

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208073Orig1s000

PHARMACOLOGY REVIEW(S)

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number: 208073
Supporting document/s: 20
Applicant's letter date: 1-22-2016
CDER stamp date: 1-22-2016
Product: Lifitegrast Ophthalmic Solution, 5.0%
Indication: Treatment of signs and symptoms of dry eye
disease
Applicant: Shire
Review Division: Transplant and Ophthalmology Products
Reviewer: María I Rivera, PhD
Supervisor/Team Leader: Lori E Kotch, PhD, DABT
Division Director: Renata Albrecht, MD
Project Managers: Christina Marshall
Eithu Lwin

1 Executive Summary

1.1 Introduction

Shire Development LLC (Shire) resubmitted a New Drug Application (NDA) for Xiidra (lifitegrast 5.0% ophthalmic solution) for the treatment of the signs and symptoms of dry eye disease (b)(4) administered twice a day ((b)(4)) into each eye using a single use container. The original NDA for Xiidra was submitted on February 25, 2015. The nonclinical review was filed in DARRTS on July 31, 2015.

1.2 Brief Discussion of Nonclinical Findings

No new nonclinical studies were submitted in the NDA resubmission. During the first cycle review, approval was recommended pending resolution of the following issues:

“The sponsor should address the request to reduce the specifications for (b)(4) (b)(4) to as low as reasonably possible, and to submit adequate safety data to support the levels of 3 leachables.”

These were unknown leachables with levels of (b)(4) µg/mL found in (b)(4) stability batch 3P80 and primary stability batches 4F14-2 and 4F90-2, with relative retention times of 0.443, 0.451, and 0.451, respectively. In addition, to these 3 leachables, the Product Quality team identified other impurities with levels above (b)(4) ppm. The nonclinical comments were conveyed to the applicant under the Product Quality complete response letter dated Oct 16, 2015.

PRODUCT QUALITY COMMENT 2

There is insufficient information about the drug to determine whether the product is safe for use under the conditions prescribed, recommended or suggested in its proposed labeling. Specifically, information to support the safety of potentially having (b)(4) ppm of (b)(4) in the drug substance has not been submitted. Since no detectable levels of (b)(4) were present in (b)(4) (b)(4) batches tested to date (detection limit of (b)(4) ppm), the acceptance limit should be revised to “less than (b)(4) ppm.”

The Sponsor accepted the Agency’s comment regarding the acceptance limit for (b)(4). The drug substance specification was updated to include an acceptance criterion of not more than (b)(4) ppm (NMT (b)(4) ppm) for (b)(4).

PRODUCT QUALITY COMMENT 3

c. Impurities have been identified which are not being tracked. While it is claimed that most of the impurities are degradants from the drug product evidence has not been provided that these impurities originate from the drug product. The remaining unknown impurities currently claimed as leachables should be identified and qualified (i.e., provide safety data).

Regarding the 3 leachables cited above, these were identified as (b) (4). The levels of (b) (4) µg/mL are lower than the specification limit of NMT than (b) (4) % in the drug product (refer to Product Quality review). In addition, in the initial NDA, the sponsor provided a rationale to justify levels (b) (4) up to (b) (4) %. Therefore, the issue is considered resolved from the nonclinical perspective.

The Product Quality review team sought nonclinical feedback to answer the following question:

PRODUCT QUALITY COMMENT 3

d. The current specification do not account for potential chemicals which may leach into the drug product from the packaging or may arise from unexpected issues in manufacturing. Changing the specification to all unidentified impurities and lowering the limit to the standard used for ophthalmic drug products (<0.1%) should minimize the chances that no harmful impurities (degradants, leachables or other) are included in the drug product.

The applicant used the following information to calculate the maximum daily dose of drug substance per day (note, slightly lower than the 5 mg/eye/day [10 mg/day] calculated by this reviewer in the 1st cycle NDA review based on a 50 µL drop volume).

Table 1: Calculation of Daily Administration of Lifitegrast Drug Substance for a Patient Treated with Lifitegrast Drug Product

Parameter	Description
(b) (4)	

The applicant continued: “Based upon a daily dose of (b) (4) mg of Lifitegrast drug substance, Attachment 1 of Q3B(R2) designates an identification threshold of (b) (4) (b) (4), whichever is lower”. Table 2 provides information regarding the determination of which is the lower criterion (b) (4). When the criterion of (b) (4) % is applied to a daily dose of (b) (4) mg, the calculated exposure of an unidentified degradation product is (b) (4) µg/day which exceeds the (b) (4) designated in Attachment 1 of Q3B(R2). Therefore, to conform with Attachment 1 of Q3B(R2), the (b) (4) (b) (4) criterion should be applied for an unidentified impurity in Lifitegrast drug product. When the (b) (4) criterion is converted to percentage (Table 2), this calculation results in an acceptance criterion of (b) (4) % for an unidentified degradation product in Lifitegrast drug product. To provide a more conservative approach, an acceptance criterion of (b) (4) % for an unidentified degradation product in Lifitegrast drug product is proposed.”

Table 2: Determination of the Unidentified Impurities Identification Threshold Limit for Lifitegrast Drug Product

Parameter	Description
(b) (4)	

This reviewer believes that the applicant justification is acceptable. Even if a total daily dose of 10 mg (5 mg/eye/day) is used, a specification of (b) (4) % proposed by the applicant will result in an exposure of (b) (4) µg, i.e., still at the identification threshold level.

1.3 Recommendations

1.3.1 Approvability: Approval is recommended, pending confirmation by the Product Quality review team that there are no issues with any other impurity/leachable.

1.3.2 Additional Non Clinical Recommendations

None

1.3.3 Labeling

The initial label recommendations were filed in DARRTS with the first cycle NDA review. A revised label taking into considerations the recommendations received from the Division of Pediatric and Maternal Health was filed in DARRTS on March 1, 2016.

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/s/

MARIA I RIVERA
04/26/2016

LORI E KOTCH
04/26/2016

(b) (4)

Data

Animal Data

(b) (4)

(b) (4) Lifitegrast administered daily by IV injection to rats from pre-mating through gestation day 17, (b) (4) (b) (4) caused an increase in mean preimplantation loss and an increased incidence of several minor skeletal anomalies at a dose 5400 fold the plasma exposure at the RHOD of 5% lifitegrast ophthalmic solution, based on AUC. No (b) (4) observed in the rat at 10 mg/kg/day (460-fold the plasma exposure at the RHOD, based on AUC). In the rabbit, an increased incidence of omphalocele was observed at the lowest dose tested, 3 mg/kg/day (400-fold the plasma exposure at the RHOD, based on AUC), when (b) (4) by IV injection daily from gestation day 7 through 19. A fetal No Observed Adverse Effect Level (NOAEL) was not identified.

8.2 Lactation

Risk Summary

There are no data on the presence of lifitegrast in human milk, the effects on the breastfed infant, or the effects on milk production; however, systemic exposure to lifitegrast from ocular administration is low [see *Clinical Pharmacology (12.3)*]. The developmental and health benefits of breastfeeding should be considered, along with the mother's clinical need for Xiidra and any potential adverse effects on the breastfed infant from Xiidra (b) (4) (b) (4).

to inform any drug associated risks, (b) (4) (b) (4)

Data

Animal Data

(b) (4)

(b) (4) Lifitegrast administered daily by IV injection to rats from pre-mating through gestation day 17 caused an increase in mean preimplantation loss and an increased incidence of several minor skeletal anomalies at a dose 5400-fold the plasma exposure at the RHOD of 5% lifitegrast ophthalmic solution, based on AUC. No (b) (4) *teratogenicity was* observed in the rat at 10 mg/kg/day (460-fold the plasma exposure at the RHOD, based on AUC). In the rabbit, an increased incidence of omphalocele was observed at the lowest dose tested, 3 mg/kg/day (400-fold the plasma exposure at the RHOD, based on AUC), when (b) (4) *administered* by IV injection daily from gestation day 7 through 19. A fetal No Observed Adverse Effect Level (NOAEL) was not identified *in the rabbit*.

8.2 Lactation

Risk Summary

(b) (4) (b) (4) *There are no data on the presence of lifitegrast in human milk, the effects on the breastfed infant, or the effects on milk production; however, systemic exposure to lifitegrast from ocular administration is low [see Clinical Pharmacology (12.3)].* The developmental and health benefits of breastfeeding should be considered along with the mother's

	clinical need for lifitegrast and any potential adverse effects on the breast-fed child from lifitegrast (b) (4).
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In addition, the following edit was made to the label recommendations initially proposed in the NDA review:

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Impairment of fertility

Lifitegrast administered at IV doses up to 30 mg/kg/day (5400-fold the *plasma exposure at the* RHOD of 5% lifitegrast ophthalmic solution) had no effect on fertility and reproductive performance in male and female treated rats.

