might be.

One study (Study 1118-ACJ-100) attempted to study the pharmacodynamic effects on expression of cellular markers of inflammation in collected tear samples and conjunctival impression cytology (CIC), however, with 60 patients enrolled there was no statistically significant reductions in the total number of neutrophils, eosinophils and lymphocytes in any of the lifitegrast group compared with placebo. It is noted, however that the subjects enrolled in this study had allergic conjunctivitis and not dry eye disease. The Phase II study in subjects with dry eye disease (Study 1118-KCS-100) also aimed to investigate the expression of cellular markers of inflammation by assessing conjunctival impression cytology in approximately 10% of subjects enrolled. The results were inconclusive due to an insufficient sample size and the observed statistical variance.

No further pharmacodynamic studies were conducted in any of the efficacy and safety studies.

Dosage selection for the pivotal studies

The 5.0% lifitegrast dose strength was selected for the pivotal efficacy studies based upon results from non-clinical toxicology studies, a Phase I dose escalation study (Study SAR1118-001) in healthy subjects, and a Phase II study in dry eye subjects (Study 1118-KCS-100). The 5.0% lifitegrast dose provided an exposure considered likely to have a therapeutic effect while maintaining an acceptable margin of safety.

No dose higher than 5% was tested in any of the dose finding or clinical studies and no justification for this is provided. Thus no upper limit of tolerability or efficacy was established. The 5.0% dose has therefore not been justified as the optimum dose.

Efficacy

Studies providing efficacy data

Pivotal studies

- Study SPD606-301/1118-KCS-200 (OPUS-1 trial): A Phase III, multicentre, randomised, 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 (OPUS-1).
- Study SPD606-302/1118-DRY-300 (OPUS-2 trial): A Phase III, multicentre, randomised, 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 (OPUS-2).
- Study SPD606-304 (OPUS-3 trial): A Phase III, multicentre, randomised, 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).

Other studies

- Study 1118-KCS-100 (Phase II): A Phase II, multicentre, randomised, double masked and placebo controlled study evaluating the efficacy of three different concentrations (0.1%, 1.0%, 5.0%) of SAR 1118 Ophthalmic solution in subjects with dry eye using the controlled adverse environment (CAE) model.

Evaluator's conclusions on efficacy

All the studies included in the submission were similar in design except that Study 1118-KCS-100 (a Phase II study) and Study 1118-KCS-200 (the OPUS-1 trial) enrolled subjects with mild to moderate symptoms whereas the Studies 1118-DRY-300 (OPUS-2 trial) and SHP606-304 (OPUS-3 trial) enrolled subjects with moderate to severe symptoms.

The studies were multicentre, randomised, double-blind, placebo-controlled studies. In all the studies, subjects were randomised to lifitegrast 5.0% (lifitegrast 5.0%) or placebo in 1:1 ratio. Study 1118-KCS-100 (Phase II) also included two additional lower strengths of lifitegrast (lifitegrast 0.1% and 1.0%). Each study had a total duration of 14 weeks with two weeks placebo run-in period followed by 12 weeks treatment period. Efficacy data in

each study were collected at Day 0 (Baseline), Day 14, Day 42, and Day 84 with the primary efficacy variables in each study evaluated at Day 84.

The primary efficacy endpoints were not the same in the studies as shown in Table 6 below.

Table 6: Primary efficacy endpoints in the submitted efficacy studies

Study ID	No of subjects	Primary efficacy endpoint(s)
1118-KCS-100 (Phase II)	230 randomised LIF 5% = 58	Single primary endpoint of Inferior corneal staining score (sign)
1118-KCS-200 (OPUS-1)	588 randomised LIF 5% = 293	Co-primary endpoints of Inferior corneal staining score (sign) and VR-OSDI Score (symptom)
1118-DRY-300 (OPUS-2)	718 randomised LIF 5% = 358	Co-primary endpoints of Inferior corneal staining score (sign) and EDS (symptom)
SHP606-304 (OPUS-3)	711 randomised LIF 5% = 355	Single primary endpoint of EDS (symptom) ICSS (sign) was a secondary safety outcome

EDS = eye dryness score; ICSS = inferior corneal staining score; LIF = lifitegrast; VD-OSDI = visual related function subscale of Ocular Surface Disease Index.

It is generally required that proof of efficacy requires two independent studies for replication of the results. One of the questions for studies in dry eye disease (DED) is: *'is a statistically significant improvement required in both the sign and symptom in the same study?'*

This question is addressed by the sponsor in the submission and in discussion with the US FDA. It is acknowledged in the literature;[11,13,14] that there is a low and inconsistent correlation between signs and subjective symptoms in DED.

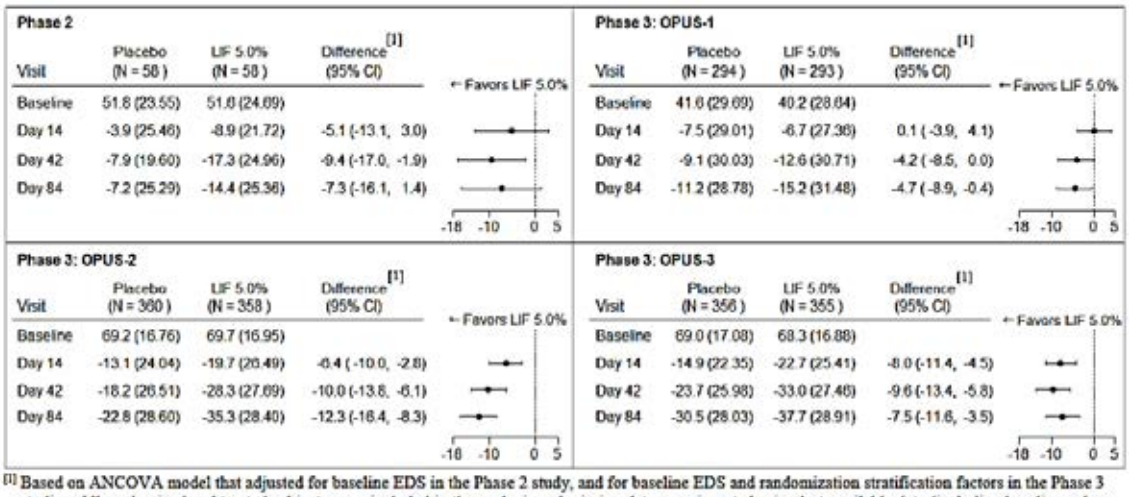
The results of the studies were not entirely consistent but the positive results for both sign and symptom were replicated in second studies.

Clinical symptoms as measured in eye dryness score (EDS)

In Studies 1118-DRY-300 (OPUS-2 trial) and SHP606-304 (OPUS-3 trial), subjects treated with lifitegrast demonstrated statistically superior improvement in the primary clinical symptom of eye dryness early on and continued improvement throughout the study compared to placebo treated subjects. At the end of the treatment period on Day 84, the improvement in clinical symptom, as measured by the eye dryness score, seen in the lifitegrast 5% treated group was higher than in the placebo treated group by about 12 units in Study 1118-DRY-300 (OPUS-2 trial), 8 units in Study SHP606-304 (OPUS-3 trial), 5 units in Study 1118-KCS-200 (OPUS-1 trial), and 7 units in Study 1118-KCS-100 (Phase II).

All randomised and treated subjects were included in the analysis and missing data were imputed using last-available data (including baseline values if all post-baseline values were missing). In the Phase II study, one lifitegrast 5.0% treated subject who did not have a baseline value was excluded from analysis.

Figure 2: Mean change in eye dryness score from Baseline



[1] Based on ANCOVA model that adjusted for baseline EDS in the Phase 2 study, and for baseline EDS and randomization stratification factors in the Phase 3 studies. All randomized and treated subjects were included in the analysis and missing data were imputed using last-available data (including baseline values if all post-baseline values were missing). In the Phase 2 study, one LIF 5.0% treated subject who did not have a baseline value was excluded from analysis.

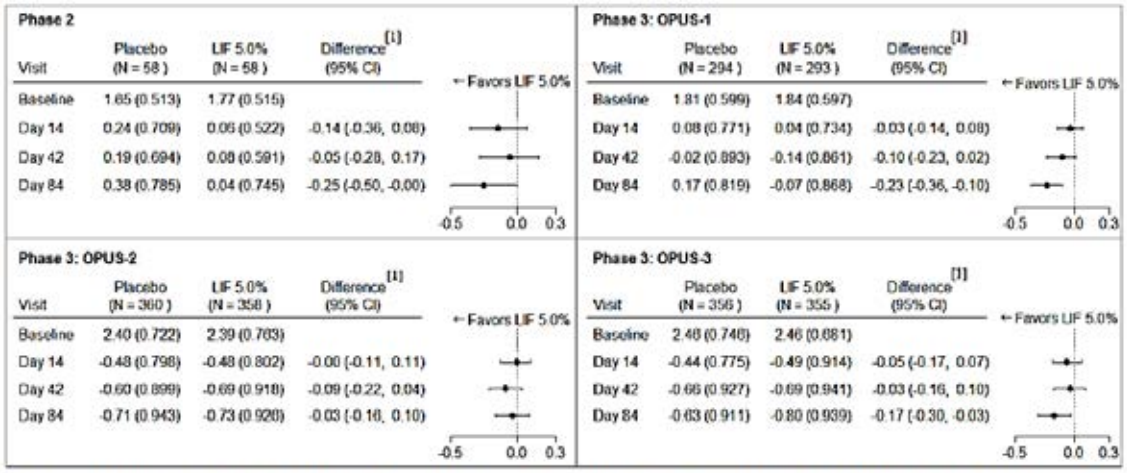
Phase II = Study 1118-KCS-100; OPUS-1 = Study 1118-KCS-200; OPUS-2 = Study 1118-DRY-300; OPUS-3 = Study SHP606-304

Clinical sign as measured by inferior corneal staining score

In Study 1118-KCS-100 (Phase II) and Study 1118-KCS-200 (OPUS-1 trial), placebo treated subjects showed worsening in the clinical sign (as measured in inferior corneal staining score (ICSS)) at Day 84 whereas lifitegrast 5.0% treated subjects in these studies showed no change from Baseline on average. In both studies, the mean reduction in inferior corneal staining score at Day 84 in the treatment arm was higher than in the placebo arm by about a quarter unit, and this difference was statistically significant in Study 1118-KCS-200 (OPUS-1 trial) ($p < 0.001$) and was marginally significant in Study 1118-KCS-100 (Phase II) ($p = 0.048$).

In Studies 1118-DRY-300 (OPUS-2 trial) and SHP606-304 (OPUS-3 trial), both placebo and lifitegrast 5% treated subjects demonstrated at least half unit improvement early on (at Day 14) and continued improving throughout the study. At the end of the treatment period on Day 84; both groups in Study 1118-DRY-300 (OPUS-2 trial) showed equal amount of improvement (about 0.7 units) from Baseline on average, and lifitegrast 5% treated group in Study SHP606-304 (OPUS-3 trial) showed about 0.8 unit improvement from baseline while placebo treated group showed about 0.6 unit improvement from Baseline.

Figure 3: Mean change in inferior corneal staining score from Baseline



[1] Based on ANCOVA model that adjusted for baseline ICSS in the Phase 2 study, and for baseline ICSS and stratification factors in the Phase 3 studies. All randomized and treated subjects were included in the analysis and missing data were imputed using last-available data (including baseline values if all post-baseline values were missing). In OPUS-1 study, one Placebo treated subject who did not have a study eye designated was excluded from analysis.

Phase II = Study 1118-KCS-100; OPUS-1 = Study 1118-KCS-200; OPUS-2 = Study 1118-DRY-300; OPUS-3 = Study SHP606-304

Therefore, based on the primary efficacy endpoints for symptom and signs the lifitegrast ophthalmic solution 5% demonstrated statistically significant efficacy evidence in improving the clinical symptoms of dry eye disease compared to placebo:

- Symptom: EDS; Positive results in Study 1118-DRY-300 (OPUS-2 trial) and Study SHP606-304 (OPUS-3 trial)
- Sign: ICSS; Positive results in Study 1118-KCS-100 (Phase II study) and Study 1118-KCS-200 (OPUS-1 trial)

The key question arises as to whether the statistically significant changes are clinically meaningful. The sponsor has not addressed this issue. A summary of the studies and the key outcomes is shown below.

Table 7: Summary of efficacy endpoints across submitted studies

Study	Endpoint	Clinically meaningful difference	Result (treatment effect)	Statistical significance
1118-KCS-100 (Phase II dry eye)	Change in Baseline to Day 84 in inferior corneal staining (ICSS)	0.30	0.27	0.1375
1118-KCS-200 (OPUS-1 trial)	Change in Baseline to Day 84 in inferior corneal staining (ICSS)	0.30	0.24	0.0007
	Change in Baseline to Day 84 in mean VR-OSDI	0.30	0.02	0.9065
1118-DRY-300 (OPUS-2 trial)	Change in Baseline to Day 84 in inferior corneal staining (ICSS)	0.25	0.02	0.6186
	Change in Baseline to Day 84 in mean eye dryness score (EDS)	10.0 unit	12.61	< 0.0001
SHP-304 (OPUS-3 trial)	Change in Baseline to Day 84 in mean eye dryness score (EDS)	10.0 unit	7.16	0.0007

From these results the studies have only demonstrated a clinically meaningful change in favour of lifitegrast in one outcome in one study.

It is also of concern that the primary outcomes are not consistently supported by the secondary outcomes. Given the very broad heterogeneous patient population enrolled in the studies, will patients be satisfied with a very mild improvement is eye dryness while still having itching, burning and discomfit. It would have added to the evidence to have a global assessment from the patient of overall satisfaction with the treatment or the full VAS as was done in Study 1118-KCS-200 (OPUS-1 trial).

Overall, it is difficult to conclude that one drop twice a day of the 5% product is effective to a sufficiently clinically meaningful way to warrant approval. As the optimum dose has not been demonstrated the product should not be approved at this time.