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/s/

MARIA I RIVERA
03/01/2016

LORI E KOTCH
03/01/2016

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number: 208073
Supporting document/s: 1, 5, 9, and 11
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CDER stamp date: 2-25-2015 (SD # 1), 6-3-2015 (SD # 5), 6-16-2015 (SD # 9), 6-19-2015 (SD # 11)
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Review Division: Transplant and Ophthalmology Products
Reviewer: María I Rivera, PhD
Supervisor/Team Leader: Lori E Kotch, PhD, DABT
Division Director: Renata Albrecht
Project Manager: Christina Marshall

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 208073 are owned by Shire or are data for which Shire has obtained a written right of reference. Any information or data necessary for approval of NDA 208073 that Shire does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 208073.

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1 Executive Summary

1.1 Introduction

Lifitegrast is a novel small-molecule antagonist of lymphocyte function-associated antigen 1 (LFA-1; also known as CD11a/CD18 or α L β 2) that is being developed by Shire as a sterile eye drop for the treatment of signs and symptoms of dry eye disease. Lifitegrast acts by inhibiting LFA-1 interaction with the cell surface glycoprotein intercellular adhesion molecule (ICAM)-1, and thereby prevents the formation of immunological synapses that are key to inflammatory cell activation and migration. The inhibition of the LFA-1/ICAM-1 interaction therefore forms the basis of the therapeutic rationale for lifitegrast as a treatment for the signs and symptoms of dry eye disease. The proposed clinical dose is 5.0% lifitegrast ophthalmic solution applied to each eye twice daily for a total dose of 5 mg/eye/day (50 μ L drop volume).

1.2 Brief Discussion of Nonclinical Findings

Repeat-dose ocular toxicity studies of up to 39-week duration were conducted in dogs and rabbits at concentrations up to 5% administered topically 3x/day. Ocular findings in both species were limited to transient blinking and squinting, indicating mild ocular irritation. The squinting and blinking was not associated with any other abnormal ocular observations. The ocular NOAEL was the highest dose evaluated, 5% 3x/day (5.25 mg/eye/day) in both rabbits and dogs. Based on total mg/eye/day, exposure margins were 0.63-fold in the dog and 1.05-fold in the rabbit. Although the exposure margins are low, the mild and transient nature of the findings observed does not present a major clinical concern. Eye irritation and eye pain were adverse reactions reported in the clinical trials with an incidence of 16% and 15%, respectively.

The tongue was identified as a potential target in both dogs and rabbits in the 39-week ocular toxicity studies. In dogs, minimal granulomatous inflammation of the tongue was noted in one high-dose male and one high-dose female at the end of the dosing phase and one high-dose female at the end of the recovery phase. In rabbits, a dose-dependent increase in the incidence and severity of myofiber regeneration of the tongue was observed at all dose levels. The finding was not present in recovery animals in rabbits. Based on plasma AUC, the exposure margins for the tongue findings are <7.3-fold (rabbit) and 16-fold (dog). It is unclear whether these findings are related to clinically observed dysgeusia.

Intravenous toxicity studies were conducted in dogs (7 and 4 weeks) and rats (13 weeks) at doses up to 30 mg/kg/day. No adverse findings were observed in the dog studies. Potential targets identified in the rat include the thymus (females only), urinary system, and male reproductive system. The NOAEL was 10 mg/kg. Based on AUC, the exposure margin for these findings is 660-fold, indicating no clinical concern.

In a fertility and embryofetal development toxicity study in rats, a fetal effect was apparent at the high dose (30 mg/kg), as reflected by an increase in mean preimplantation loss and increased incidence of several minor skeletal variations and

malformations limited to 1 or 2 fetuses and litters. In males, there was a slight decrease in prostate (16%) and seminal vesicle (19%) weights at 30 mg/kg, but no effects were noted in fertility index. The NOAEL for male and female fertility was the high dose of 30 mg/kg; the NOAEL for embryofetal development was the mid dose of 10 mg/kg. Based on AUC, the exposure margin for the fetal findings is 460-fold, indicating minimal clinical concern.

In a rabbit embryofetal development study, omphalocele was noted in a single fetus at the low dose of 3 mg/kg/day and the high dose of 30 mg/kg/day. In addition, there was an increased incidence of subclavian vein-supernumerary branch at the high dose, and bipartite ossification of the sternbrae at the mid dose and high dose. Omphalocele is an extremely rare malformation (i.e., noted in 1 fetus each in 2 litters from a total of 2237 litters in the historical database). As 2 litters had an affected fetus in the current study, it is difficult to definitely rule out a test article-related effect. The bipartite sternal ossification likely would not be adverse (expected to ossify as the animal continues growing). Based on the finding of omphalocele at the low dose and high dose, a fetal NOAEL was not identified in this study. Based on AUC, the exposure margin at the low dose of 3 mg/kg/day is 400-fold, indicating minimal clinical concern.

The sponsor has been asked to reduce the specification for (b) (4) a potentially genotoxic impurity, to as low as reasonably possible (see Section 2.5 Comments on Impurities/Degradants of Concern). In addition, 3 leachables were found in developmental stability batch 3P80 and primary stability batches 4F14-2 and 4F90-2 at levels above (b) (4) ppm. The sponsor has been asked to identify these leachables and provide safety data to support these levels.

1.3 Recommendations

1.3.1 Approvability: Pending resolution of impurity issues, approval is recommended.

The sponsor should address the request to reduce the specifications for (b) (4) (b) (4) to as low as reasonably possible, and to submit adequate safety data to support the levels of 3 leachables.

1.3.2 Additional Non Clinical Recommendations

None

1.3.3 Labeling

Note: Information recommended by the reviewer is presented in bold italic style.

8.1 Pregnancy

Applicant's Proposed Text:

Risk Summary

(b) (4)

Data

Animal Data

(b) (4)

8.2 Lactation

Risk Summary

There are no data (b) (4) or (b) (4) (b) (4) effects on milk production (b) (4). Systemic exposure to lifitegrast 5% (b) (4) (b) (4) is very low [see *Clinical Pharmacology (12.3)*]. The developmental and health benefits of breastfeeding should be considered, along with the mother's clinical need for Xiidra and any potential adverse effects on the breastfed child from Xiidra (b) (4) underlying maternal condition.

(b) (4)

Reviewer's Recommendations:

Risk Summary

(b) (4)

(b) (4)

*Data**Animal Data*

(b) (4)

(b) (4)

(b) (4) **Lifitegrast administered daily by IV injection to rats from pre-mating through gestation day 17 caused an increase in mean preimplantation loss and an increased incidence of several minor skeletal anomalies at a dose 5400-fold the plasma exposure at the RHOD of 5% lifitegrast ophthalmic solution, based on AUC. No (b) (4) observed in the rat at 10 mg/kg/day (460-fold the plasma exposure at the RHOD, based on AUC). In the rabbit, an increased incidence of omphalocele was observed at the lowest dose tested, 3 mg/kg/day (400-fold the plasma exposure at the RHOD, based on AUC), when given by IV injection daily from gestation day 7 through 19. A fetal No Observed Adverse Effect Level (NOAEL) was not identified.**

8.2 LactationRisk Summary

(b) (4)

12 Clinical Pharmacology

Applicant's Proposed Text:

12.1 Mechanism of Action

Lifitegrast binds to the integrin lymphocyte function-associated antigen-1 (LFA-1), a cell surface protein found on leukocytes and blocks the interaction of LFA-1 with its cognate ligand intercellular adhesion molecule-1 (ICAM-1). ICAM-1 (b) (4) over-expressed in corneal and conjunctival tissues in dry eye disease. LFA-1/ICAM-1 interaction (b) (4) to formation of an immunological synapse resulting in T-cell activation and migration to target tissues. *In vitro* studies (b) (4) demonstrated that lifitegrast inhibits T-cell adhesion to ICAM-1 (b) (4)

(b) (4) the exact mechanism of action of lifitegrast in dry eye disease is not known.

Reviewer's Recommendations:

Lifitegrast binds to the integrin lymphocyte function-associated antigen-1 (LFA-1), a cell surface protein found on leukocytes and blocks the interaction of LFA-1 with its cognate ligand intercellular adhesion molecule-1 (ICAM-1). ICAM-1 (b) (4) over-expressed in corneal and conjunctival tissues in dry eye disease. LFA-1/ICAM-1 interaction contributes to formation of an immunological synapse resulting in T-cell activation and migration to target tissues. *In vitro* studies (b) (4) demonstrated that lifitegrast inhibits T-cell adhesion to ICAM-1 **in a human T-cell line** (b) (4) and inhibits secretion of key inflammatory cytokines (b) (4)

(b) (4) **in human peripheral blood mononuclear cells,** (b) (4)

(b) (4) the exact mechanism of action of lifitegrast in dry eye disease is not known.

13 NONCLINICAL TOXICOLOGY

Applicant's Proposed Text:

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

[Redacted text] (b) (4)

Mutagenesis

[Redacted text] (b) (4)
Lifitegrast was not mutagenic in the *in vitro* Ames assay. (b) (4)
[Redacted text] (b) (4)

Impairment of fertility

Lifitegrast at IV doses of up to 30 mg/kg/day ([Redacted text] (b) (4)) had no effect on fertility and reproductive performance in male and female treated rats.

Reviewer's Recommendations:

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

[Redacted text] (b) (4)

Animal studies have not been conducted to determine the carcinogenic potential of lifitegrast.

Mutagenesis

[Redacted text] (b) (4)

Lifitegrast was not mutagenic in the *in vitro* Ames assay. Lifitegrast was not clastogenic in the *in vivo* mouse micronucleus assay. In an *in vitro* chromosomal aberration assay using mammalian cells (Chinese hamster ovary cells), lifitegrast was positive at the highest concentration tested, without metabolic activation.

Impairment of fertility

Lifitegrast **administered** at IV doses of up to 30 mg/kg/day

(b) (4)

(b) (4)

(5400-fold the RHOD of 5% lifitegrast ophthalmic solution) had no effect on fertility and reproductive performance in male and female treated rats.

2 Drug Information

2.1 Drug

CAS Registry Number: 1025967-78-5

Generic Name: Lifitegrast

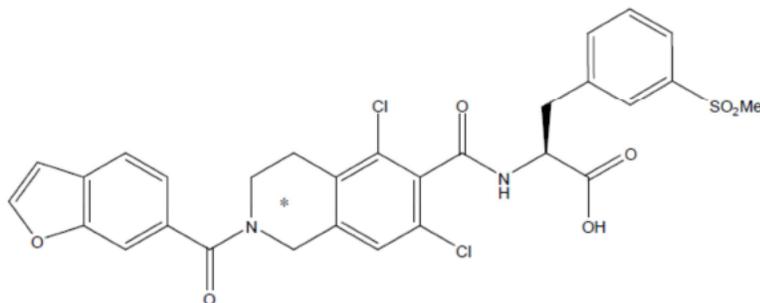
Code Name: SSP-005493, SAR 1118, SPD606,

(b) (4)

Chemical Name; (S)-2-(2-(benzofuran-6-carbonyl)-5,7-dichloro-1,2,3,4-tetrahydroisoquinoline-6-carboxamido)-3-(3-(methylsulfonyl)phenyl)propanoic acid

Molecular Formula/Molecular Weight: C₂₉H₂₄Cl₂N₂O₇S/615.48 g/mol

Structure:



Pharmacologic Class: Anti-inflammatory small-molecule antagonist of lymphocyte function-associated antigen-1, (LFA-1; also known as CD11a/CD18 or αLβ2)

2.2 Relevant INDs, NDAs, BLAs and DMFs

IND 77885 (SAR 1118)

2.3 Drug Formulation

Lifitegrast Ophthalmic Solution, 5.0% is a sterile, non-preserved, isotonic ophthalmic solution. The composition is shown in Table 1.

Table 1: Composition of the Drug Product Dosage Form

Ingredient	Amount	Unit	Function	Reference to Standards
Drug substance(s)				
Lifitegrast (S)-2-(2-(benzofuran-6-carbonyl)-5,7-dichloro-1,2,3,4-tetrahydroisoquinoline-6-carboxamido)-3-(3-(methylsulfonyl)phenyl)propanoic acid	5.0	%w/v	Active Ingredient	Module 3.2.S for NDA 208073.
Excipient(s)				
Sodium Chloride	(b) (4)			USP/NF
Sodium Phosphate Dibasic, anhydrous	(b) (4)			USP/NF
Sodium Thiosulfate, pentahydrate	(b) (4)			USP/NF
Sodium Hydroxide, (b) (4)	(b) (4) pH adjuster			USP/NF
(b) (4)	(b) (4)			USP/NF
Hydrochloric Acid solution, (b) (4)	(b) (4)			USP/NF
Water for Injection	(b) (4)			USP/NF
(b) (4)				

a Alternate concentrations may be used with appropriate adjustments to quantities.

2.4 Comments on Novel Excipients

None

2.5 Comments on Impurities/Degradants of Concern

On a letter dated 6-2-2015, the Division asked the sponsor to provide additional information to support the ocular safety of the proposed acceptance criteria for five potentially genotoxic impurities (b) (4) in the drug substance. The response was received on 6-16-2015 (SD # 9) with an amended report on 6-19-2015 (SD # 11). The amendment provided a revised report excluding reference to a publication used as supportive evidence for (b) (4) which was submitted in the original language without English translation. The information provided in the sponsor's response is reviewed below.

Impurities (b) (4): The additional information provided is considered to provide adequate support for the proposed specification limits as described below.

The initial batches of lifitegrast (also known as SSP-005493 or SAR 1118) used in the GLP topical ocular nonclinical toxicity studies were manufactured and released by (b) (4). The certificates of analysis (CoA) for these API lots did not explicitly report the percentage amount for 3 of the aforementioned impurities; (b) (4). With the progression of the development program, the API manufacture was transferred to (b) (4). Using a modified method (the proposed regulatory release HPLC method), (b) (4) reanalyzed the (b) (4) batches of lifitegrast in 2011 and compiled a summary table of impurity data for both the (b) (4) batches of API. The impurity levels from both (b) (4) are presented in Table 2.

Table 2: Impurity Total Daily Ocular Dose in Pivotal Nonclinical Ocular Toxicity Studies

Impurity	Impurity Level (%)		Total Daily Ocular Dose (mg/eye) ^a	
	13 weeks	39 weeks	13 weeks	39 weeks
(b) (4)				

^aDosing regimen of (b) (4) drop volume
^bThe report states that levels (b) (4) % could not be used to calculate margins. Apparently this was the lower limit of quantitation (LLOQ).
 ND: Not detected
 NA: Not applicable

At the proposed specification limit, the total daily dose of each impurity at the intended dosing regimen is (b) (4). As shown in Table 2, the total daily ocular dose of each impurity at the NOAEL in the 13-week and/or 39-week ocular toxicity studies in rabbits was higher than the total ocular daily exposure in humans at the proposed specification limit of (b) (4) %.

All five impurities were negative in the Ames test and in vitro chromosomal aberration assay in Chinese Hamster Ovary (CHO) cells (See Section 2.4 Other Genetic Toxicity Studies). Three of these impurities, (b) (4) were tested at the proposed (b) (4) level in a 28-day IV toxicity study in rats (Study # R6706M-SHP606 under Section 10. Special Toxicology Studies). There were no adverse effects that could be attributed to the impurities. The impurities are therefore considered qualified at the proposed specification limit.

(b) (4) may potentially form in (b) (4) the API process and is considered potentially genotoxic. The sponsor is proposing a (b) (4) ppm specification limit. This value was derived by the sponsor as described in the following excerpt from the NDA:

“The potential maximum total daily dose for lifitegrast API is (b) (4) API/day). These values assume complete consumption of (b) (4) and are higher than the recommended and prescribed daily API dose of 10 mg.

Using this conservative estimate of the total daily dose; and based on the threshold of toxicological concern (TTC) of (b) (4) µg/day as set forth in ICH M7 Guidance, the acceptable daily intake limit for (b) (4) in the API is calculated to be (b) (4) ppm.

Using the prescribed daily dose of 10 mg, the TTC-based acceptable daily intake limit of (b) (4) would be (b) (4) ppm. Therefore, (b) (4) ppm is considered to be justified as the acceptance criterion for (b) (4) in the API.”

The sponsor justification is considered adequate for risk assessment for systemic genotoxicity. However, the TTC approach was not derived to determine local (ocular) effects for drugs administered directly to the eye.

At a level of (b) (4) ppm ((b) (4) ng/mg API), the resulting concentration of (b) (4) At this concentration, the ocular total daily (b) (4) dose is (b) (4). This reviewer is not certain if these low levels of exposure in the eye can result in genotoxicity. Since no detectable levels of (b) (4) were present in the (b) (4) process batches tested to date (detection limit of (b) (4) ppm), we will retain our previous recommendation (letter dated 6-2-2015) to reduce the specifications as low as reasonably possible.

(b) (4)

The concentration of the API in the drug product is 5% (i.e., 50 mg/mL). The proposed specification limit for (b) (4) of (b) (4) µg/mg) relative to the amount of the API would result in a concentration of (b) (4). The total ocular daily dose is therefore (b) (4).

The sponsor referred to an eye irritation study published in the ECHA database¹. In this study undiluted (b) (4) was irritating when administered to rabbit eyes.