The sponsor has argued, since the lack of consistent correlation between the sign and symptom variables is well established and the sign and symptom endpoints respond in a paradoxical manner in subjects treated with lifitegrast, the applicant believes a more appropriate interpretation of the data is to evaluate the primary efficacy endpoints independently, thus the totality of clinical evidence.

It is difficult to accept this argument when there is no evidence of a local pharmacological action beyond the use of lubricating eye drops.

The patient population included in the study is very heterogeneous with few patients included who had Sjögren's syndrome or other recognised disease states known to cause dry eye. The studies generally excluded subjects with many conditions known to result in dry eye. The main inclusion criterion was the patient's history or desire to use artificial tears. Given the lack of a clinically meaningful effect in this very mixed population (as seen by the tables of ocular medical history, it may have been more appropriate to focus on the subset of patients with more severe disease, with confirmed dry eye, to demonstrate an effect.

Safety

Studies providing safety data

The Summary of Clinical Safety and Clinical Overview presents the safety analysis using the following integrated analyses and these pools are used in this report, as shown in Table 8 below.

Table 8: Integrated Summary of Safety pooling strategy

Pool	Studies included in safety pool	Dose groups
All dry eye studies	1118-KCS-100 1118-KCS-200 (OPUS-1) 1118-DRY-300 (OPUS-2), SHP606-304 (OPUS-3) 1118-DRY-400 (SONATA)	Placebo All lifitegrast dose groups combined (0.1%, 1.0%, 5.0%), lifitegrast 5.0%
12 week dry eye studies	1118-KCS-100 (lifitegrast 5.0% population only) 1118-KCS-200 (OPUS-1) 1118-DRY-300 (OPUS-2) SHP606-304 (OPUS-3)	Placebo lifitegrast 5.0%
Controlled adverse environment (CAE) studies	1118-KCS-100 (lifitegrast 5.0% population only) 1118-KCS-200 (OPUS-1)	Placebo lifitegrast 5.0%
Non-controlled adverse environment (non-CAE) studies	1118-DRY-300 (OPUS-2) SHP606-304 (OPUS-3)	Placebo lifitegrast 5.0%

Patient exposure

A total of 2578 subjects with dry eye disease have participated in clinical studies, with 1401 subjects receiving at least 1 dose of lifitegrast (1287 of which received lifitegrast 5%).

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).

Table 9: Exposure to Xiidra (5%) and placebo in clinical studies (safety population)

Study type/ Indication	Controlled studies	
	Xiidra lifitegrast 5%	Placebo
Dose Finding/Allergic Conjunctivitis		
Study 1118-ACJ-100/Allergic Conjunctivitis	15	15
Clinical pharmacology/Healthy Volunteers		
Study SAR-1118-001/Clinical pharmacology	5	8
Dose finding/Dry Eye Disease		
Study 1118-KCS-100	58	58
Pivotal/Dry Eye Disease		
Study 1118-KCS-200 (OPUS-1)	293	295
Study 1118-DRY-300 (OPUS-2)	359	359
Study SHP606-304 (OPUS-3)	357	354
Safety/Dry Eye Disease		
Study 1118-DRY-400	220	111
TOTAL	1307	1200

Table 10: 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]			

	Placebo N=1177	All LIF N=1401	All Subjects N=2578
0 to 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)

Max = maximum; min = minimum; SD = standard deviation; a) Total treatment exposure is from first randomised 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 the SONATA trial.

Safety issues with the potential for major regulatory impact

Deaths

There were 2 deaths reported during the clinical studies with lifitegrast, neither of which were considered ocular in nature, nor related to the investigational product.

- One subject, a 72 year old male in the lifitegrast 1.0% group of Study 1118-KCS-100 (Phase II dry eye study) with a relevant medical history of hypercholesterolaemia and hypertension, died of cardiac arrest after 53 days of exposure to lifitegrast 1.0%
- One subject, a 68 year old female in the placebo group of Study SPD-DRY-400 (the SONATA trial) with a relevant medical history of hypertension, chronic obstructive pulmonary disease, and sleep apnoea, died of arrhythmia after 54 days of exposure to placebo.

Serious adverse events

In Study 1118-DRY-400 (SONATA trial), overall, 6 (5.4%) of subjects in the placebo group and 9 (4.1%) of subjects in the lifitegrast 5.0% group had at least 1 serious adverse event (SAE). Chronic obstructive pulmonary disease was the only SAE that occurred in more than 1 subject (2 subjects in placebo group).

Liver function and liver toxicity

Clinical laboratory evaluations were only conducted in Study SAR1118-001 (Phase I study) and as part of the long term Study 1118-DRY-400 (SONATA trial).

In Study SAR1118-001 (Phase I Study) there was only one subject (0.1% lifitegrast) with an abnormal aspartate transaminase (AST) level (100 U/L, ref range 14 to 47 U/L) on Day 17 of Period 3. All other results were within the reference range. This was reported as a mild treatment emergent adverse event (AE) that was not related to the study drug. The AST level returned to normal by Day 28.

In Study 1118-DRY-400 (SONATA trial) the liver panels (albumin, alanine transaminase, AST, alkaline phosphatase, total bilirubin, direct bilirubin (conjugated bilirubin), and gamma glutamic transpeptidase) changes were minimal and similar between treatment groups. No individual changes in liver function were considered clinically meaningful.

Renal function and renal toxicity

Clinical laboratory evaluations were only conducted in Study SAR1118-001 (Phase I study) and as part of the long term Study 1118-DRY-400 (SONATA trial).

In Study SAR1118-001 (Phase I study) the mean changes in urinalysis and clinical chemistry (blood urea nitrogen and creatinine) results were minimal and similar between treatment groups

In Study 1118-DRY-400 (SONATA trial) the renal panels (sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, and glucose) changes were minimal and similar between treatment groups. No individual changes in renal function were considered clinically meaningful.

Haematology and haematological toxicity

Clinical laboratory evaluations were only conducted in Study SAR1118-001 (Phase I study) and as part of the long term Study 1118-DRY-400 (SONATA trial).

In Study SAR1118-001 (Phase I study) the mean changes in haematology results were minimal and similar between the treatment groups.

In Study 1118-DRY-400 (SONATA trial) the mean changes in haematology results were minimal and similar between the treatment groups. There were a number of isolated incidents of values outside the reference range but none were considered clinically meaningful. There were no trends in the results which suggested a safety signal due to a drug effect.

Electrocardiograph findings and cardiovascular safety

ECGs were only performed in the Study SAR1118-001 (Phase I study). No clinically meaningful changes from Baseline in ECG results were observed during the study.

Vital signs and clinical examination findings

Vital signs were only collected during the Study SAR1118-001 (Phase I study). There were no clinically meaningful changes from baseline in vital signs during the study.

Other safety parameters

Schirmer tear test

The Schirmer tear test was a safety measure in Study SAR1118-00 (Phase I study) and Study SHP606-304 (OPUS-3 trial); was an efficacy measure in the Studies 1118-KCS-100 (Phase II dry eye disease), Study 1118-KCS-200 (OPUS-1 trial), and Study 1118-DRY-300 (OPUS-2 trial). The changes from Baseline in Schirmer tear test scores were similar between treatment groups.

Tear film break-up time

Tear film break-up time was a safety measure in the Study SAR1118-00 (Phase I) and was an efficacy measure in the Studies 1118-KCS-100 (Phase II dry eye disease) and Study 1118-KCS-200 (OPUS-1 trial). The changes from Baseline to each measured time point were minimal and similar between treatment groups.

Best corrected visual acuity

Overall, no significant changes were observed in best corrected visual acuity test. The minimal changes between visits in visual acuity were similar between treatment groups in each study.

Slit lamp biomicroscopy

Overall, no significant changes were observed in slit lamp biomicroscopy. Clinically significant slit lamp biomicroscopy abnormalities occurred infrequently in all treatment groups.

Dilated fundoscopy

Overall, no significant changes were observed in dilated fundoscopy. The percentage of subjects with dilated fundoscopy abnormalities was minimal and similar between treatment groups in the six lifitegrast studies in which dilated fundoscopy was measured.

Corneal fluorescein staining

Corneal fluorescein staining was a safety measure in Studies SHP606-304 (OPUS-3 trial) and 1118-DRY-400 (SONATA trial) and was an efficacy measure in all other dry eye studies.

In Study SHP606-304 (OPUS-3 trial) corneal fluorescein staining scores did not worsen for the lifitegrast 5% or placebo groups through Day 84. Mean decreases (improvements) from Baseline were slightly greater for the lifitegrast group in all regions and at all time points (Days 14, 42, and 84.

No worsening in corneal fluorescein staining was observed in any region for either treatment group over approximately 360 days in the Study 1118-DRY-400 (SONATA trial) suggesting that long-term administration of lifitegrast was not associated with corneal damage.

Intraocular pressure

Overall, no significant changes were observed in intra-ocular pressure. The mean changes in intraocular pressure were minimal and similar between treatment groups in the four lifitegrast studies in which intraocular pressure was measured.

Corneal sensitivity

Overall, no significant changes were observed in corneal sensitivity. The mean changes in corneal sensitivity as measured by a Cochet-Bonnet aesthesiometer were minimal and similar between treatment groups in the two lifitegrast studies in which corneal sensitivity was measured, indicating a lack of an anaesthetic effect of lifitegrast. The sponsor concludes that the symptom benefit observed for lifitegrast cannot be explained by an anaesthetic effect.

Conjunctival redness score

Conjunctival redness score was a safety measure in Study SHP606-304 (OPUS-3 trial) and was an efficacy measure in Study 1118-KCS-100 (Phase II dry eye disease), Study 1118-KCS-200 (OPUS-1 trial), and Study 1118-DRY-300 (OPUS-2 trial).

In Study SHP606-304 (OPUS-3 trial), the placebo and lifitegrast groups had decreases (improvements) in conjunctival redness score from Baseline to each visit based on observed data; mean decreases were slightly greater for the lifitegrast group. Conjunctival redness scores did not worsen for the lifitegrast group over time.

Conjunctival staining score with lissamine green

Conjunctival staining score with lissamine green was a safety measure in Study SHP606-304 (OPUS-3 trial) and was an efficacy measure in Study 1118-KCS-100 (Phase II dry eye disease), Study 1118-KCS-200 (OPUS-1 trial), and Study 1118-DRY-300 (OPUS-2 trial).

In Study SHP606-304 (OPUS-3 trial), the placebo and lifitegrast groups had decreases (improvements) in conjunctival lissamine green staining score from baseline to each visit for the total score and each region based on observed data. Conjunctival staining scores

with lissamine green did not worsen for the lifitegrast group over time, and mean decreases were slightly greater for the lifitegrast group at all time points (Days 14, 42, and 84).

Drop comfort score

Drop comfort score was measured upon instillation and at 1, 2, and 3 minutes post-instillation in Studies 1118-ACJ-100 (Phase II allergic conjunctivitis), 1118-KCS-100 (Phase II dry eye), 1118-KCS-200 (OPUS-1 trial), 1118-DRY-300 (OPUS-2 trial), SHP606-304 (OPUS-3 trial), and 1118-DRY-400 (SONATA trial). In addition, in Study SHP606-304 (OPUS-3 trial), drop comfort score was measured at 5, 10, and 15 minutes post-instillation, as needed, for subjects who did not have drop comfort scores ≤ 3 at 3 minutes post-instillation until the score was ≤ 3. If the score was > 3 at minute 15, an AE was recorded.

Overall, numerical improvements in mean drop comfort scores were observed within 2 to 3 minutes following instillation of investigational product in both the placebo and lifitegrast 5.0% groups at each visit. In Study SHP606-304 (OPUS-3 trial), numerical improvements in mean drop comfort scores were observed over time at each post-instillation time point through Minute 3, with the majority of subjects reporting drop comfort scores < 3 within 3 minutes post-instillation and a decreased number of subjects experiencing discomfort (drop comfort score > 3) over all successive study visits and over post-instillation time after Minute 3.

In Study 1118-ACJ-100 (Phase II allergic conjunctivitis), the mean drop comfort scores of lifitegrast 0.1% and 1.0% were similar to placebo, but placebo had a lower mean score (more comfortable) than lifitegrast 5.0%.

In Study 1118-DRY-400 (SONATA trial), the mean drop comfort score of placebo was more comfortable than the drop comfort score of lifitegrast 5.0% at each time point and visit. However, in general, numerical improvement in drop comfort score was observed within each visit (at each time point post-instillation) in the lifitegrast 5.0% group. By 3 minutes post-instillation, the lifitegrast 5.0% group had mean drop comfort scores below 2 at each visit. No mean increase in discomfort was observed for long-term treatment (1 year) with lifitegrast as compared to short-term treatment (12 weeks).

In the 12 week dry eye studies pool, numerical improvements in drop comfort scores were observed at each time point (1, 2, and 3 minutes) after instillation at all visits for both treatment groups. At all time points and all visits, the lifitegrast 5.0% group had a higher drop comfort score (more uncomfortable) than the placebo group. By 3 minutes post-instillation, the placebo and lifitegrast 5.0% groups had mean drop comfort scores at or below 1.3 and 2.6, respectively, at Visits 3, 4, and 5.

In the CAE studies pool and non-CAE studies pool, numerical improvements in drop comfort scores were observed within 2 to 3 minutes following instillation of investigational product in both the placebo and lifitegrast 5.0% groups at each visit. In the CAE studies pool non-CAEE studies pool, the lifitegrast 5.0% group had a higher drop comfort score (more uncomfortable) than the placebo group at all time points and visits. In the CAE studies pool, by 3 minutes post-instillation, the placebo and lifitegrast 5.0% groups had mean drop comfort scores at or below 1.4 and 3.5, respectively, at Visits 3, 4, and 5. In the non-CAE studies pool, by 3 minutes post-instillation, the placebo and lifitegrast 5.0% groups had mean drop comfort scores at or below 1.3 and 2.2, respectively, at Visits 3, 4, and 5. Generally, subjects in the CAE studies pool had higher mean drop comfort scores than subjects in the non-CAE studies pool.