¹ <http://echa.europa.eu/web/guest/information-on-chemicals/registered-substances>

Findings included increased cornea, conjunctiva, iris, and chemosis irritation scores, as well as mucous bleeding, pupil retraction, ciliary injection, and misty opacity. These changes were reversible within 5-8 days. The database contains a second study where administration of (b) (4) μL of undiluted (b) (4) to rabbits resulted in more severe findings that were not reversible within a 7-day recovery period. Based on its reported density of (b) (4), a dose volume of (b) (4) μL of undiluted (b) (4). This data provides an exposure margin of (b) (4)-fold the total ocular daily dose of (b) (4)/eye. The applicant also noted that in terms of concentration, the amount of (b) (4) in the drug product represents a (b) (4).

Based on its physicochemical properties, (b) (4) is expected to have (b) (4) solubility and negligible potential for accumulation in lipids. The applicant then anticipates that (b) (4) would be removed from the eyes *via* the natural movement of tear fluid (which is primarily aqueous) into the nasolacrimal ducts and then into the nasal and oral cavities, with eventual entry into the gastrointestinal (GI) tract. In this regard, systemic exposure to (b) (4) following topical ocular administration would not fundamentally differ from that which occurs following oral administration.

The reported LD_{50} values for (b) (4) are very high (e.g., (b) (4) mg/kg orally for Sprague-Dawley rats, (b) (4) mg/kg intraperitoneally for NMRI mice). The NOAEL in a maternal and fetal toxicity study in rats² was (b) (4) administered by oral gavage. The maximum amount of (b) (4) to which a patient may be exposed is calculated to be (b) (4) mg/mL (b) (4) concentration * (b) (4) drops/day), equivalent to (b) (4) kg human body weight). Assuming (b) (4)% systemic absorption, this NOAEL provides an exposure margin over (b) (4) fold on a (b) (4) basis.

The applicant, therefore, concluded that exposure to (b) (4)/eye is not expected to be of toxicological concern. This reviewer agrees the applicant has provided adequate evidence to support the ocular and systemic safety of (b) (4) at the proposed specification limit.

(b) (4): In response to the Division's letter dated 6-2-2015, Shire clarified that (b) (4) described in Study Report # V6321M-SPD606 are the same as leachable (b) (4)

(b) (4) Both are extractables and leachables which are attributed to the foil laminate pouch that is used in the packaging of the drug product. Levels of (b) (4) ppm respectively, after up to (b) (4) months of storage. As such, it is not necessary to request identification.

Study Report # V6321M-SPD606 used a quantitative structural activity relationship (QSAR) program to predict the potential for carcinogenicity, chromosome

(b) (4)

damage, genotoxicity, or mutagenicity of (b) (4). According to the summary of the results provided, neither (b) (4) triggered alerts for any of these endpoints. These leachables were regarded by the applicant as negative for these endpoints and, as a result and due to their very low detected levels, the applicant concluded that routine control of these leachables in the drug product was deemed unnecessary.

At levels of (b) (4) respectively.

A consultation request was sent to CDER Computational Toxicology Consulting Service to confirm that these leachables have no genotoxic potential. (b) (4) was predicted to be negative for rodent carcinogenicity and genetic toxicity in the ICH S2 battery of assays. (b) (4) was predicted to be positive in the *in vitro* chromosomal aberration assay and negative in the bacterial mutation, mouse lymphoma, and *in vivo* micronucleus assays as well as in the rodent carcinogenicity assays (see Section 7.4 Other Genetic Toxicity Studies for further details).

Since the predictions for bacterial mutation assay and the *in vivo* assays (in vivo micronucleus and rodent carcinogenicity) were negative, this reviewer believes that the positive prediction for the *in vitro* chromosomal aberration assay for (b) (4) is not clinically relevant. Based on these results, the applicant proposal is considered acceptable.

Leachables in Drug Product

Several leachables were found in developmental stability batch 3P80 and primary stability batches 4F14-2 and 4F90-2 at levels above (b) (4) ppm.

Batch 3P80 (b) (4)

Note: The relevance of the leachable found in batch 3P80 is under review/discussion with CMC.

Batch 4F14-2 (Primary stability registration batch) - Unknown (b) (4) leachable at (b) (4). These level would result in a total daily exposure of (b) (4).

Batch 4F90-2 (Primary stability registration batch) - Unknown (b) (4) leachable at (b) (4). These level would result in a total daily exposure of (b) (4).

The sponsor will be asked to identify these leachables and provide safety data to qualify these levels.

2.6 Proposed Clinical Population and Dosing Regimen

One drop twice a day in each eye (b) (4) for the treatment of the signs and symptoms of dry eye disease (b) (4).

2.7 Regulatory Background

An End of Phase 2 meeting was held on 12-15-2010. The Division agreed that the completed and proposed studies appeared adequate to support the Phase 3 program and the NDA. The proposed studies included a fertility and early embryonic development study in the rat and embryofetal developmental toxicology studies in the rat and rabbit, together with a 9-month repeated daily (TID dosing) topical ocular toxicology study in dogs. The Division agreed that a carcinogenicity program was not indicated for SAR 1118 Ophthalmic Solution given existent mutagenicity data and the low systemic exposure following topical ocular administration.

3 Studies Submitted

3.1 Studies Reviewed

Secondary Pharmacology

- (b) (4) Full Profile Study of SSP-005493 Shire Pharmaceutical Development Ltd. (Study # V6435M-SPD606)

PK/ADME

- Pharmacokinetics, Distribution, Metabolism, and Excretion of [¹⁴C]-SAR 1118 Following Ocular or Intravenous Administration to Rats (Study # R6319M-SPD606)
- Determination and Pharmacokinetics in Tears and Plasma of SAR 1118 (b) (4) Following a Single Topical Ocular Administration to New Zealand White Rabbits (Study # L6318M-SPD606)
- Ocular Distribution and Pharmacokinetics of SSP-005493X following Repeated Topical Ocular Dose Regimen to Pigmented Rabbits (Study L6776M-SHP606)
- Pharmacokinetics, Distribution, Metabolism, and Excretion of ¹⁴C-SAR 1118 Following Ocular or Intravenous Administration to Dogs (Study # D6320M-SPD606)
- The *In Vitro* Protein Binding of SAR1118- (b) (4) in Rat, Rabbit, Dog, Monkey, and Human Plasma, and the Binding to Human Albumin, Human α 1-Acid Glycoprotein, and Melanin (Study # V6316M-SPD606)

General Toxicology

- 39-Week Topical Ocular Instillation Toxicity and Toxicokinetic Study with SAR 1118 in Dogs with a 13-Week Recovery (Study # D6336M-SPD606)
- 39-Week Topical Ocular Instillation Toxicity and Toxicokinetic Study with SAR 1118 in Rabbits with a 13-Week Recovery Phase (Study # L6329M-SPD606)

Other Genetic Toxicity Studies

- SPD606: Bacterial Reverse Mutation Assay, Synthon B (Study # V6745M-SHP606)
- (b) (4) Bacterial Reverse Mutation Assay (Study # V6987M-SHP606)
- (b) (4) Bacterial Reverse Mutation Assay (Study # V6988M-SHP606)
- (b) (4) Bacterial Reverse Mutation Assay (Study # V6989M-SHP606)
- (b) (4) Bacterial Reverse Mutation Assay (Study # V6990M-SHP606)
- (b) (4) Bacterial Reverse Mutation Assay (Study # V6991M-SHP606)
- (b) (4) Chromosomal Aberrations in Chinese Hamster Ovary (CHO) Cells (Study # V6992M-SHP606)
- (b) (4) Chromosomal Aberrations in Chinese Hamster Ovary (CHO) Cells (Study # V6993M-SHP606)
- (b) (4) Chromosomal Aberrations in Chinese Hamster Ovary (CHO) Cells (Study # V6994M-SHP606)
- (b) (4) Chromosomal Aberrations in Chinese Hamster Ovary (CHO) Cells (Study # V6995M-SHP606)
- (b) (4) Chromosomal Aberrations in Chinese Hamster Ovary (CHO) Cells (Study # V6996M-SHP606)
- Toxicological Analysis of Extractables 1 and 2 using Derek Nexus for Carcinogenicity, Chromosome Damage, Genotoxicity, Mutagenicity and Rapid Prototypes: Chromosome Damage In Vitro (Study # V6321M-SPD606)

Reproductive and Developmental Toxicology

- Intravenous Injection Combination Fertility/Embryofetal Development Study with SAR 1118 (b) (4) in Female Rats (Study # R6341M-SPD606)
- Intravenous Injection Study for Effects on Embryofetal Development and Toxicokinetic with SAR 1118 (b) (4) in Rabbits (Study # L6340M-SPD606)

Special Toxicology Studies

- SHP606: 28 Day Intravenous (Bolus) Administration Toxicity Study in the Rat (Study # R6706M-SHP606)

Studies Previously Reviewed under IND 77885**Safety Pharmacology**

- Effects of SAR1118- (b) (4) on Cloned hERG Potassium Channels Expressed in Human Embryonic Kidney Cells (Study # 7898-120)

- Respiratory Safety Pharmacology Study Using the Head-Out Body Plethysmography Model of Intravenous-Bolus Administered SAR1118 (b) (4) in Rats (Study # 7898-118)
- Central Nervous System Safety Pharmacology and Pharmacokinetic Study of SAR1118 (b) (4) Administered by Intravenous Injection in Rats (Study # 7898-117)
- A Latin Square Cardiovascular Safety Pharmacology Study of SAR1118 (b) (4) Administered to Conscious Telemetry-Instrumented Beagle Dogs by Intravenous Bolus Injection (Study # 7898-116)

PK/ADME

- Determination and Pharmacokinetics in Tears and Plasma of SAR1118 (b) (4) Following a Single Topical Ocular Administration to New Zealand White Rabbits (Study # 7898-122)
- *In Vitro* Metabolism of 14C-SAR1118 (b) (4) by Rat, Dog, Monkey, and Human Hepatocytes (Study # 7898-115)

General Toxicology

- Single-Dose Intravenous Injection Toxicity Study with SAR1118 (b) (4) in Rats (Study # 7898-107)
- Ocular Tolerance Study Following Topical Instillation with SAR1118 (b) (4) in New Zealand White Rabbits (Study # 7898-102)
- Escalating-Dose Range-Finding IV Study and 7-Day Repeat-Dose Toxicity and Toxicokinetic Study with SAR1118 (b) (4) in Dogs (Study # 7898-119)
- Topical Instillation Escalating Dose Tolerance Study with SAR1118 (b) (4) in Dogs (Study # 7898-100)
- 4-Week Intravenous Injection Toxicity and Toxicokinetic Study with SAR1118 in Dogs with a 2-Week Recovery Period (Study # 7898-106)
- 13-Week Intravenous Injection Toxicity and Toxicokinetic Study with SAR1118 (b) (4) in Rats with a 4-Week Recovery Period (Study # 7898-105)
- 13-Week Topical Instillation Ocular Study with SAR1118 (b) (4) in Rabbits with a 4-Week Recovery Period (Study # 7898-103)
- 13-Week Ocular Toxicity and Toxicokinetic Study with SAR1118 (b) (4) in Dogs with a 4-Week Recovery Period (Study # 7898-104)

Genetic Toxicity

- Salmonella-Escherichia coli/Mammalian-Microsome Reverse Mutation Assay with a Confirmatory Assay (Study # 7898-109)
- Chromosomal Aberrations in Chinese Hamster Ovary (CHO) Cells (7898-110)
- *In Vivo* Mouse Bone Marrow Micronucleus Assay (Study # 7898-111)

Special Toxicology Studies

- Hemolytic Potential and Plasma Compatibility Testing with SAR1118 (b) (4) (Study # 7898-114)
- *In Vitro* Toxicity Evaluation of SAR1118 on Corneal Epithelial Cells (Study # SAR0705)

3.2 Studies Not Reviewed

- Study Report No. AA94555 (Study # V6757M-SHP606)
- Delivery of SAR 1118 to Retina Via Ophthalmic Drops and its Effectiveness in Reduction of Retinal Leukostasis and Vascular Leakiness in Rat Streptozotocin (STZ) Model of Diabetic Retinopathy (DR) (Study # R6346M-SPD606)
- Analytical Methods (Module 4.4.2.1)
- Pharmacokinetic Drug Interactions (Module 4.2.2.5)
- Escalating-Dose Range-Finding IV Study and 7-Day Repeat-Dose Toxicity and Toxicokinetic Study with SAR1118-^{(b)(4)} in Dog (Study # D6331M-SPD606) – used lower doses than the 4-week study
- Collection of Samples for Determination of the Pharmacokinetics, Tolerability, and Systemic Exposure of SAR1118 Following Dermal Administration in Various Formulations to Minipigs (Study # Z6357M-SPD606)
- Collection of Samples for Determination of the Pharmacokinetics, Tolerability, and Systemic Exposure of SAR1118-^{(b)(4)} Following Dermal and Intradermal Administration in Various Formulations to Rats (Study # R6356M-SPD606)

3.3 Previous Reviews Referenced

Nonclinical review IND 77885

4 Pharmacology

4.1 Primary Pharmacology

Lifitegrast binds to LFA-1, a cell surface protein found on leukocytes, and blocks the interaction of LFA-1 with its cognate ligand intercellular adhesion molecule-1 (ICAM-1). ICAM-1 has been found to be over-expressed in corneal and conjunctival tissues in dry eye disease. LFA-1/ICAM-1 interaction contributes to formation of an immunological synapse resulting in T-cell activation and migration to target tissues. In vitro studies demonstrated that lifitegrast inhibits T-cell adhesion to ICAM-1 in the immortalized Jurkat human T-cell line (Study # V6308M-SPD606) and inhibits secretion of key inflammatory cytokines (IFN γ , TNF α , IL-2) as well as inhibiting other pro-inflammatory cytokines: IL-1 α , IL-1 β , , IL-4, IL-5, and IL-13), all of which are known to be associated with dry eye disease in human peripheral blood mononuclear cells (Study # V6310M-SPD606 and Study # V6757M-SHP606). However the exact mechanism of action of lifitegrast in dry eye disease is not known.

The primary pharmacology studies were previously reviewed under the initial IND by Dr. Zhou Chen. The main findings are listed in the table below.

Table 3: Main Findings of Primary Pharmacology Studies

Study No.	Species/ Strain	Method of dosing	Dose and duration	No./ Group	Noteworthy findings
SAR0702	Human/ Jurkat, Clone E6-1	<i>In vitro</i> incubation	0.05, 0.1, 0.5, 1, 5 nM, 0.01, 0.05, 0.1, 0.5, 1, 5 μ M	Single well/ concentration	Dose dependent inhibition of LFA-1 mediated Jurkat cell attachment to ICAM-1 (intercellular adhesion molecule-1) with an EC ₅₀ of 3.69 nM. SAR 1118 is an antagonist of LFA-1/ICAM-1 binding.
SAR0703	Human/ Peripheral blood mononucleocytes	<i>In vitro</i> incubation	0.00001 to 1000 μ M in log increments	Duplicate/ concentration	Dose dependent inhibition of inflammatory cytokine release, particularly IL-2 and IL-4. Concentrations of SAR1118 in excess of levels achievable via tear drops (ie 1 μ M) resulted in > 50% inhibition of cytokine release.
SAR0701	Canine/ various	Topical ocular instillation	1% per eye, TID x12 weeks	12 (The study is ongoing, 4 dogs were used.)	Increased Schirmer tear test values after 12 weeks of treatment.
SAR0704 IVRS2792	Mouse/ MRL/MpJ- <i>FasIpr/J</i> mice	Topical ocular instillation	0, 0.1, 1.0, 10.0% per eye, TID (3 weeks)	8	In conjunctival histopathology, 7-week old (at termination) MRL/MpJ- <i>FasIpr/J</i> mice administered vehicle did not exhibit substantially increased inflammation compared to wild-type mice. It is difficult to evaluate SAR1118's effects in this study.
SAR0706 IVRS16155	Mouse/ MRL/MpJ- <i>FasIpr/J</i> mice	Topical ocular instillation	0, 0.1, 1.0, 10.0% per eye, TID (6 weeks)	12	Neither SAR1118 nor mAbM17 (positive control, anti-LFA-1 monoclonal antibody) reduced the inflammation occurring in the MRL/MpJ- <i>FasIpr/J</i> mice suggesting this model may not be the most robust or representative of KCS peri-ocular inflammation.

Note: A different study number was assigned in the NDA: Study SAR0702 (V6308M-SPD606), SAR0703 (V6310M-SPD606), SAR0701 (D6344M-SPD606), SAR0704 (M6758M-SHP606), and SAR0706 (M6311M-SPD606).

The EC₅₀ of 3.69 nM observed in Study # SAR0702 is equivalent to 2.271 ng/mL.

4.2 Secondary Pharmacology

(b) (4) **Full Profile Study of SSP-005493 Shire Pharmaceutical Development Ltd. (Study # V6435M-SPD606)** – Lifitegrast (10 μ M) showed no significant interaction in a broad selectivity screen against a panel of 139 receptors, ion channels, transporters, and enzymes. Lifitegrast (10 μ M) significantly inhibited CYP2C9 (94%); IC₅₀ = 11 μ M (6.77 μ g/mL).

As noted by the applicant, compared to the C_{max} of 2.76 nM (1.70 ng/mL) determined in Phase 1 studies (Clinical Study # SAR 1118-001) following ocular dosing of 5.0% lifitegrast twice daily, this represents a 3985-fold exposure multiple. Therefore, this interaction is unlikely to be clinically relevant.

4.3 Safety Pharmacology

These studies were previously reviewed under the initial IND by Dr. Zhou Chen. Lifitegrast showed no significant effects on cardiovascular, pulmonary, or CNS function (Table 4).