In Study SHP606-304 (OPUS-3 trial) the mean drop comfort score of placebo was lower (more comfortable) than the drop comfort score of lifitegrast at each time point and visit. However, a numerical improvement in drop comfort score was observed over time within

both treatment groups at each post-instillation time point through Minute 3 and the majority of subjects had drop comfort scores < 3 within 3 minutes post-instillation.

By 3 minutes post-instillation, the lifitegrast group had mean drop comfort scores at or below 2.0 at Days 14, 42, and 84 (Visits 3, 4, and 5). For subjects who did not have drop comfort scores ≤ 3 at 3 minutes post-instillation, the drop comfort assessment was repeated at 5, 10, and 15 minutes post-instillation, as needed, until the score was ≤ 3. If the score was > 3 at minute 15, an AE was recorded.

For those subjects with drop comfort scores > 3 at 3 minutes post-instillation, the placebo and lifitegrast groups had similar mean drop comfort scores at 5, 10, and 15 minutes post-instillation, with decreasing numbers of subjects experiencing discomfort (drop comfort scores > 3) over time at each post-instillation time point in both treatment groups. For these subjects, results from drop comfort score evaluation indicate that the number of subjects experiencing drop discomfort (drop comfort score > 3) decreases with time (for example, at Day 0 (Visit 2), 24 subjects in the placebo group and 41 subjects in the lifitegrast group had scores reassessed at 15 minutes post-instillation. In contrast, 15 minute post-instillation at Day 84 (Visit 5), 10 and 17 subjects in the placebo and lifitegrast groups, respectively, were reassessed for drop comfort.

Post marketing data

Lifitegrast (Xiidra, ophthalmic solution 5.0%) was approved by the US FDA on 11 July 2016 for the treatment of the signs and symptoms of dry eye disease. Lifitegrast has been marketed in the United States since 22 August 2016.

Based on the marketing data from United States IMS National Sales Perspectives (NSP) as of 31 December 2016, the estimated patient exposure to lifitegrast is 22,524 person-years treatment since launch.[15]

One Periodic Safety Update Report (PSUR) was included in the submission. It covered the period 11 July 2016 to 10 January 2017. This is the first PSUR and the first Periodic Benefit-Risk Evaluation Report (PBRER).

As of 10 January 2017, there were 56 initial 15 day reports corresponding to 157 post-marketing AEs submitted to the FDA. Among the 157 events, there were 72 serious events and 85 non-serious events. The most frequently reported events were for the Eye Disorders System Organ Class (SOC): vision blurred (13), ulcerative keratitis (10) and eye haemorrhage (7).

Post-marketing spontaneous and solicited (for example, patient support program) safety reports received during the reporting period of 11 July 2016 to 10 January 2017 has identified Hypersensitivity as a new safety concern. These included one report of anaphylactic reaction, two reports of hypersensitivity and one report or type IV hypersensitivity reaction. In addition to these there have been 69 spontaneous reports (with total of 75) non serious localised allergic reactions and one spontaneous report of a SAE of eye swelling (required hospitalisation). The non-serious reports included: eye swelling (48 events), eyelid oedema (16 events), erythema of eyelid (8 events), and 1 report each of conjunctivitis allergic, eczema eyelids, and eye oedema.

The sponsor is currently reviewing the details of these reactions.

[15] The method of calculating patient exposure is (NSP Ext. Units/2)/365 days. NSP Ext. Units represent the number of containers sold. The dose of lifitegrast is 1 container twice per day (morning/night).

Evaluator's conclusions on safety

The safety database consists of three pharmacokinetic/dose finding studies and four efficacy and safety studies, totally 1067 subjects treated for 12 weeks (mean (standard deviation (SD)) exposure = 79.8 (16.38) days) and 220 subjects treated in the long term study (mean (SD) exposure = 304.4 (112.50) days).

The most common AEs reported were ocular and included reduced visual acuity, blurred vision, eye pain, eye irritation, eye pruritus, lacrimation increased, and instillation site reaction.

The most common non-ocular AEs reported were dysgeusia and headache.

Other adverse reactions reported included: instillation site irritation, instillation site pain, eye irritation, instillation site pruritus, increased lacrimation, ocular hyperaemia, conjunctival hyperaemia, eye discharge, instillation site foreign body sensation and sinusitis.

Clinical laboratory evaluations were only measured in the initial pharmacokinetic study (Study SAR1118-001) and the long term study (Study 1118-DRY-400 (SONATA trial)). From this limited data there did not appear to be any changes which suggested a relationship to study drug.

The ocular tests (Schirmer tear test, tear film break-up time, best corrected visual acuity, slit lamp biomicroscopy, dilated fundoscopy, intraocular pressure (IOP), corneal sensitivity, conjunctival redness score, and drop comfort score, whether used as safety or efficacy tests did not indicate any significant changes from placebo.

First round benefit-risk assessment

Table 11: First round assessment of benefits

Indication: Dry eye disease	
Benefits	**Strengths and Uncertainties**
A statistically significant response for the objective sign endpoint of change from baseline to Day 84 in inferior corneal staining score (ICSS) was demonstrated in Studies 1118-KCS-100 (Phase II) and 1118-KCS-200 (OPUS-1 trial). A statistically significant response for the subjective symptom endpoint of change from baseline in eye dryness score (VAS) was demonstrated in Studies 1118-DRY-300 OPUS-2 and SHP606-304 (OPUS-3 trial). Overall pharmacokinetic profile demonstrated minimal systemic exposure with no systemic accumulation over time.	Replication of change in ICSS in two studies Also seen in the post hoc analysis in Study SHP606-304 (OPUS-3) (nominal statistical significance). Replication of symptomatic response in two studies. The treatment effect favouring lifitegrast was also observed in the post hoc analysis of Study 1118-KCS-200 (OPUS-1 trial) in the subgroup of subjects similar to those enrolled in Study 1118-DRY-300 (OPUS-2 trial) and Study SHP606-304 (OPUS-3 trial). Uncertainties: Results of ICSS not clinically meaningful in either study demonstrating statistical significance Results of eye dryness score response only clinically meaningful in one study Very heterogeneous pollution of patients

Indication: Dry eye disease	
Benefits	**Strengths and Uncertainties**
	with mild to moderate disease, no evidence of effect in patients with severe disease for example, Sjögren's disease, radiation induced, thyrotoxicosis and so on. Patient population expected to have greatest benefit not defined

Table 12: First round assessment of risks

Risks	Strengths and Uncertainties
The most common AEs reported were ocular and included reduced visual acuity, blurred vision, eye pain, eye irritation, eye pruritus, lacrimation increased, and instillation site reaction. More AEs with active treatment. The most common non-ocular AEs reported were dysgeusia and headache.	Consistent findings in all trials. No new safety issues found in long term (12 months study).

First round assessment of benefit-risk balance

The benefit risk balance for the use of Xiidra for the proposed indication of the treatment of the signs and symptoms of dry eye disease in adults is unfavourable.

The positive efficacy conclusion was only clinically meaningful in one study, and only slightly above the clinically meaningful threshold.

The safety conclusion is based on an adequate number of patients treated for at least one year, although this is at the low end of the number required. There is minimal systemic absorption with no evidence of accumulation over time. The AEs documented are mostly related to local reactions which were much greater with active treatment than with placebo. The most concerning AE is the low level of reduced visual acuity. This is mostly perceived by the patients but not documented by any reduction in measured visual acuity. While the number and percentage of patients is low, it should be closely monitored in the post market. A medicine aimed at symptomatic treatment of a benign condition needs to have a low level of risk to be acceptable.

The sponsor has failed to demonstrate the pharmacodynamic active in the clinical studies and has failed to demonstrate the optimal dose and dose regimen of the product.

'Treatment' needs to be further justified. Studies show some improvement in symptoms, but no evidence that is definitively affects the pathophysiology of disease.

'Dry eye disease' is a term given to a range of disorders of multiple aetiology and severity, the sponsor has not adequately demonstrated efficacy for this broad patient group.

First round recommendation regarding authorisation

The evaluator is not able to recommend approval of Xiidra for the indication as requested due to the lack of efficacy and the failure to demonstrate an optimal dose.

Clinical questions and second round evaluation

Pharmacokinetics

Question 1

Please explain why a dose higher than one drop of 5% solution was not tested. How does the sponsor justify that one drop of the 5% solution is the optimal dose.

While twice daily versus three times daily was tested in one study why no higher dose regimen was used, for example four times daily, or greater as is recommended for artificial tears.

Evaluation of response

The sponsor states that to ensure an ophthalmic solution with a physiological pH for human use, the highest dosing strength used in the animal studies and carried forward to the clinical trials was up to 50 mg/mL (5%).

The sponsor has reiterated the non-clinical data and the data from Studies SAR 1118-001 and 1118-KCS-100 which demonstrated that of the concentrations tested (up to 5.0%) the 5% formulation was chosen based on the finding that:

> Although there were no statistical separations between treatment arms, the 5% lifitegrast group had the greatest improvement in inferior corneal staining score (ICSS), compared with placebo, at Day 84. Improvement in total corneal staining score (TCSS) at Day 84 showed a similar trend. In addition, there were increasing numerical improvements as the lifitegrast dose increased, suggesting a numerical dose-response. The frequency of subjects with ocular and non-ocular treatment emergent AEs increased with increasing dose thus precluding the potential for testing any higher dose strengths than the 5% solution.

It is accepted that based of the concentrations tested the 5% solution was the most appropriate. However, the sponsor has not addressed the issue of dosing and dosing regimens within the 5% solution, that is, would two drops of 5% offer any additional benefit over one drop or would four times a day be better than three times a day.

The sponsor reiterates that no dose regimens beyond that in Study SAR 1118-001, that is single drop three times daily versus twice daily were conducted.

Pharmacodynamics

Question 2

The Clinical Overview contained the following statements which were unreferenced:

> ***Notably, conjunctival biopsies from patients with dry eye disease (DED) exhibit significant expression of ICAM-1 compared with normal controls.***
>
> ***Studies indicate that T-cells play a critical role in the development of dry eye disease.***

No clinical data in humans is provided to substantiate these statements. Can the sponsor comment as to whether it is all patients from the heterogenous group included in the clinical studies or clarify the subset of patients and types of studies that demonstrate this activity.

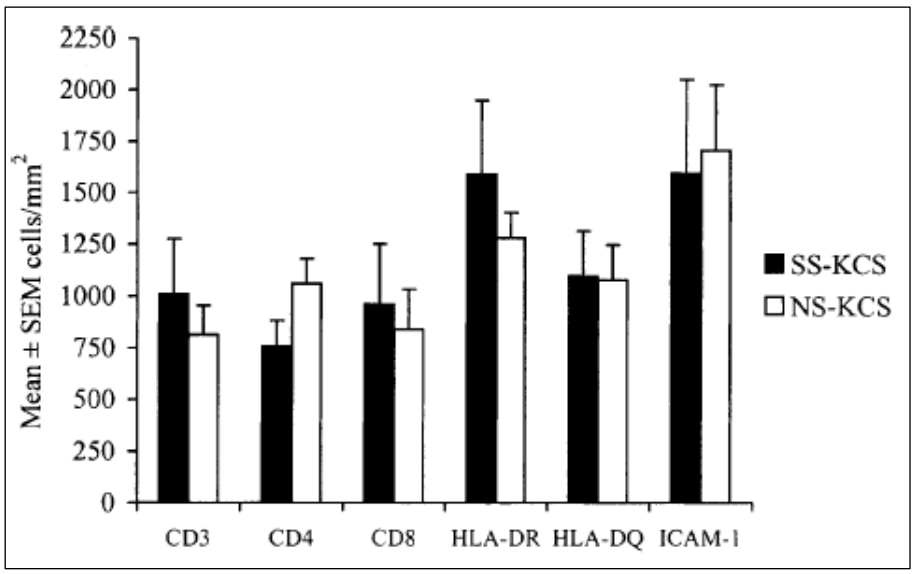
Evaluation of response

The sponsor has provided the same reference for both of these statements.[16]

This was an in-vitro study in conjunctival biopsy specimens from 15 patients with Sjögren's syndrome keratoconjunctivitis sicca (SS-KCS) and non-Sjögren's syndrome keratoconjunctivitis sicca (NS-KCS) defined as meeting the criteria for dry eye (keratoconjunctivitis sicca (KCS) with Schirmer results within the described limit of ≤ 10 mm/5 min with anaesthesia), and with concomitant corneal or conjunctival staining.

The results found that 'large numbers of infiltrating lymphocytes were found in both Sjögren's keratoconjunctivitis sicca and non-Sjögren's keratoconjunctivitis sicca specimens' and that 'most of the infiltrating cells were positive for CD3 (a marker definitive for T cells)'. Further, 'ICAM-1 immunoreactivity was detected on the vascular endothelial cells infiltrating lymphocytes in the substantial propria and in the residual epithelial cells of the conjunctival tissue in SS-KCS and NS-KCS'.

Figure 4: Comparison of the presence of cellular markers of inflammation and immune activation between patients with Sjögren's keratoconjunctivitis sicca (SS-KCS n = 12 to 13) and those with non-Sjögren's keratoconjunctivitis sicca (NS-KCS n = 12 to 15)



The conclusion of the study was:

> The authors' findings indicate that patients with Sjögren's keratoconjunctivitis sicca and non-Sjögren's keratoconjunctivitis sicca have conjunctival inflammation manifested by inflammatory cell infiltrates and upregulation of expression in markers of immune activation.

Question 3

The mechanism of action proposed is anti-inflammatory but no topical anti-inflammatory or effect on T cells has been demonstrated in the in humans in the clinical setting. Please comment.

[16] Stern ME, et al. 2002. Conjunctival T-cell subpopulations in Sjögren's and non-Sjögren's patients with dry eye. *Invest Ophthalmol.Vis Sci.*, 2002; 43: 2609-2614

Evaluation of response

The sponsor responded that the topical anti-inflammatory effect resulting in corneal epithelial healing was demonstrated in each lifitegrast trial in the submission and referred to their response to the efficacy questions below.