Table 4: Main Findings of Safety Pharmacology Studies

Study Number	System Evaluated	Species/ Strain	Method of Administration	Doses (mg/kg)	N	Noteworthy Findings
7898-116	Cardiovascular	Beagle dog	Intravenous	0 (vehicle), 1, 3, 10	4 males/group Latin Square design	No effects on electrocardiography or hemodynamic parameters observed
7898-117	Central nervous system	Rat / Hsd:SD	Intravenous, single dose	0 (vehicle), 0.2, 1, 10	6 males/group	Transient miosis was observed in animals given 10 mg/kg from 1 minute to 6 hrs postdose in 1 or 2 of 6 animals at each time point. No effect on any other parameters was observed.
7898-118	Respiratory	Rat / Hsd:SD	Intravenous single dose	0 (vehicle), 0.2, 1, 10	8 males/group	No adverse changes in respiratory function were observed at any dosage. No adverse effects seen at any dose.
7898-120	<i>In vitro</i> hERG	human ether-à-go-go-related gene)	Co-incubation	0, 20, 100, 200, and 600 µM		SAR1118 ^{(b)(4)} at 20, 100, 200 and 600 µM inhibited hERG potassium current by 7.0%, 22.9%, 38.9% and 52.0%, respectively. The IC ₅₀ for the inhibitory effect was 478 µM.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

Pharmacokinetics, Distribution, Metabolism, and Excretion of [¹⁴C]-SAR 1118 Following Ocular or Intravenous Administration to Rats (Study # R6319M-SPD606) – Sprague Dawley rats (3-9/sex/group or 5-6 males/group) were given a topical dose of 1 mg/eye (40 µCi/eye; 15.5 µL/eye) to both eyes or a 10 mg/kg intravenously (IV) dose (100 µCi/kg). Blood and urine were collected for up to 168 hours postdose; ocular tissues were collected for up to 24 hours postdose.

Following ocular administration, maximal concentrations of radioactivity in plasma were 194 and 695 ng equivalents/g at 0.25 hour (male) or 0.083 hour (female) postdose and concentrations declined rapidly and were below the lower limit of quantitation (BLQ) at 24 hours postdose. While the levels were low, the results indicated that [¹⁴C]-SAR 1118-derived radioactivity entered the systemic circulation. The elimination half-lives ($t_{1/2}$) for radioactivity in plasma were relatively short (2.84 and 3.17 hours for male and female rats, respectively). This was in contrast to the elimination $t_{1/2}$ for radioactivity determined after IV administration (36.2 and 40.7 hours for male and female rats, respectively). This is probably explained by the high volume of distribution observed after IV administration (21.2 and 21.3 L/kg for males and females, respectively).

Following a topical ocular administration of [¹⁴C]-SAR 1118 to male rats, concentrations of radioactivity were determined in all the ocular tissues collected (Table 5). The highest mean concentrations were determined in the anterior tissues; bulbar conjunctiva, palpebral conjunctiva, cornea and iris/ciliary body (ICB). The maximal concentrations were observed at 0.5 hour postdose. Except for the aqueous humor, ICB, and retina/choroid, radioactivity was still present in all ocular tissues at 24 hours postdose.

the IV route). After ocular administration, high concentrations were found in the nasal turbinates by QWBA analysis (see below). Radioactivity remaining in the carcasses accounted for 0.29 to 3.23% of the administered dose, and radioactivity levels were still detectable in urine and feces at 168 hour postdose.

The distribution of radioactivity into tissues following an ocular dose of [¹⁴C]-SAR 1118 was limited and radioactivity was generally associated with the gastrointestinal tract contents, the tissues associated with excretion, and the eye. The highest concentrations were determined at 0.5 hour postdose in the esophageal contents, nasal turbinates and the small intestinal contents, with concentrations of 399000; 352000; and 349000 ng equivalents/g, respectively. Radioactivity in the eye at this time point was lower than in these systemic tissues (18100 ng equivalents/g). Low levels of radioactivity were also associated with the liver (272 ng equivalents/g), kidney (151 ng equivalents/g) and uveal tract (9330 ng equivalents/g).

Concentrations declined steadily over time and by 24 hours postdose were mostly not detectable. The results indicated that the dose administered passed through the nasal turbinates and into the esophagus, ultimately being excreted through the gastrointestinal tract. As radioactivity was determined in the liver and kidneys, it is probable that absorption did occur.

A comparison of the distribution of radioactivity between Sprague Dawley (albino) and Long Evans (pigmented) rats, following either an ocular or IV dose administration, suggest that [¹⁴C]-SAR1118-derived radioactivity did not significantly bind to melanin.

Following either an ocular or IV bolus dose of [¹⁴C]-SAR 1118 to male and female rats, no metabolites were characterized from pooled plasma, urine and fecal homogenate samples. However, 3 radiolabeled components, thought to be impurities or degradants of [¹⁴C]-SAR 1118 were identified. These included (b) (4) with C_{max} values (b) (4) % (males only) of parent C_{max} levels in plasma, respectively, after ocular administration. Up to 10 additional impurities were also quantified in plasma but identification was not possible due to low mass and/or matrix interference. These impurities were observed at levels up to (b) (4) % (plasma), (b) (4) % (urine), and (b) (4) % (feces) those of SAR 1118.

Determination and Pharmacokinetics in Tears and Plasma of SAR 1118 (b) (4) Following a Single Topical Ocular Administration to New Zealand White Rabbits (Study # L6318M-SPD606) – This study was previously reviewed under the Initial IND by Dr. Zhou Chen. After a single topical ocular dose of 0.3% (0.105 mg/eye), 1% (0.35 mg/eye), and 3% (1.05 mg/eye) to both eyes, all animals showed systemic exposure (11.7-38.9 ng/mL and 5.19-22.9 ng•hr/mL). These mean plasma levels were 700-7000-fold lower than those observed in the tears (based on AUC).

Ocular Distribution and Pharmacokinetics of SSP-005493X following Repeated Topical Ocular Dose Regimen to Pigmented Rabbits (Study L6776M-SHP606) -

Two different clinical formulations of lifitegrast (1GC6 and 2F11) were administered to female New Zealand Red/White F1 pigmented rabbits at a dose level of 1.75 mg/eye/dose for 5 consecutive days. Animals received a single topical ocular dose in each eye twice daily (except on Study Day 5), approximately 12 hours apart (\pm 1 hour) for a total of 9 administrations.

Exposure of lifitegrast (AUC_{0-8}) following administration of either formulation was highest in the conjunctiva (palpebral), followed by cornea, sclera (anterior), conjunctiva (bulbar), sclera (posterior), iris-ciliary body, aqueous humor, and choroid-retinal pigment epithelium (RPE) (Table 6). The PK parameters derived from the two formulations were generally similar.

Table 6: Ocular Pharmacokinetic Parameters of Lifitegrast in Female Pigmented Rabbits Following Topical Ocular Instillation of Two Different Formulations for 5 Days

Matrix	C_{max} (ng/mL or ng/g)		T_{max} (hr)		AUC_{0-8} (ng•hr/mL or ng•hr/g)	
	1GC6	2F11	1GC6	2F11	1GC6	2F11
Aqueous humor	79.0	89.5	3.00	1.00	530	340
Choroid-RPE	119	45.9	0.250	3.00	492	231
Conjunctiva	14 200	9370	0.250	0.250	13 400	12 000
Conjunctiva	11 900	9620	0.250	0.250	30 800	36 600
Cornea	5930	5190	0.250	1.00	25 500	15 200
Iris-ciliary body	190	195	0.250	1.00	1130	778
Lens	3.85	0.794	1.00	3.00	5.44	NR
Optic nerve	36.0	10.8	1.00	0.250	NR	NR
Plasma	17.4	9.52	0.250	0.250	11.2	16.4
Retina	31.2	NR	1.00	NR	NR	NR
Sclera (anterior)	11 200	5870	0.250	0.500	17500	11 200
Sclera (posterior)	826	369	0.250	0.500	2360	1570
Vitreous humor	2.09	0.372	0.250	0.250	NR	NR

Source: Study Report [L6776M-SHP606 \(8300033\)](#)

AUC =area under the concentration curve; C_{max} =maximum concentration; NR=not reported due to limited measurable data; RPE= retinal pigment epithelium; T_{max} =time to maximum concentration

Due to the lack of a distinct elimination phase, estimation of elimination $t_{1/2}$ value was not calculated for most ocular tissues. The elimination $t_{1/2}$ values in the anterior sclera and bulbar conjunctiva for Group 1 (1GC6 formulation) were 1.97 and 2.02 hours, respectively, and the anterior sclera for Group 2 (2F11 formulation) was 2.32 hours.