Efficacy

Question 4

The sponsor should comment on the issues raised in the clinical evaluator's comments on efficacy, especially on the choice of primary endpoints and the lack of correlation between the symptoms and signs used in the studies.

Evaluation of response

The sponsor has provided a lengthy response to this question. They have identified a number of questions within the first round evaluator's comments and they are noted below.

Question 4, Part 1A

The key question arises as to whether the statistically significant changes are clinically meaningful. The sponsor has not addressed this issue.

Evaluation of response

The sponsor has questioned the first round evaluator's presentation of the results stating that:

> the values in the 'Clinically meaningful difference' are treatment difference assumptions used to determine the sample size in each of the trials' statistical analysis plan The assumptions used in calculating sample sizes are a statistical tool and do not reflect a minimally clinically important difference (MCID) These sample size assumptions should not be used to define the threshold of clinical meaningfulness, which has relevance at the patient level. Due to the wide variety of methods to measure the signs and symptoms of dry eye disease, there are no established MCIDs for the primary sign and symptom measurements utilised in the lifitegrast trials.

The sponsor proposes that guidance provided by the FDA and supported by at least one publication;[17] suggest that the threshold should be set at 25% for the sign benchmark of Inferior corneal staining score (ICSS) (that is, on a sign scale of 0 to 4 points, a clinically meaningful threshold corresponds to at least a one grade difference) and 30% for the symptom benchmark of EDS.

Using these definitions of clinically meaningful difference, the key studies for symptom response, Study 1118-DRY-300 (OPUS-2 trial) and Study SHP606-304 (OPUS-3 trial) which both had EDS measured by a VAS of 1 to100, thus requiring a treatment effect of 30% to be clinically meaningful, rather than the 10% used in the first round evaluation.

Accepting this change from that presented in the original application the change to the table presented in the first round becomes as shown in the table below.

[17] Foulks, G. 2003. Challenges and pitfalls in clinical trials of treatments for dry eye. *Ocular Surf*, 1, 20-30

Table 13: Summary of clinical study endpoints

Study	Endpoint	Clinically meaningful difference	Result (Treatment effect) Active - Placebo	Statistical significance
1118-KCS-100 (Phase II dry eye)	change in baseline to Day 84 in inferior corneal staining (ICSS)	0.25	0.27	0.1375
1118-KCS-200 (OPUS-1)	change in baseline to Day 84 in inferior corneal staining (ICSS)	0.25	0.24	0.0007
	change in baseline to Day 84 in mean VR-OSDI	0.30	0.02	0.9065
1118-DRY-300 (OPUS-2)	change in baseline to Day 84 in inferior corneal staining (ICSS)	0.25	0.02	0.6186
	change in baseline to Day 84 in mean eye dryness score (EDS)	30 units	12.61	-
SHP-304 (OPUS-3)	change in baseline to Day 84 in mean eye dryness score (EDS)	30 units	7.16	-

If one accepts the sponsor's contention that the relevant outcome to be considered is the change from baseline and not the difference between active and placebo and that a change of 30 units is the clinically meaningful difference, then the results of the studies is as follows:

Table 14: Eye dryness score (VAS); Mean change from Baseline to Day 84 (Week 12) in OPUS-2 and OPUS-3 trials and non-CAE studies pool (ITT population with last observation carried forward)

	OPUS-2		OPUS-3		Non-CAE Studies Pool	
	Placebo N=360	Lifitegrast N=358	Placebo N=356	Lifitegrast N=355	Placebo N=716	Lifitegrast N=713
Baseline (Day 0)						
N	360	358	356	355	716	713
mean (SD)	69.22 (16.761)	69.68 (16.954)	68.96 (17.079)	68.31 (16.883)	69.09 (16.909)	69.00 (16.921)
Change from baseline to Day 84 (Week 12)						
N	360	358	353	353	713	711

	OPUS-2		OPUS-3		Non-CAE Studies Pool	
	Placebo N=360	Lifitegrast N=358	Placebo N=356	Lifitegrast N=355	Placebo N=716	Lifitegrast N=713
mean (SD)	-22.75 (28.600)	-35.30 (28.400)	-30.73 (28.006)	-37.87 (28.847)	-26.70 (28.568)	-36.57 (28.632)
Treatment Effect, (SE)	12.61 (2.085)		7.16 (2.096)		9.92 (1.484)	
95% CI for Treatment Effect	8.51, 16.70		3.04, 11.28		7.01, 12.83	
p-value	< 0.0001		0.0007		< 0.001	

OPUS-2 = Study 1118-DRY-300; OPUS-3 = Study SHP606-304; ANOVA = analysis of variance; CI=confidence interval; ITT = intent-to-treat; LOCF = last observation carried forward; SD = standard deviation; SE = standard error; VAS= visual analogue scale; Note: p-values and treatment difference from OPUS-2 and OPUS-3 are from ANOVA model of change with treatment, stratum and treatment by stratum interaction; weights set to stratum size. Note: Eye dryness score (VAS) uses 0 to100 point scale (0 = no discomfort; 100 = maximal discomfort).

Using this method of assessment, it is notable how effective is the placebo. In the OPUS-3 study it meets the definition of clinically meaningful effect. The active ingredient adds little extra benefit for a significant difference in side effects.

Table 15: Study SHP606-304 (OPUS-3) Summary of the most frequent (> 5%) treatment emergent AEs considered related to investigational product (Safety population)

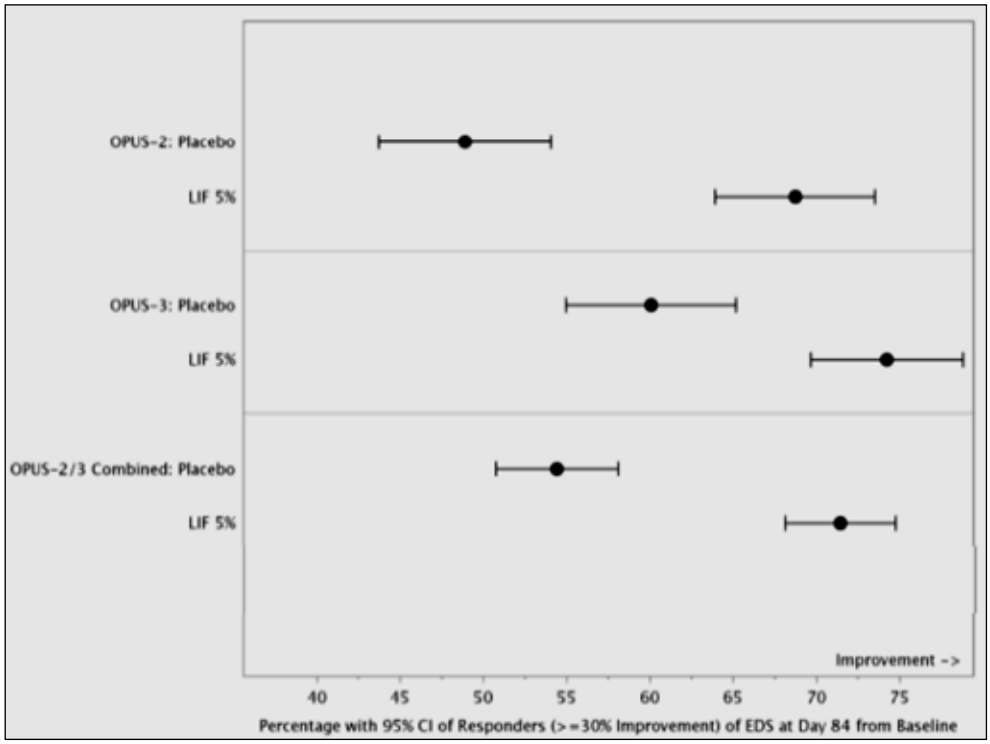
Treatment emergent AE	Placebo N = 354 n (%)	Lifitegrast N = 357 n (%)	Total N = 711 n (%)
Ocular Treatment emergent AEs			
Instillation site irritation	11 (3.1)	65 (18.2)	76 (10.7)
Instillation site reaction	19 (5.4)	45 (12.6)	64 (9.0)
Non-ocular treatment emergent AEs			
Dysgeusia	1 (0.3)	46 (12.9)	47 (6.6)

The sponsor also provides details of the post hoc analysis which calculated the symptom responder analysis, rather than the change from baseline or treatment difference.

> 'To delineate clinically meaningful improvement, a critical distinction needs to be made between the mean effect seen (which is influenced by the variability and repeatability of the scales used) and a change in an individual measure that would be considered important, for example, healing of the corneal surface.'

The sponsor has produced responder analysis and Forest plots to compare lifitegrast and placebo treated subjects that demonstrate improvement ≥ 30% in Eye dryness score from baseline to Day 84. These are shown below.

Figure 5: Forest plot of responders percentage with 95%CI in Eye dryness score (≥ 30% improvement from baseline at Day 84 for OPUS-2, OPUS-3, and OPUS-2 and OPUS-3 data pooled (Intention to treat population with Last observation carried forward)



For the results for corneal staining, again the sponsor has provided the results for the percentage of the patients who reached a clinically meaningful result (responder rate) not the change from baseline which was the primary outcome set in the clinical trial.

Using this new endpoint the results are as follows.

In OPUS-1 more lifitegrast subjects (22.2%) than placebo subjects (13.9%) reached a clinically meaningful threshold of improvement in ICSS (≥ 1 point improvement, nominal p = 0.0095). A numerically higher proportion of lifitegrast subjects (12.3%) than placebo (8.5%) reached a clinically meaningful threshold of improvement in total corneal staining score (TCSS) (≥ 3 point improvement, nominal p = 0.1331).

Table 16: Responder analyses OPUS-1 Corneal Staining Scores

Response Category	Placebo (N=295)	Lifitegrast (N=293)	Nominal P-value
≥ 1 point improvement in Inferior Corneal Staining Score (0 to 4 point scale)	41 (13.9%)	65 (22.2%)	0.0095
≥ 3 point improvement in Total Corneal Staining Score (0 to 12 point scale)	25 (8.5%)	36 (12.3%)	0.1331

In OPUS-3 more lifitegrast subjects (50.4%) than placebo subjects (42.1%) reached a clinically meaningful threshold of improvement in ICSS (≥ 1 point improvement, nominal p = 0.0267). More lifitegrast subjects (33.0%) than placebo subjects (23.0%) reached a clinically meaningful threshold of improvement in TCSS (≥ 3 point improvement) as well (nominal p = 0.0032).

Table 17: Responder Analyses OPUS-3 Corneal Staining Scores

Response Category	Placebo (N=356)	Lifitegrast (N=355)	Nominal P-value
≥ 1 point improvement in Inferior Corneal Staining Score (0 to 4 point scale)	150 (42.1%)	179 (50.4%)	0.0267
≥ 3 point improvement in Total Corneal Staining Score (0 to 12 point scale)	82 (23.0%)	117 (33.0%)	0.0032

While it is accepted that the results for lifitegrast are higher than for placebo using this new definition of response, it is noteworthy that in OPUS-1 only 22% of patients had a clinically meaningful result and only 50% in OPUS-3. Thus in neither study was the treatment effect clinically meaningful in the majority of patients.

Question 4, Part 2

It is also of concern that the primary outcomes are not consistently supported by the secondary outcomes. Given the very broad heterogeneous patient population enrolled in the studies, will patients be satisfied with a very mild improvement is eye dryness while still having itching, burning and discomfit. It would have added to the evidence to have a global assessment from the patient of overall satisfaction with the treatment or the full VAS scores as was done in Study 1118-KCS-200 (OPUS-1).

Evaluation of response

In response to the concern over the primary outcomes not being consistently supported by the secondary outcomes, the sponsor has argued that eye dryness is the "core symptom of dry eye disease and therefore reflects the most patient relevant symptom for assessment". In support of this statement they provided a study reference.[18]

This was a prospective, case control, observational study in a total of 217 patients with mild to moderate dry eye disease and 67 normal controls. The aim of the study was to initiate a 5 year natural history study of dry eye disease to test the hypothesis that the disease is progressive. This publication presented the baseline data. The results in terms of the symptomatology were:

> 'Symptoms reported as a problem at least some of the time in at least 80% of dry eye disease patients included eye dryness (93%), foreign body sensation (84%), light sensitivity (80%), intermittent blurred vision (81%), and tired/fatigued eyes (88%) during the week prior to the baseline study visit.'

It was also noted in the study that "The median acuities in both patients and normals were 20/20, yet the majority of patients reported moderate-to-severe symptoms of blurred vision."

This conclusion of the range of symptoms reported by patients is also supported by Foulks (2003)[17]:

[18] McDonnell PJ, et al. 2017. Study design and baseline findings from the progression of ocular findings (PROOF) natural history study of dry eye. *BMC Ophthalmol*, 2017; 17: 265-280

> 'The generally accepted symptoms of dry eye are sensation of something gritty in the eye, burning, foreign body sensation, pain, dryness, fluctuation of vision with blink, and sensitivity to light. It is important to recognise that the way the question is asked can affect the patient's response. Some patients with dry eye, when asked if they feel a foreign body sensation, will answer "no," but will answer "yes" when asked if they feel like there is something in the eye. Some patients will say they feel dryness, but will have difficulty describing exactly the sensation. Recent surveys of the symptoms of dry eye have identified dryness, soreness, itching, burning, visual blur, and light sensitivity as prominent symptoms of dry eye.'

The sponsor has provided the summary of the 7 item symptom score from the Summary of Clinical Efficacy. The results showed benefit for eye dryness ($p < 0.0001$), eye discomfit ($p < 0.0001$), foreign body sensation ($p = 0.0323$) and marginal benefit for itching ($p = 0.0462$), but no benefit for burning/stinging ($p = 0.5877$), photophobia ($p = 0.1595$) and pain ($p = 0.0738$). The perception of blurred vision is not part of the symptom assessment.

The sponsor has presented the results as follows:

Table 18: Visual analogue scores (VAS) reaching nominal statistical significance

Measure	Baseline VAS	Change from baseline	% Improvement from baseline
Itching	44.32	-18.57	41.90 % improvement in itching
Foreign body sensation	45.17	-19.56	43.30 % improvement in foreign body sensation
Eye discomfort	55.05	-26.42	47.99 % improvement in eye discomfort

Question 4, Part 4

The sponsor has argued since the lack of consistent correlation between the sign and symptom variables is well established and the sign and symptom endpoints respond in a paradoxical manner in subjects treated with lifitegrast, the applicant believes a more appropriate interpretation of the data is to evaluate the primary efficacy endpoints independently, thus the totality of clinical evidence.

It is difficult to accept this argument when there is no evidence of a local pharmacological action beyond the use of lubricating eye drops.

Evaluation of response

The sponsor has responded that the healing of the damaged epithelium over the ocular surface in the clinical studies is evidence of a local pharmacological effect.

Question 4, Part 5

The patient population included in the study is very heterogeneous with few patients included who had Sjögren's syndrome or other recognised disease states known to cause dry eye. The studies generally excluded subjects with many conditions known to result in dry eye. The main inclusion criteria were the patient's history or desire to use artificial tears. Given the lack of a clinically meaningful effect in this very mixed population (as seen by the tables of ocular medical history, it may have been more appropriate to focus on the subset of patients with more severe disease, with confirmed dry eye, to demonstrate an effect.

Evaluation of response

The sponsor has responded by providing details of the clinical development strategy:

> 'Throughout the clinical development of lifitegrast, studies were conducted in a sequential manner to leverage study findings and apply learnings to the next study. The Phase II and OPUS-1 trials enrolled a heterogeneous population with a wide range of dry eye disease severity. Use of a controlled adverse environment (CAE) as part of the inclusion criteria in the Phase II and OPUS-1 trials ensured that only subjects with modifiable dry eye disease would be enrolled. Post hoc analyses using prespecified stratification factors (recent history of artificial tears use and a minimum symptom threshold of Eye dryness score ≥ 40) identified a subgroup of subjects in OPUS-1 who were more responsive on Eye dryness score to treatment with lifitegrast. As the reviewer has pointed out, the observed treatment effect on Eye dryness score was nearly identical across OPUS-1, OPUS-2 and OPUS-3, which confirmed that a history of artificial tear use and baseline Eye dryness score ≥ 40 were appropriate criteria to narrow the target population to subjects with moderate to severe dry eye disease who would benefit from lifitegrast. This is why in subsequent studies, OPUS-2 and OPUS-3, the minimal threshold of 40 in Eye dryness score was used as key inclusion criterion.'

The sponsor states that the inclusion criteria were aimed at minimising confounders and including patients who had aqueous deficient dry eye disease and would therefore be more likely to be responsive to lifitegrast. While aqueous deficient dry eye disease may include some Sjögren's patients, the trials also included others without Sjögren's disease.

The sponsor states that the clinical studies were open to dry eye disease patients with Sjögren's patients, or in those without Sjögren's disease, only 14 subjects enrolled in OPUS-2 (7 each treated with lifitegrast or placebo) and 10 enrolled in OPUS-3 (4 treated with lifitegrast and 6 placebo treated).

The sponsor also states that patients who were within one year post laser assisted in situ keratomileusis (LASIK) were excluded from the trial as about 95% of patients undergoing LASIK experience postoperative dry eye which typically resolves within one year of after surgery.

Question 5

Dry eye can be due to lack of tear production, increased evaporative loss or disorders of the cornea, however, the signs for efficacy used in the studies were primarily looking at corneal epithelial defects. Please comment on how this correlates with symptoms.

Evaluation of response

The sponsor responded by stating the fluorescein staining is a physical manifestation of ocular surface damage. Fluorescein dye identifies corneal epithelial damage primarily by passing through compromised tight junctions and diffusing into intercellular spaces. Of the signs evaluated in the lifitegrast program, corneal fluorescein staining was consistently found across subjects and responsive to change with treatment, which makes it an appropriate outcome to measure.

The presence of both signs and symptoms is necessary to establish a diagnosis of dry eye disease, however, although signs and symptoms coexist in dry eye patients and the presence of both a key premise behind the differential diagnosis of dry eye disease, it is well established in the literature that they are loosely associated. The sponsor acknowledges that this was reflected in the lifitegrast trials and discussed in the Clinical Overview.

Question 6

Could the Schirmer's Test results have been influenced by the lubricating effect of eye drops, please comment on how this correlates with symptoms.

Evaluation of response

The sponsor's response stated that it was not possible for the Schirmer's test results, which was performed without topical anaesthetic to have been influenced by the lubricating effect of the investigational product due to the testing procedure which stated that the subjects withheld the morning dose of study drug prior to study visits and the Schirmer's Test was always conducted prior to administration of the study drug, thus ensuring that the study drug was always administered approximately 12 hours prior to testing.

Question 7

Could there be long term consequences of the eye irritation observed from the eye drops?

Evaluation of response

The sponsor has responded by stating that eye irritation is a generalised term that represents a symptom of discomfort, associated with instillation of the ophthalmic product. There are no data to suggest that there are clinical consequences of such discomfort from clinical trial data in adult patients with dry eye disease.

In the year-long safety study (SHP606-303, SONATA) the following were safety endpoints: slit lamp biomicroscopy, corneal fluorescent staining, drop comfort, best corrected visual acuity, intraocular pressure, corneal endothelial cell count as well as adverse event assessment. Any adverse finding on testing was captured and reported as AEs.

The sponsor repeated the results that demonstrated that the lifitegrast treated patients had higher overall incidence of eye irritation 3.6% versus 0.9% for placebo, and a higher incidence of possibly related and probably related relationship and a higher incidence of both mild and moderate severity compared to placebo.

The sponsor argues that overall the ocular safety parameter of drop comfort was comparable between the lifitegrast and placebo groups. Numerical improvements in drop comfort were observed over time in both treatment groups, but the lifitegrast group had consistently higher drop comfort scores (indicating a higher level of discomfort) than the placebo group.

The sponsor argues that the level of eye irritation is low and no objective clinical consequence to eye irritation was reported in the SONATA study.

Other issues

Question 8

Evaluator commentary on the AEs in the SONATA trial, the reviewer states: Of concern was the patient perception of reduced visual acuity which was reported by 11.4% compared to 6.3% with placebo.

Evaluation of response

The sponsor has qualified the finding of reduced visual acuity by presenting the data on relatedness for this AE. The data present the relatedness as reported by the investigator and concludes that when considering reduced visual events with possible or probable relationship to the investigational product, the AEs in the SONATA trial show similar frequencies in the placebo and lifitegrast groups: lifitegrast 5.0% versus placebo 4.5%.

While respecting the best judgement of the investigators in the studies, this is a new, first in class product and so clinical experience is limited as to what AEs are related to the drug. The concern raised by the first round evaluator is a genuine one for a product with limited experience.

Question 9

Use of Artificial Tears

Evaluator commentary OPUS-1: The study protocol did not specify if patients could take breakthrough medication. It is stated that about half (46.1%) of patients on lifitegrast took prior or concomitant medications of which the most common was artificial tears but the number who used artificial tears during the study is not provided. It is therefore unknown if this affected the outcome.

Evaluation of response

The sponsor has clarified that, with the exception of the long term safety study (SONATA), patients were not allowed to use artificial tears during the OPUS-1 study. The reference to use of artificial tears as "prior to concomitant medications" should have been amended to state that the reference to artificial tears was PRIOR to the study.

In the pivotal trials subjects were required to have used artificial tears within 30 days prior to enrolment but use was prohibited within 72 hours of Visit 1.

In the long term study (SONATA) use of artificial tears was prohibited during the washout period within 72 hours of Visit 1 (Day -7) and up to Visit 3 (Day 14) with Visit 2 (Day 0) being the first day of study drug. Use of artificial tears was allowed after Visit 3 through to study end.

Second round benefit-risk assessment

As no new clinical data was submitted and after consideration of the response to the clinical questions, the assessment of the benefit risk balance is unchanged from the first round evaluator's conclusion.

The benefit risk balance for the use of Xiidra for the proposed indication of the treatment of the signs and symptoms of dry eye disease in adults is unfavourable.

VI. Pharmacovigilance findings

Risk management plan

The sponsor submitted EU risk management plan (RMP) version 1.0 (7 July 2017; data lock point (DLP) 21 June 2017) and Australian Specific Annex (ASA) version 1.0 (21 August 2017) in support of this application at the first round, and submitted an Australian RMP version 1.0 (24 May 2018; DLP 30 September 2017) to replace EU-RMP version 1.0 at the second round. The sponsor submitted EU-RMP version 1.0 (7 November 2018; DLP 10 July 2018) and ASA version 1.1 (5 December 2018) to replace these documents at the post-second round reconciliation.

The proposed Summary of Safety Concerns and their associated risk monitoring and mitigation strategies are summarised in the table below.

Table 19: Summary of Safety Concerns in the RMP

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	Hypersensitivity	ü	–	ü	–
Important potential risks	Nil	–	–	–	–
Missing information	Use in children	ü	–	ü	–
	Use in pregnant or breast-feeding women	ü	–	ü	–
	Off-label use	ü	–	ü	–

Summary of RMP evaluation[19]

- The Summary of Safety Concerns is acceptable from an RMP perspective.
- The sponsor has proposed no additional pharmacovigilance activities, which is acceptable given the nature of the safety concerns.
- The sponsor has proposed no additional risk minimisation activities, which is acceptable given the nature of the safety concerns.

New and outstanding recommendations from second round evaluation

There is one outstanding recommendation at the post-second round reconciliation.

- The sponsor has replaced the previous RMP documents with an updated EU-RMP version 1.0 and updated ASA version 1.1. These are acceptable for evaluation. It is noted that the 'table of risks not considered important for inclusion in the list of safety concerns' previously provided in the Australian RMP version 1.0 has not been included in the replacement EU-RMP. The sponsor should commit to including this information in SVII.1.1 in future RMP updates in accordance with EU-RMP and TGA requirements, and to commit to reporting on these risks in the Periodic Safety Update Reports (PSUR).

[19] *Routine risk minimisation* activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.
Routine pharmacovigilance practices involve the following activities:
- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labelling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

Proposed wording for conditions of registration

- Any changes to which the sponsor has agreed should be included in a revised RMP and ASA. However, irrespective of whether or not they are included in the currently available version of the RMP document, the agreed changes become part of the risk management system.
- The suggested wording is:
  - The Xiidra EU-Risk Management Plan version 1.0 (7 November 2018; DLP 10 July 2018), with Australian Specific Annex version 1.1 (5 December 2018), included with submission PM-2017-03384-1-5, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.
- The following wording is recommended for the PSUR requirement:
  - An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of Periodic Safety Update Reports (PSURs).
  - Unless agreed separately between the supplier who is the recipient of the approval and the TGA, the first report must be submitted to TGA no later than 15 calendar months after the date of this approval letter. The subsequent reports must be submitted no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of this approval letter. The annual submission may be made up of two PSURs each covering six months. If the sponsor wishes, the six monthly reports may be submitted separately as they become available.
  - The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII-Periodic Safety Update Report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration. Each report must have been prepared within ninety calendar days of the data lock point for that report.
- As Xiidra is a new chemical entity it should be included in the Black Triangle Scheme as a condition of registration. The following wording is recommended for the condition of registration:
  - Lifetegrast (Xiidra) is to be included in the Black Triangle Scheme. The PI and CMI for XIIDRA must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product.

VII. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations.

Introduction

Background

Dry eye disease is common; the estimated prevalence in USA and Europe is between 4.3 to 21.9%. Although not life threatening, dry eye disease can cause distressing symptoms and

result in loss of work productivity and quality of life. In rare situations it can lead to corneal ulcers and scarring.

The prevalence of dry eye disease increases with age. There are a number of environmental factors (such as exposure to medications (anti-histamine, diuretics), contact lens uses, dry environment) and diseases (such as connective tissue disease, post laser) that contribute to its development. Symptoms are more striking than signs.

There are currently limited treatment options available for dry eye disease. Avoiding environmental triggers is important. Artificial tears and eye lubricants may provide some relief but require frequent application. There are lubricants available which do not contain a preservative that are suitable for long term use, however those which do contain a preservative may be associated with ocular surface damage. Punctate plugs (tiny devices inserted into tear ducts to block drainage) are occasionally used for persistent symptoms or due to dry eye associated with surgery.

Ciclosporin 0.05% (Restasis) eye drops are registered in USA for the treatment of dry eye disease. Restasis is thought to work by modulating the immune system, increasing the production of tear cells from lacrimal glands. Interestingly, tear production does not occur immediately but may be noticed 3-6 months after starting treatment. Ciclosporin eye drops are not on the ARTG, however are used off label for this indication in Australia.

The problems in performing studies with dry eye disease have been described in many articles, including a recent review.[20] These include lack of consistent relationship between symptoms and signs, multifactorial aetiology, variability in disease state, and subjective nature of questionnaires.

Rationale for treatment

The tear film covers the cornea and plays a role in refraction and lubrication of the cornea. The tear film consists of an aqueous portion produced by the lacrimal glands, an outer lipid coating from the Meibomian glands, and an inner mucin layer from conjunctival goblet cells.

Ocular surface inflammation also is a key component to dry eye. Conjunctival biopsies from patients with dry eye disease exhibit greater expression of ICAM-1 compared to controls. ICAM-1 is a member of the immunoglobulin superfamily and is normally expressed in low levels on leukocytes, endothelium and epithelium.

Lifitegrast targets the interaction between LFA-1 and ICAM-1. LFA-1 mediates cell-cell interactions essential to immune and inflammatory response. Its expression is limited to leucocytes.