After a topical ocular dose of the 1GC6 formulation concentrations of SSP-005493X declined with a plasma $t_{1/2}$ value of 0.850 hours. Due to the lack of a distinct elimination phase, estimation of elimination $t_{1/2}$ for the 2F11 formulation was not calculated.

Pharmacokinetics, Distribution, Metabolism, and Excretion of ^{14}C -SAR 1118 Following Ocular or Intravenous Administration to Dogs (Study # D6320M-SPD606) – Beagle dogs (4-5/sex/group) were given a topical dose of 3 mg/eye (30 μ Ci/eye; 30 μ L/eye) to both eyes or a 3 mg/animal IV dose (262 μ Ci/animal). Blood and

urine were collected for up to 168 hours postdose; ocular tissues were collected for up to 24 hours postdose.

After ocular administration, plasma C_{max} radioactivity values were 19.5 and 15.0 ng equivalents/g, respectively, observed at the first time point (0.25 hour post dose). Total plasma radioactivity declined rapidly, and by 8 hours postdose the concentrations were BLLQ. Due to the limited SAR 1118 concentration data obtained, it was not possible to perform PK analysis on plasma radioactivity concentrations after ocular administration.

After IV administration, the mean elimination $t_{1/2}$ values for plasma radioactivity were 108 and 113 hours for male and female dogs respectively, indicating that drug-related material was slowly eliminated following an IV bolus administration. Clearance values were low (25.6 and 21.7 mL/min for males and females, respectively) and volumes of distribution were moderate (250 and 209 L for males and females, respectively). The pharmacokinetic parameters suggested that compound-related radioactivity entered the tissues, although at low levels, and was slowly eliminated from the body over time.

Following a topical ocular administration of [14 C]-SAR1118, concentrations of radioactivity were determined in most ocular tissues collected (Table 7). No radioactivity was observed in the choroid/RPE, ciliary body, retina, and vitreous in males and in choroid/RPE, retina, and vitreous in females. The highest mean concentrations were determined in the anterior tissues (bulbar conjunctiva, palpebral conjunctiva, and cornea). The maximal concentrations in these tissues were observed at 0.5 hour postdose. By 24 hours postdose, concentrations had decreased but were still detectable in these ocular tissues.

Table 7: Mean Concentrations (Right and Left Eyes) of Radioactivity in Ocular Tissues after a Single 3 mg/eye Topical Ocular Administration of [¹⁴C]-SAR 1118 to Dogs**A. Males**

Sample	ng Equivalents [¹⁴ C]-SAR1118/g				
	Animal Number (Termination Time)				
	M07260 (0.5 Hour)	M07261 (2 Hours)	M07262 ^a (8 Hours)	M07263 (12 Hours)	M07264 (24 Hours)
Aqueous humor	15.2	26.0	21.2	11.7	4.20
Choroid (RPE)	BLQ	BLQ	BLQ	BLQ	BLQ
Ciliary body	BLQ	BLQ	BLQ	BLQ	BLQ
Conjunctiva (bulbar)	4510	1280	884	1920	2170
Conjunctiva (palpebral)	3790	1670	1560	4530	1040
Cornea	2130	1510	1240	690	498
Extraocular muscle	111	73.1	19.3	734	171
Iris	BLQ	250	178	189	BLQ
Lens	1.33	2.38	2.23	4.01	2.86
Optic nerve	BLQ	42.7	BLQ	17.6	BLQ
Retina	BLQ	BLQ	BLQ	BLQ	BLQ
Sclera	295	175	106	82.3	108
Vitreous humor	BLQ	BLQ	BLQ	BLQ	BLQ

BLQ Below the limit of quantitation.

RPE Retinal pigmented epithelium.

a This was a replacement animal for Phase 3.

B. Females

Sample	ng Equivalents [¹⁴ C]-SAR1118/g				
	Animal Number (Termination Time)				
	M07265 (0.5 Hour)	M07266 (2 Hours)	M07267 (8 Hours)	M07268 (12 Hours)	M07269 (24 Hours)
Aqueous humor	26.1	53.8	9.92	12.1	2.35
Choroid (RPE)	BLQ	BLQ	BLQ	BLQ	BLQ
Ciliary body	32.5	50.5	BLQ	BLQ	BLQ
Conjunctiva (bulbar)	3670	2810	591	1430	465
Conjunctiva (palpebral)	4500	4790	1280	1210	1650
Cornea	3230	3240	759	745	271
Extraocular muscle	203	636	11.0	282	111
Iris	82.0	270	169	BLQ	BLQ
Lens	3.53	2.85	3.38	3.84	1.43
Optic nerve	59.5	11.1	4.65	28.7	10.5
Retina	BLQ	BLQ	BLQ	BLQ	BLQ
Sclera	590	359	92.3	171	36.7
Vitreous humor	BLQ	BLQ	BLQ	BLQ	BLQ

BLQ Below the limit of quantitation.

RPE Retinal pigmented epithelium.

Following either a topical ocular or IV bolus administration of [¹⁴C]-SAR 1118, the concentrations of radioactivity in blood and plasma indicated no preferential uptake of [¹⁴C]-SAR 1118-derived radioactivity into red blood cells (blood:plasma concentration ratios < 1).

The main route of excretion was via feces (19% by the ocular route; 90% by the IV route). Some radioactivity was detected in the urine (2% by the ocular route; 3% by the IV route).

Following an ocular dose, radioactivity was generally associated with the upper section of the gastrointestinal tract (stomach, duodenum, and jejunum) and the tissues associated with excretion (bile, liver and kidneys). The highest radioactivity concentration at 24 hours was in the bile residual, providing additional support for biliary excretion as a main route of elimination. Radioactivity persisted in the ileum, liver, kidney and lungs, gastrointestinal tract, and contents (stomach, cecum, small intestines, ileum, and rectum). For all other tissues, with the exception of brown and reproductive fat (female dog), and residual urine, radioactivity was not detectable at 24 hours postdose.

Following either an ocular or IV bolus dose administration of [¹⁴C]-SAR 1118 to male and female rats, no metabolites were characterized from pooled plasma, urine and fecal homogenate samples. Three radiolabeled components, thought to be impurities or degradants of [¹⁴C]-SAR 1118 were identified. These included (b) (4)

(b) (4) was found at C_{max} levels (b) (4)-fold higher than those of [C]-SAR 1118 in plasma. Levels in urine and/or feces of these 3 impurities/degradants were low (b) (4)% of [¹⁴C]-SAR 1118 levels). After ocular administration, one unknown impurity (b) (4) was detected in the plasma at levels of (b) (4)% (males) and (b) (4)% (females) the radioactivity levels related to [¹⁴C]-SAR 1118. Up to 16 additional minor components were also quantified but identification was not possible due to low mass and/or matrix interference.

The *In Vitro* Protein Binding of SAR1118 (b) (4) in Rat, Rabbit, Dog, Monkey, and Human Plasma, and the Binding to Human Albumin, Human α ₁-Acid Glycoprotein, and Melanin (Study # V6316M-SPD606) - SAR1118 (b) (4) was highly bound to plasma proteins from all species, with mean percentage bound values ranging from 96.1% to 99.5%. SAR1118 (b) (4) was highly bound to human serum albumin (mean of 94.8% to 97.6%) and was moderately bound to human α ₁-acid glycoprotein (mean of 31.6% to 51.1%) and to *Sepia officinalis* melanin (mean of 35.2% to 60.4% bound). The plasma protein binding of SAR1118 (b) (4) was independent of concentration in all species over the target concentration range of 50 to 1000 ng/mL (100-1000 ng/mL for melanin binding).

***In Vitro* Metabolism of ¹⁴C-SAR1118 (b) (4) by Rat, Dog, Monkey, and Human Hepatocytes (Study # V6317M-SPD606)** - This study was previously reviewed under the initial IND by Dr. Zhou Chen. The relative velocities of metabolism (disappearance

of parent compound over time) of ^{14}C -SAR1118 ^{(b) (4)} were in the rank order: rat > human \approx monkey \approx dog. However, metabolism was slow in all species with % of parent remaining from an initial concentration of 10 $\mu\text{g/mL}$ /100 $\mu\text{g/mL}$ of 84%/93.7%, 91.5%/94.3%, 93.6%/94.8% and 94%/95.3%, respectively. Eight minor metabolites/degradations products were identified. The average percentage of total radioactivity ranged from 0.56-3.02%. All were considered possible degradation products as they were also present in control incubations.

Hepatic Clearance of SAR 1118 (Study # V6390M-SPD606) – Following administration of SAR 1118 to male Sprague-Dawley rats, a high clearance (CI) was observed (54 ± 15 mL/min/kg). The primary route of elimination for SAR 1118 was by biliary excretion. The CI and biliary excretion were significantly reduced by cyclosporine (61%) and probenecid (68%), both inhibitors and/or substrates of multiple transporters. SAR 1118 uptake into fresh rat hepatocytes was significantly inhibited (55.8 to 74.5%) by inhibitors of the organic-anion transporter (Oatp).