Table 20: Dry Eye disease subdivided into types

Evaporative Dry Eye	Aqueous Deficient Dry Eye
Meibomian oil deficiency	Sjögrens syndrome – primary or secondary
Disorder of lid aperture	Aging
Low blink rate	Lacrimal deficiency
Drug action	Systemic drugs
Vitamin A deficiency	Lacrimal gland duct obstruction

[20]Clayton JA Dry Eye, *N Engl J Med* , 2018; 378: 2212-2223

Evaporative Dry Eye	Aqueous Deficient Dry Eye
Topical drugs and preservatives Contact lens use Other ocular surface disease	Graft versus host disease Congenital abnormalities Connective tissue disease Reflex block Neuropathic disorders Contact lens use

Quality

Lifitegrast is packaged as a 5% (50 mg/mL) solution in single use low density polyethylene ampoules with 5 ampoules per aluminium laminate pouch, in packs of 20 and 60 ampoules.

Lifitegrast is made by chemical synthesis. The active pharmaceutical ingredient contains one chiral centre and is the isomer with S configuration as proven by single crystal X-ray crystallography. Six polymorphic forms of lifitegrast are known, with Form 1 synthesised consistently by the drug substance manufacturer and confirmed in the specification by powder X-ray diffraction. The drug substance is appropriately controlled by acceptable tests and limits for appearance, identity, assay, related substances, residual solvents, palladium content, powder x-ray diffraction and microbial limits. Related substances, residual solvents and heavy metal impurities have been controlled according to the ICH guidelines.

The formulation includes sodium thiosulfate as an antioxidant. The manufacturing process for lifitegrast eye drops involves mixing the ingredients together under nitrogen and ensuring the pH is between 7.2 and 7.5.

The finished product is appropriately controlled using the finished product specifications. The specifications include acceptable tests and limits for appearance, identity (UV and HPLC), colour, pH, osmolality, assay, related substances, minimum fill volume, sodium thiosulfate assay, particulate matter, sterility and endotoxin limits. No degradation impurities have been identified in the finished product and all individual degradation products are controlled according to the ICH identification threshold.

A shelf-life of 12 months stored below 25°C and protected from light is recommended in the proposed container closure.

Chemistry and quality control aspects were considered acceptable.

Nonclinical

In vitro, lifitegrast was shown to inhibit human T-cell adhesion to ICAM-1 with nanomolar potency, and to inhibit inflammatory cytokine release from human peripheral blood mononuclear cells.

In vivo pharmacology studies showed that corneal inflammation following topical ocular administration of lifitegrast was reduced in one study in mice, increased lacrimal gland inflammation was seen in another study in mice and no effect or only a slight reduction in conjunctival inflammation was observed in dogs.

No significant secondary pharmacological targets for lifitegrast were identified in screening assays. Safety pharmacology studies indicated no clinically relevant effects on the CNS, cardiovascular or respiratory systems.

Systemic absorption of lifitegrast after topical ocular administration was shown to be rapid but low in laboratory animal species, as in humans. Ocular distribution studies in rats, rabbits and dogs showed highest exposure in anterior tissues (conjunctiva and cornea), with drug levels in posterior ocular tissues and the aqueous and vitreous humour markedly lower. Clearance was rapid. Lifitegrast was shown to be minimally metabolised by CYP enzymes *in vitro* in experiments with rat, dog, monkey and human hepatocytes. Excretion in rats and dogs was predominantly via bile/faeces.

Lifitegrast had a low order of acute toxicity in single-dose toxicity studies performed by the topical ocular route in rabbits.

Repeat-dose toxicity studies by the ocular route were performed in rabbits and dogs (up to 9 months duration in both species). No toxicologically significant adverse effects were observed. Treatment-related findings were limited to transient signs of mild ocular irritation, and minor histological changes in the tongue.

The weight of evidence supports that lifitegrast is not genotoxic. Carcinogenicity studies have not been performed; this is considered acceptable under ICH S1A.[7]

Lifitegrast did not affect male or female fertility (in rats) or embryofetal development (in rats and rabbits) at IV doses yielding systemic exposure levels vastly in excess of that in patients at the maximum recommended human dose. Assignment to Pregnancy Category B1 was supported.[8]

Lifitegrast was shown to not be phototoxic in an *in vitro* assay. Cytotoxicity to human corneal epithelial cells was observed with lifitegrast *in vitro*, but under conditions that exaggerate sensitivity; the finding is not considered to predict ocular cytotoxicity *in vivo* in patients.

There were no nonclinical objections to the registration of Xiidra.

Clinical

Pharmacokinetics

Pharmacokinetic studies were performed in healthy individuals to determine the pharmacokinetic characteristics of lifitegrast in tears. Lifitegrast tear concentration increased in a roughly dose proportional manner from 0.1 to 5%, with high interpatient variability of around 100% for C_{max} and AUC. Patients with dry eye disease may have less tears, thus it is not known if the pharmacokinetic characteristics in healthy subjects would apply to this population.

Systemic absorption only occurred in the 1% and 5% eye drops, time of maximal observed concentration during a dosing interval ($T_{max)}$ was at 5 to 13 minutes, the levels were below detectable limits after 1 hour.

Pharmacodynamics

No pharmacodynamic studies were included in the dossier.

Dose Selection

The 5% lifitegrast dose was selected for the pivotal efficacy studies based upon results of the non-clinical studies, a Phase I dose escalation study in healthy subjects

(Study SAR118-001) and a Phase II study in dry eye subjects (Study 1118-KCS-100). The dose escalation study was primarily to assess the pharmacokinetic characteristics. In the Phase II clinical study, there was greater efficacy in those who received the 5% strength; however there was no statistically significant difference in this parameter when compared to placebo. Thus, the dose used in the clinical studies was not well justified.

It is also important to note that the formulations used across the clinical development program were slightly different:

- Phase I formulation = Study SAR1118-001;
- Phase II formulation = Study 1118-KCS-100;
- Opus-1 trial formulation = Study 1118-KCS-200; and
- OPUS-2/OPUS 3/SONATA trial formulation (intended commercial formulation) = Study 1118-DRY-300 (OPUS 2 trial), Study SHP606-304 (OPUS 3 trial); Study 1118-DRY-400 (SONATA trial)

One excipient; sodium thiosulphate pentahydrate is a chemical used in photographic processing, gold extraction, iodometry, and neutralising chlorinated water. It is used as a medicine intravenously for cyanide poisoning, calciphylaxis in haemodialysis patients, preventing tissue destruction in extravasation during chemotherapy, neutralise renal toxicity of cisplatin. It is used topically to treat ringworm. It is on the ARTG and not scheduled. It may be harmful if swallowed. Inhalation: may cause respiratory tract irritation. May be harmful if inhaled. Chronic: prolonged or repeated skin contact may cause dermatitis. Range of toxicity: ingestion of 12 g of sodium thiosulfate was virtually non-toxic except for producing violent catharsis. The lowest toxic intravenous doses for humans were 0.2 to 1.5 g/kg.

Efficacy

An overview of the clinical studies is provided in Table 21 below.

Efficacy measures included symptoms and signs.

- Ocular Surface Disease Index (OSDI): Is a validated symptoms score for dry eye.
- Eye dryness score (EDS): In the OPUS-2 and OPUS-3 trials, a VAS was used to record results of the EDS. This differs from the OSDI in that it asks patients to record ocular symptoms in real time.

The sponsor analysed the concordance between the EDS-VAS and OSDI, Ocular discomfort score and a single item of responsiveness. The correlation between the tests was moderate at baseline (Pearson correlation coefficient 0.3). Responsiveness or the ability to assess change over time for OSDI versus EDS was 69 to 72%.

The FDA requested a review of the patient reported outcome measures, VAS and ocular discomfort score. The conclusion by the experts in the Division of Transplant and Ophthalmology was that these were fit for purpose.

Inferior corneal staining score (ICSS) and total corneal staining score: Corneal fluorescein staining is a standard measure of efficacy in dry eye disease. The sodium fluorescein stains the devitalised corneal epithelial cells.

Clinical significance

The sponsor considered an improvement of more than 30% in the ocular surface disease index or the eye dryness score (relative) or more than 15 points on the eye dryness score (absolute) to be clinically significant.

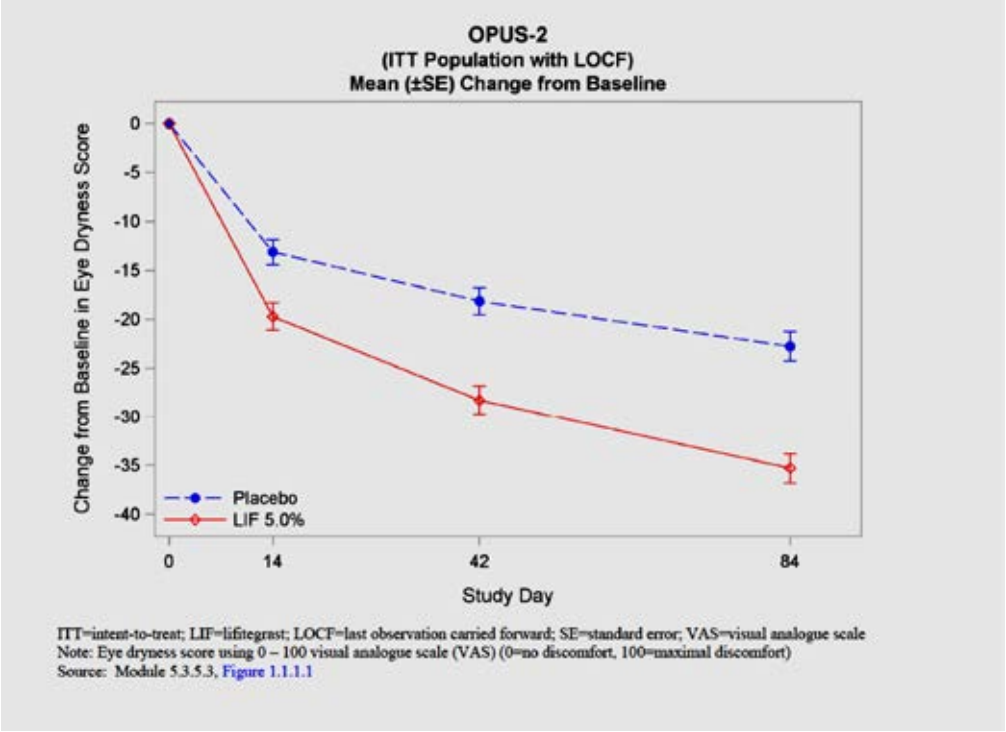
The sponsor also considered stability in the inferior corneal staining score (rather than worsening) to be evidence of improvement.

Table 21: Overview of clinical studies included in submission

Trial:	OPUS-1	OPUS-2	OPUS-3
Year	August 2011 to April 2012	December 2012 to October 2013	November 2014 to October 2015
Objectives	Primary: Efficacy was assessed by co-primary endpoints inferior fluorescein staining and VR-Ocular Surface Disease Index Secondary: Ocular signs by Schirmer's tear test and symptoms by total Ocular Surface Disease Index	Primary: Efficacy by inferior fluorescein staining score and eye dryness score visual analogue score Secondary: Total corneal staining score and nasal conjunctival lissamine green staining score , eye discomfort visual analogue score and ocular discomfort score	Primary: Visual analogue score eye dryness scale Secondary: Other symptom scores
Treatment	5% lifitegrast for 12 weeks versus placebo (which contained the same fluid and excipients but no active drug) Patients were not allowed to use lubricants during the study		
Inclusion criteria	History of dry eye Best corrected visual acuity score of > 0.7 Logarithm of the minimum angle of resolution R; or Corneal fluorescein staining score of > 2 in at least one area in at least 1 eye Corneal redness > 1 Positive response to controlled adverse environment	As OPUS-1 trial but all patients used artificial tears within 30 days of screening	As for OPUS-2 trial
Exclusion criteria	Pre-auricular lymphadenopathy Ocular conditions such as glaucoma, diabetic retinopathy, blepharitis, meibomian gland disease, follicular conjunctivitis, iritis, uveitis, herpes of ocular infection, history of LASIK or other ophthalmic surgery	As per OPUS-1 trial	As for OPUS-2 trial
Patients	About 50% using artificial	N = 718	N = 711

Trial:	OPUS-1	OPUS-2	OPUS-3
	tears N = 588 total		
Results	Improvement in inferior corneal staining score of -0.07 in the lifitegrast group, compared to deterioration by +0.17 in the placebo group (p = 0.0007). Improvement in OSDI of -0.12 in the treatment group and -0.11 in the placebo group (not significant)	Improvement on inferior corneal fluorescein staining in both groups, -0.71 in placebo and -0.73 in lifitegrast, - not significantly different Greater improvement in visual analogue score for dry eye in the lifitegrast (-35.30) compared to placebo group (-22.75) p < 0.0001 Secondary endpoints- improvement in symptom scale greater in lifitegrast group	Statistically significant improvement in visual analogue score eye dryness in lifitegrast (-37.9) versus placebo (-30.7) No difference in ocular discomfort score Significant difference in visual analogue score for itch, foreign body sensation, eye discomfort. No significant difference in burning, stinging, photophobia, pain
Comments	Seems unusual that in this study with the milder symptoms there was a difference in signs not symptoms. Usually there are symptoms before signs.	Improvement in symptoms not signs.	There was a discrepancy between the two different subjective scales measuring eye discomfort.

Figure 6: EDS-VAS; mean change from Baseline in all visits in the OPUS-2 trial



ITT=intent-to-treat; LIF=lifitegrast; LOCF=last observation carried forward; SE=standard error; VAS=visual analogue scale
Note: Eye dryness score using 0 – 100 visual analogue scale (VAS) (0=no discomfort, 100=maximal discomfort)
Source: Module 5.3.5.3, Figure 1.1.1.1

Figure 6 demonstrates that there was a progressive improvement in symptoms during the duration of the study in both the placebo and lifitegrast treatment groups.

Safety

An integrated summary of safety was provided and included data from all dry eye studies (Study KCS-100 and the OPUS-1, OPUS-2, OPUS-3 and SONATA trials).

The SONATA trial was a Phase III, multicentre, randomised, double masked, placebo controlled study evaluating the safety of 5% lifitegrast solution in subjects with dry eye over a period of 360 days. Outcome variables included symptoms, eye examination, clinical laboratory values, concentration of lifitegrast in plasma, lymphocyte counts. The study enrolled 111 subjects in the placebo arm, and 221 in the lifitegrast arm. More patients withdrew due to adverse events in the lifitegrast group (12.2%) compared to the placebo group (8.1%). There were also more patients who developed treatment emergent adverse events in the lifitegrast group (72.7%) than the placebo group (53.2%).

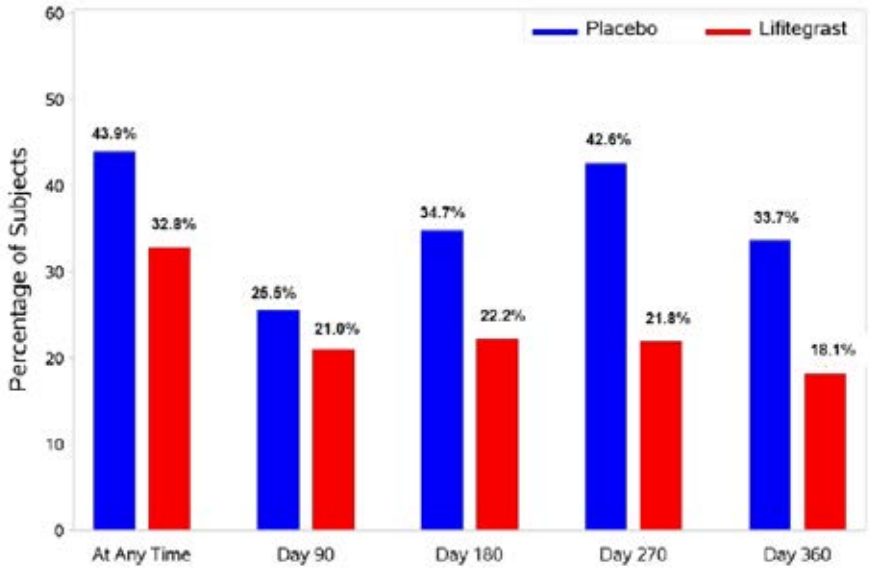
More patients in the lifitegrast (53.6%) than placebo (34.2%) groups developed ocular adverse events. There were also more non ocular adverse events in the lifitegrast group (47.3% compared to 36%). The most common non-ocular treatment emergent AE was dysgeusia, occurring in 16.4% of those treated with lifitegrast and 1.8% of the placebo group.

Table 22: Study 1118-DRY-400 (SONATA trial) Summary of the most frequent (> 5%) ocular treatment emergent AEs in treatment groups (safety population)

System Organ Class Preferred Term	Lifitegrast N=111 n (%)	Placebo N=220 n (%)	Total N=331 n (%)
Subjects with at least 1 ocular TEAE	38 (34.2)	118 (53.6)	156 (47.1)
Eye disorders	33 (29.7)	82 (37.3)	115 (34.7)
Visual acuity reduced	7 (6.3)	25 (11.4)	32 (9.7)
Dry eye	6 (5.4)	4 (1.8)	10 (3.0)
General disorders and administration site conditions	7 (6.3)	51 (23.2)	58 (17.5)
Instillation site irritation	5 (4.5)	33 (15.0)	38 (11.5)
Instillation site reaction	2 (1.8)	29 (13.2)	31 (9.4)

TEAE=treatment-emergent adverse event

Figure 7: Artificial tear use by treatment group in the Phase III long term safety Study 1118-DRY-400 (SONATA trial)



For days 90-360, the percentage of subjects is based on the number reporting artificial tear use since the last visit divided by the total number in the safety population with data at the visit.

Source: Module 5.3.5.3, Figure 1.1.32

There were no differences in laboratory values for renal disease, liver disease or blood count. There was no significant change in blood lymphocyte count. Corneal endothelia cell counts decreased in the placebo group but increased in the lifitegrast group.

In the summary of safety analysis from all clinical studies, a total of 1401 subjects had been exposed to lifitegrast. Of these, 177 had been exposed for > 6 months and 170 for > 12 months. A similar pattern of adverse events to that observed in the SONATA trial were identified.

There were no significant differences in Schirmer's tear test, tear film break up time, best corrected visual acuity, slit lamp biomicroscopy or dilated fundoscopy. There was no significant difference in corneal sensitivity or intraocular pressure between treatment groups.

Table 23: Summary of common (> 5% of subjects in either treatment group) treatment emergent AEs; 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)

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

Clinical evaluator's recommendation

The clinical evaluator recommended rejection. The sponsor spoke with the Delegate on receipt of the clinical evaluation report and requested a stop clock to prepare a response to the evaluator's and Delegate's concerns. These are summarised below.

In addition, the sponsor proposed a new indication:

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

1. Current use and adverse effects in the USA

   Market authorisation for the treatment of dry eye disease was granted in the USA in July 2016, and in Canada in December 2017. The global cumulative post market exposure as of June 30 2018 was estimated to be 154, 295 person years (considering the size of the US population and prevalence of the condition, this use is quite low). In addition, the sponsor estimated the number of new to brand patients during a 12 month period between July 2017 and July 2018. It was estimated that there were 342, 917 new users, as this is larger than the number of patient-years of exposure it would suggest many patients use the medication for a short period of time. There were a small number of adverse event reports, the most common problems included installation site pain (0.137%), installation site reaction (0.127%), installation site erythema (0.024%), instillation site pruritus (0.024%), vision blurred (0.106%), dysguesia (0.048%).

2. Evidence of pharmacodynamic effects

   The abstracts of two publications were included:

   a. Suppression of Th1-mediated keratoconjunctivitis sicca by lifitegrast.[21] Mice were treated with vehicle or lifitegrast twice daily for 5 days. The expression of Th1 family genes (IFN-γ, CXCL9, and CXCL11) was evaluated by real-time polymerase chain reaction. Corneal barrier function was assessed by Oregon Green dextran staining and goblet cell number and area were measured. Compared to the vehicle-treated group, the lifitegrast-treated group had

[21] Guimaraes et al.2018, Suppression of Th1-Mediated Keratoconjunctivitis Sicca by Lifitegrast. *J Ocul Pharmacol Ther* 2018; 34: 543-549

significantly lower expression of Th1 family genes, less corneal barrier disruption, and greater conjunctival goblet cell density/area.

b. Mechanisms of action of the leukocyte function-associated antigen-1 (LFA-1) antagonist lifitegrast in dry eye disease.[22] This study was performed in mice who received scopolamine to induce dry eye disease. Mice were treated with topical lifitegrast three times a day. Efficacy was assessed by corneal fluorescein score, corneal conjunctival T cells, and inflammatory markers.

   Corneal fluorescein score was significantly reduced at Days 10 and 15 in dry eye disease mice treated with lifitegrast, compared to DED mice treated with normal saline ($p < 0.001$). Lifitegrast did not result in changes in corneal and conjunctival T cells by flow cytometry ($p > 0.05$). However, on Day 15 after dry eye disease induction, the density of Tred cells in focal areas of the conjunctiva were reduced in the DED-lifitegrast versus dry eye disease-normal saline treated mice ($p = 0.021$). The density of T cells did not change with any treatment group in the tears ($p > 0.05$). IL-17 and IL-6 mRNA levels were decreased, FoxP3 mRNA level was increased in tears of DED lifitegrast versus normal saline-treated controls ($p < 0.05$). Interestingly, lifitegrast treatment resulted in significantly reduced density of Th1 cells in lymph nodes at Day 10 following DED induction compared with DED-normal saline treated group ($p < 0.05$).

3. The sponsor also submitted a number of subgroup analysis from the OPUS trials to support the new indication.

   The subgroup analyses were based on randomisation stratification factors prospectively assigned in OPUS-2 and OPUS-3; wherein subjects were stratified on the basis of their baseline ICSS (> 1.5 or ≤ 1.5) and baseline EDS (≥ 60 or < 60). Across these Phase III efficacy studies, there were substantially more subjects in the lifitegrast arm with more severe disease (ICSS > 1.5 and EDS ≥ 60) and a history of artificial tear use who experienced a clinically meaningful response (based on composite responder analysis of sign and symptom improvement) compared to subjects in the placebo arm.

Table 24: Summary of the response in the combined OPUS-2 and OPUS-3 trials group based on those with both inferior corneal staining score > 1.5 and Eye dryness score ≥ 60

	Lifitegrast	Placebo	Treatment effect
Eye Dryness Score Baseline score was 78 in both groups	N = 399 Delta EDS -41.93 (SD 29)	N = 404 Delta EDS -29.77 (SD 30.3)	12.16 ($p < 0.001$)
Change in Ocular Surface Disease Index (just OPUS-2)	N = 204 Baseline 42.7 (± 22) Delta -15.43 (± 20.9)	N = 209 Baseline 44.3 (±20.5) Delta -7.8 (±21.4)	7.64 ($p = 0.0003$) Overall, patients and clinicians consider an Ocular Surface Disease Index total score change of 4.5 to 7.3 to be meaningful for patients

[22] Ortiz et al. b) Mechanisms of Action of the Leukocyte Function-Associated Antigen-1 (LFA-1) Antagonist Lifitegrast in Dry Eye Disease Invest Ophthalmol Vis Sci 2018 59:3315

	Lifitegrast	Placebo	Treatment effect
			with mild to moderate symptoms; a greater OSDI score change of 7.3 to 13.4 is required before patients with severe symptoms consider the change to be meaningful
Inferior corneal staining (4 point scale) OPUS- 3	N = 195 Baseline 2.56 (± 0.56) Delta -0.88 (± 0.93)	N = 195 Baseline 2.65 (± 0.62) Delta -0.78 (± 0.953)	
≥ 3 point improvement in Total corneal stain score	70 of 355	52 of 356	

The sponsor also performed a composite response score based on either ICSS > 1 or total corneal stain score > 3, with improvement in symptoms. The only subgroup in which lifitegrast has a statistically significant treatment effect were those with Inferior corneal staining score > 1.5 and EDS ≥ 60.

Risk management plan

The summary of safety concerns contains the following:

- Important identified risks: Hypersensitivity
- Important potential risks: Nil
- Missing information:
  - Use in children
  - Use in pregnancy and breast feeding women
  - Off label use

Routine pharmacovigilance and risk mitigation is proposed.

The clinical evaluator and RMP evaluator recommended that ocular events and long term safety should be included in the RMP, however the sponsor did not agree.

Risk-benefit analysis

Clinical efficacy studies included three studies in patients with dry eye disease of varying severity. A number of conditions commonly associated with dry eye disease were excluded. The efficacy outcome measured differed between studies. The improvement in symptoms was more consistent than improvement in signs, however even so was inconsistent across scales used. The efficacy was greatest in patients with more severe disease at Baseline, or who had a history of use of artificial tears.

Assessment for the presence of inflammation in the eye at baseline would have been helpful in predicting which patients were more likely to respond, however there are no available tests to do this in routine clinical practice.

The main safety concerns were local irritation and dysguesia. Safety beyond 12 months has not been studied; the current labelling does not specify a duration of treatment.

Proposed indication

The revised indication is an improvement on the previous indication in that it more accurately describes the patient population for whom the medicine is likely to show benefit.

However, even in this revised indication the results for efficacy are not consistent and it would allow treatment of a number of conditions that have not been studied in the clinical development program.

Deficiencies of the data

Inflammation is believed to be important in the pathophysiology of dry eye disease; however, in the reviews submitted it is not clear if the evidence in support of this comes from human studies or in-vitro or animal models. It is also unclear whether the evidence to support the role of LFA-1 and ICAM-1 come from human or in-vitro-animal studies, and if the impact on systemic inflammation can be extrapolated to local inflammation in the eye at the doses suggested. It is unclear if treatment alters the natural history of the disease.

The dose finding studies were limited, it is not known if higher doses may have had greater efficacy.

The benefits of treatment include improved symptoms, reduced use of artificial tears. However the improvements were not observed in all patients, and there was a large placebo effect. There is no good evidence that it reduces signs or improved visual outcome.[23]

The risks of treatment include local irritation and unknown long term effects. Sodium thiosulfate is a novel excipient by the ocular route in Australia.

There is limited information about use with other eye drops.

Delegate's considerations

The dossier was deficient in terms of pharmacodynamics in the population of interest, in dose finding studies, drug interactions, and long term safety. The evidence for efficacy is not robust, however the difficulties in performing studies in this population are noted. The treatment with lifitegrast did improve symptoms of dry eye and reduce artificial tear use some patients.

Approval may be considered with amendments to the RMP, PI and CMI to clarify the limitations of the data and ensure there is ongoing monitoring of safety.

Questions for the sponsor

1. Please comment on the proposed treatment duration for patients with dry eye.
2. Please comment on the similarities and differences in pathophysiology and disease between the conditions included and excluded in the clinical studies.

[23] Clarification: Parameters directly measuring visual outcomes were not collected as efficacy endpoints during the conduct of the clinical studies.

3. Please comment on the known safety profile of sodium thiosulfate when used topically on the eye.
4. Please comment on how long term safety of this product will be assessed.

Proposed action

The Delegate is not in a position to say, at this time, that the application for lifitegrast should be approved for registration

Request for ACM advice

1. What proportion of patients with dry eye syndrome improves spontaneously, and what proportion would develop visual impairment or impaired quality of life due to this condition?
2. What proportion of patients with dry eye disease has inflammation? Is it possible to detect those with diagnostic tests?
3. Please comment of the exclusion criteria in the clinic studies. Is it appropriate to extrapolate efficacy in these patients, or should they be included as a precaution?
4. Please comment on the efficacy results in view of the inconsistency between studies, and the inconsistency within the same study when a different scale is used. Is this typical of studies used for dry eye disease?

Response from sponsor

Proposed indication

The revised indication is driven by subgroup analyses from, OPUS-2 trial (Study 3 in the PI), and OPUS-3 trial (Study 4 in the PI). The subgroup analyses were based on randomisation stratification factors prospectively assigned in the OPUS-2 and OPUS-3 trials; wherein subjects were stratified on the basis of their baseline ICSS (> 1.5 or ≤ 1.5) and baseline EDS (≥ 60 or < 60). Across these Phase III efficacy studies, there were substantially more subjects in the lifitegrast arm with more severe disease (ICSS > 1.5 and EDS ≥ 60) and a history of artificial tear use who experienced a clinically meaningful response (based on composite responder analysis of sign and symptom improvement) compared to subjects in the placebo arm. On the basis of these analyses, we would like to propose a revised indication that narrows the population, thereby reducing the heterogeneity of the population.

Original indication proposed submitted to TGA in September 2017:

> *Treatment of the signs and symptoms of dry eye disease in adults.*

The revised indication is:

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

Questions to the sponsor (from the Delegate)

1. Please comment on the proposed treatment duration for patients with dry eye.

Dry eye disease is a chronic condition that may require treatment on a long term basis. After initiation of treatment with lifitegrast, it is recommended that patients consult with their eye care provider after the first 3 months, and return periodically as deemed medically necessary, to assess the need for continuation of treatment.

2. Please comment on the similarities and differences in pathophysiology and disease between the conditions included and excluded in the clinical studies.

The pathophysiology of dry eye disease, regardless of aetiology, is driven by inflammation of the ocular surface and manifests as the signs and symptoms measured in the lifitegrast trials. Some diseases that are comorbid with dry eye disease can be considered primary drivers of inflammation, resulting in dry eye disease that is essentially a secondary process. When dry eye disease is dependent on the existence of a comorbid condition, lifitegrast will treat the inflammation damaging the ocular surface, but may not address the underlying aetiology of that inflammation.

The eligibility criteria in the lifitegrast trials was developed to ensure that subjects had primarily aqueous deficient dry eye disease (based on inclusion criteria) that was not attributable to another cause (based on exclusion criteria). Subjects with ocular conditions that are independently associated with dry eye disease or other significant ocular pathology were not eligible for the lifitegrast trials, including:

- Ocular conditions such as lid margin disorders (for example, blepharitis including staphylococcal, demodex, or seborrheic; meibomian gland disease, excessive lid laxity, floppy eyelid syndrome, ectropion, entropion), advanced conjunctivochalasis, Salzmann's nodular degeneration, and asthenopia-related conditions, glaucoma, diabetic retinopathy, follicular conjunctivitis, iritis, uveitis, wet-exudative age-related macular, degeneration retinal vein occlusion, tinea versicolor, and/or active ocular inflammation (unrelated to dry eye disease).
- Currently active or history of ocular herpes or any other ocular infection within the past 30 days.
- Conjunctival scarring, xerosis or distortion (irradiation, alkali burns, Stevens-Johnson syndrome, cicatrical pemphigoid, vitamin A deficiency, advanced conjunctivochalasis)
- Disordered ocular sensation (post-LASIK or refractive surgery, postoperative status, advanced keratitis)
- Allergic conjunctivitis
- Thyroid disease.

Eye dryness is a common side effect of many medications.[24] In the OPUS-2 and OPUS-3 trial protocols, patients with intermittent recent use (within 30 days) of any oral or topical medications known to cause ocular drying were not eligible to participate in the lifitegrast trials. These medications include, but were not limited to:

- Aspirin and antihistamines (specified in protocol)
- Antiarrhythmic medication
- Anti-Parkinsonian medication
- Antihypertensive medication
- Antidepressants
- Opiates.

Keratitis/keratoconjunctivitis sicca, the dry eye component of Sjögren's syndrome, is caused by a decrease in the secretion of the aqueous component of the tear film resulting

[24] Fraunfelder, F. T., Sciubba, J. J. and Mathers, W. D. 2012. The Role of Medications in Causing Dry Eye. *Journal of Ophthalmology*, 2012, 1-8.

from infiltration of the lacrimal gland with T cells and B cells.[25] Patients with primary Sjorgen's syndrome are typically treated with systemic immunosuppressant medications that require titration, and these patients were thus excluded from the lifitegrast studies. However, since aqueous-deficient dry eye is a defining symptom of Sjorgren's syndrome, patients with secondary Sjorgren's syndrome were eligible for inclusion in the lifitegrast trials.

3. Please comment on the known safety profile of sodium thiosulfate when used topically on the eye.

Sodium thiosulfate was used as an ingredient in an ophthalmic solution supplied by Allergan Australia under the tradename Bleph-10 according to the CMI for this product retrievable from the Australian National Prescribing Service website Bleph 10 was also supplied by Allergan in New Zealand and the Medsafe Product Detail page for Bleph 10 shows the product was first approved in New Zealand on 31 December 1969.

We believe this date reflects the approximate timing of approval in Australia as well because many companies operating in Australia and New Zealand tend to market the same product in both territories. Furthermore, Bleph-10 was a benefit on the Australian Pharmaceutical Benefit Scheme (PBS) and record shows the product was delisted from PBS on 1 June 2011. From this information, it can be estimated that sodium thiosulfate had been used as an ingredient in an ophthalmic eye drop product in the Australian market for over 40 years indicating a long history of use with no apparent safety concerns with the ingredient when used as an excipient in eye drops.

In addition to the inclusion of sodium thiosulfate in Xiidra, it is commonly used as an excipient in ophthalmic preparations (antibiotic and steroid/antibiotic combinations as an eye drop solution, suspension, and ointment) in the United States, in concentrations ranging from 0.2 to 0.5% (FDA Inactive Ingredient Search for Approved Drug Products). Sodium thiosulfate is also present in a decongestant / lubricant eye drop formulation marketed in Brazil, (Allergan).

4. Please comment on how long term safety of this product will be assessed.

Shire is committed to routine pharmacovigilance, including ongoing post market surveillance on lifitegrast upon approval and launch of the product in Australia. Routine pharmacovigilance includes but is not limited to individual submitted case reports to the drug safety database and health authorities, preparation of aggregate reports (PBRER/PSUR), and ongoing signal detection activities for the life of the product.

Other issues

The sponsor commits to finalising the RMP in collaboration with the TGA. It is the intention of the sponsor, pending outcome of the deliberation of our application by the ACM, to work with the Delegate to amend the RMP, PI, and CMI to the satisfaction of the TGA.

It has been estimated that dry eye disease affected 14 to 33% of the population worldwide, and Australian data from the Blue Mountain Eye Study show dry eye disease were reported in 15 to 56% of a population over the age of 50 years.[26] Dry eye disease also has a major impact on the quality of life and work productivity of patients. Currently, dry eye disease patients use artificial tears and ocular lubricants which may not adequately treat their dry eye disease, and patients remain symptomatic. No ophthalmic preparations

[25] Rao, N., Goldstein, M. and Tu, E. 2014. Dry Eye. In: Yanoff, M. & Duker, S. (eds.) *Ophthalmology* 4th edition.
[26] Coroneo, M. 2013. High and dry: an update on dry eye syndrome. *Medicine Today* (Neutral Bay, NSW), 14, 53-61

that contain a pharmacologically active agent have been approved to treat dry eye disease in Australia.

Xiidra eye drops contain the active drug lifitegrast, which via a novel mechanism of action, inhibits an ocular pathway responsible for inflammation, the main driver of dry eye disease. If approved, Xiidra would be the first ophthalmic eye drop developed specifically for the treatment of dry eye disease in the country. The product has already received approval in major regions such as the USA and Canada. Many patients with dry eye disease are not sufficiently managed by the use of artificial tears alone. The sponsor is aware many of these patients are being treated with an unapproved anti-inflammatory ophthalmic preparation under the Special Access Scheme and this confirms the unmet clinical need for a treatment with a different mechanism of action to artificial tears.

Despite the development challenges due to the current state of the art and knowledge in performing clinical investigation of dry eye disease, results from the clinical development program undertaken for Xiidra demonstrated the product is efficacious and generally safe in patients with moderate to severe dry eye disease who are inadequately treated with artificial tears alone.

Advisory committee considerations[27]

The Advisory Committee on Medicines (ACM) taking into account the submitted evidence of efficacy, safety and quality, considered Xiidra, single use eyes drops containing 10 mg lifitegrast in 0.2 mL single use container, to have an overall positive benefit-risk profile for the indication:

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

In providing this advice the ACM noted the following:

- Three pivotal studies were presented to support registration: the OPUS-1, OPUS-2, and OPUS-3 trials. These were Phase III, randomised, placebo controlled trials.
- The co-primary endpoints in the OPUS-1 trial were inferior fluorescein staining (objective outcome) and visual-related function Ocular Surface Disease Index (VR-OSDI) (subjective outcome). There was improvement in inferior corneal staining in the lifitegrast group compared to deterioration in the placebo group; there was a similar improvement in VR-OSDI in both placebo and lifitegrast groups.
- The co-primary endpoints in the OPUS-2 trial were inferior corneal fluorescein staining score (signs) and eye dryness score (symptoms). There was a similar improvement in inferior corneal staining in both the placebo and active treatment groups; there was statistically significant greater improvement in eye dryness score in the lifitegrast group compared to the placebo group.

[27] The ACM provides independent medical and scientific advice to the Minister for Health and the Therapeutic Goods Administration (TGA) on issues relating to the safety, quality and efficacy of medicines supplied in Australia including issues relating to pre-market and post-market functions for medicines.
The Committee is established under Regulation 35 of the Therapeutic Goods Regulations 1990. Members are appointed by the Minister. The ACM was established in January 2017 replacing Advisory Committee on Prescription Medicines (ACPM) which was formed in January 2010. ACM encompass pre and post-market advice for medicines, following the consolidation of the previous functions of the Advisory Committee on Prescription Medicines (ACPM), the Advisory Committee on the Safety of Medicines (ACSOM) and the Advisory Committee on Non-Prescription Medicines (ACNM). Membership comprises of professionals with specific scientific, medical or clinical expertise, as well as appropriate consumer health issues relating to medicines.

- The primary endpoint in the OPUS-3 trial was change in the eye dryness scale measures on a Visual Analogue Scale. A statistically significant improvement in eye dryness score was observed in the lifitegrast group compared to the placebo group.
- Instillation site irritation and reactions occurred in higher rates in the lifitegrast groups compared to the placebo groups, but were mostly mild to moderate in severity.
- Use of lifitegrast may reduce the requirement for topical ocular lubricants.
- Lifitegrast is approved in the US and Canada, and an application for registration is currently under consideration in the EU.

Specific advice

The ACM advised the following in response to the Delegate's specific questions on the submission:

1. What proportion of patients with dry eye syndrome improve spontaneously, and what proportion would develop visual impairment or impaired quality of life due to this condition?

The ACM discussed that dry eye disease can have a number of different aetiologies (including corneal erosion), and vary in level of severity. The Committee was of the view that approximately 10 to 80% of patients with dry eye syndrome would develop visual impairment and that dry eye disease can significantly affect quality of life.

2. What proportion of patients with dry eye disease have inflammation? Is it possible to detect those with diagnostic tests?

The ACM advised that inflammation generally underpins all forms of dry eye of a long standing nature. There is currently no clinical test utilised to detect inflammation in dry eye disease.

3. Please comment on the exclusion criteria in the clinic studies. Is it appropriate to extrapolate efficacy in these patients, should they be included as a precaution, or is it sufficient to just mention this under clinical trials?

The ACM considered that it would be sufficient to list the exclusion criteria in the clinical studies under the clinical trials section of the PI, noting that use of lifitegrast in some of the ocular conditions excluded in the trials may be appropriate based on clinician judgement.

The ACM discussed whether lifitegrast should only be prescribed by ophthalmologists. However, it was noted that not all patients may be able to access an ophthalmologist in a timely manner, and that other medical practitioners should also be able to prescribe lifitegrast if they were able to perform the required eye examination to exclude causes that may require alternative treatment (such as viral infections, iritis). If there was a broader group of prescribers able to prescribe lifitegrast, the use of risk mitigation activities such as an additional statement in the precautions section of the PI to note the importance of a comprehensive eye examination would be required; and education of GPs about the investigation and treatment of dry eye disease should be considered.

4. Please comment on the efficacy results in view of the inconsistency between studies, and the inconsistency within the same study when a different scale is used. Is this typical of studies used for dry eye disease?

The ACM advised that such inconsistencies were typical in studies for dry eye disease, where a significant placebo effect is observed. Further, the Committee was of the view that corneal staining alone does not fully describe the pathophysiological changes with dry eye disease, and therefore a lack of improvement in fluorescein staining does not necessarily mean there is no improvement in the condition. Despite the inconsistencies, the Committee considered that the studies generally demonstrated improvement in symptoms of dry eye disease which could be clinically significant.

The ACM advised that implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of this product.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Xiidra lifitegrast 50 mg/mL eye drops for one drop in each eye, twice daily, indicated for:

> *Xiidra is indicated for the treatment of moderate to severe dry eye disease in adults for whom prior use of artificial tears has not been sufficient.*

Specific conditions of registration applying to these goods

- Xiidra (lifitegrast) is to be included in the Black Triangle Scheme. The PI and CMI for Xiidra must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product.
- The Xiidra (lifitegrast) EU-Risk Management Plan (EU-RMP), version 1.0, dated 7 November 2018 (DLP 10 July 2018), with Australian Specific Annex, version 1.1 dated 5 December 2018 included with submission PM-2017-03384-1-5, and any subsequent revisions, as agreed with the TGA will be implemented in Australia. An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of Periodic Safety Update Reports (PSURs). Unless agreed separately between the supplier who is the recipient of the approval and the TGA, the first report must be submitted to TGA no later than 15 calendar months after the date of this approval letter. The subsequent reports must be submitted no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of this approval letter. The annual submission may be made up of two PSURs each covering six months. If the sponsor wishes, the six monthly reports may be submitted separately as they become available.

  The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII-Periodic Safety Update Report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration. Each report must have been prepared within ninety calendar days of the data lock point for that report.

Attachment 1. Product Information

The PI for Xiidra approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Therapeutic Goods Administration

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