5.2 Toxicokinetics

Refer to individual studies under Section 6. General Toxicology.

6 General Toxicology

6.1 Single-Dose Toxicity

Single-dose toxicity studies were conducted in Sprague-Dawley rats and New Zealand White (NZW) rabbits. The main findings are summarized in Table 8. The increase in mean corpuscular hemoglobin concentration was $\leq 2\%$ ($p < 0.05$) compared to controls. No effects in mean corpuscular hemoglobin concentration were noted in the 13-week repeat-dose study in rats at doses up to 30 mg/kg/day.

Table 8: Single-Dose Toxicity Studies Conducted with SAR 1118

Species	Route	Formulation	Dose (Number/Group)	Results	GLP Status	Study Report Number
Sprague-Dawley Rat	IV	(b) (4) lifitegrast in PBS	0, 0.2, 1.0, or 10.0 mg/kg (5/sex/dose)	Non-adverse increase in mean corpuscular hemoglobin concentration in males given 1 or 10 mg/kg and females given 10 mg/kg	GLP	R6328M-SPD606 (7898-107)
New Zealand White Rabbit	topical ocular instillation	(b) (4) lifitegrast in PBS	0, 0.35, 1.05, and 3.5 mg/eye (0%, 1.0%, 3.0%, 10.0%) (5 male/dose)	Non-adverse mild irritation indicated by squinting immediately following dosing on Day 1 (lasted ≤4 minutes)	GLP	L6756M-SHP606 (7898-102)

IV=intravenous; GLP=Good Laboratory Practices; PBS=phosphate-buffered saline

6.2 Repeat-Dose Toxicity

Ocular Route Repeat-Dose Toxicology Studies

Study title: 39-Week Topical Ocular Instillation Toxicity and Toxicokinetic Study with SAR 1118 in Dogs with a 13-Week Recovery

Study no.: D6336M-SPD606
 Study report location: FDR Module 4 2 3 2
 Conducting laboratory and location: (b) (4)
 Date of study initiation: April 11, 2012
 GLP compliance: Yes
 QA statement: Yes
 Drug, lot #, and % purity: SAR 1118 (b) (4) lot # VEN-Y-108(1), 99.2% pure

Dosing formulations were prepared every 2 weeks and once for the final week of dosing.

Key Study Findings

- A dose-dependent irritation response characterized by blinking and squinting was noted in test-article treated animals shortly postdose. However, findings were very mild and transient and did not result in any abnormal ocular observations.
- Granulomatous inflammation (minimal) of the tongue was noted at the high dose.
- SAR 1118 was detected in the vitreous of only 3 animals, suggesting limited distribution to posterior eye structures.
- The high-dose level of 5% 3x/day (5.25 mg/eye/day) is considered the NOAEL, which corresponds to a plasma level of C_{max} of 12.9 ng/mL and an AUC_{last} of 7.49 ng•hr/mL following 39 weeks of topical instillation of SAR 1118.

Methods

Doses: 0, 1, 3 or 5% (0, 0.35, 1.05, and 1.75 mg/eye/dose or 0, 1.05, 3.15, and 5.25 mg/eye/day, respectively)

Note: The dose levels and concentrations reflect the amount of SAR 1118- (b) (4) in each formulation.

Frequency of dosing: 3x/day (4 to 4.5 hours apart)

Route of administration: Topical ocular instillation to both eyes

Dose volume: 35 μ L

Formulation/Vehicle: Sodium thiosulfate pentahydrate (b) (4)%, dibasic sodium phosphate (b) (4)%, sodium chloride (b) (4) for the 1, 3, and 5% formulations, respectively), and Sterile Water for Injection, USP (q.s. to final volume); pH 7.2-7.5

Note: This study used the intended clinical formulation.

Species/Strain: Beagle dogs

Number/Sex/Group: 5/sex/group in control and high-dose groups; 3/sex/group in low and mid-dose groups

Two dogs/sex/group in control and high-dose groups underwent a 13-week recovery phase.

Age: 7 months old

Weight: 7.1 to 11.7 kg for males; 6.2 to 9.6 kg for females

Satellite groups: None

Unique study design: None

Deviation from study protocol: The analyses of dose formulations were not performed under GLP.

Observations and Results

Mortality (2x/day)

None

Clinical Signs (Daily cageside observations; weekly detailed observations)

High-dose female # H05859 had clear discharge in the right eye throughout the dosing phase. Mid-dose male # H05841 showed clear discharge in the right eye at several observations during Days 37 to 142.

Body Weights (Weekly)

No test article-related effects

Feed Consumption (Weekly)

No test article-related effects

Ocular Squinting (Within 2 minutes following each dose beginning with the 1st daily dose on Day 1 and continuing through the 3rd daily dose on Day 7; once weekly following each of the 3 daily doses during the dosing phase starting on Day 8)

Squinting or blinking was observed in test article-treated animals in a dose-related manner. The frequency of blinking or squinting lasting for >60 seconds also increased with increasing dose (i.e., not observed in control or low-dose groups, 4 occasions in mid-dose group and 28 occasions in high-dose group). The frequency and/or duration of the blinking or squinting were higher during the first 4 days of the dosing phase. After Day 4, the finding was still present throughout the study primarily at the high dose but with lower frequency and/or duration.

Ophthalmoscopy (Slit lamp and indirect ophthalmoscopy predose, on Days 1, 4, 86, 177 and 268 of the dosing phase [at least 30 minutes after the 1st daily dose], and on Days 2, 44, and 86 of the recovery phase; findings scored using a modified McDonald-Shadduck scoring system)

During the dosing phase, mild (1+) conjunctival hyperemia was sporadically noted in both eyes of four animals: control male # H05835 (Week 13; also at predose), low-dose male H05838 (Weeks 13 and 26), mid-dose female # H05856 (Week 13), and mid-dose male # H05841 (Week 39). Animal # H05841 also had moderate (2+) serous ocular discharge and mild blepharospasm during Week 39 of the dosing phase. The latter findings may not be test article-related as they were not observed in high-dose animals. There were no adverse findings at recovery evaluations.

Intraocular pressure (Predose, on Days 4, 86, 177, and 268 of the dosing phase, and on Days 2, 44, and 86 of the recovery phase at least 30 minutes after the 1st daily dose)

No test article-related effects

Pachymetry (Predose, on Days 3, 87, 178, and 269 of the dosing phase; and on Days 3, 45, and 87 of the recovery phase)

No test article-related effects

Electroretinography (Predose and during Weeks 18 and 38 of the dosing phase)

The following findings were noted at the low and mid-dose. However, given that a similar effect was not noted at the high-dose, these findings are likely due to random factors. As a note, a-wave amplitude measurements had a high within-group variability to allow the capture a subtle change. The % change is based on concurrent control value.

- There was a decrease in mean Scotopic -24 dB White Single Flash stimulus, B-wave amplitude and oscillatory potentials (0 dB White Single Flash Bandpass Filtered 80-100 Hz) in low dose males at Week 38 (17-37% and 23-37%, respectively), but a similar effect was not noted at the mid and high dose.
- Low dose females showed decreased mean Photopic 30 Hz White stimulus amplitude at Weeks 18 and 38 (18-49%) and decreased mean latency (4-5%) at Week 38. Mid-dose females also showed a decrease in mean Photopic 30 Hz White stimulus amplitude at Weeks 18 and 38 (3-38%), but the magnitude of the effect was lower.
- Similarly, low dose females showed decreased mean Photopic Single White stimulus (0 dB Single Flash), B-wave amplitude at Weeks 18 and 38 (26-41%). Mid-dose females also showed a decrease in mean Photopic Single White stimulus (0 dB Single Flash), B-wave amplitude at Weeks 18 and 38 (5-28%), but the magnitude of the effect was lower.

Hematology and Coagulation (Predose, on Day 128 and 268 of the dosing phase, and on Day 88 of the recovery phase)

No test article-related effects

Clinical Chemistry (Predose, on Day 128 and 268 of the dosing phase, and on Day 88 of the recovery phase)

No test article-related effects

Urinalysis (Predose, on Day 128 and 268 of the dosing phase, and on Day 88 of the recovery phase)

Two high-dose males (# H05846 and H05847) showed an increase in WBC in the urine on Day 268 (score of 3 vs 0-1 in controls or baseline). The finding was not observed at recovery in these 2 animals.

Gross Pathology (Day 274 of the dosing phase and Day 92 of the recovery phase)

No test article-related findings

Organ Weights (Adrenals, brain, epididymis, gall bladder, heart, kidney, liver, lung/large bronchi, ovary, pituitary gland, prostate, mandibular salivary gland, spleen, testis, thymus, thyroid/parathyroid, uterus)

At the end of the dosing phase, nonstatistically significant increases were observed in the weight of the heart, kidney, spleen, liver/gall bladder, testis, and salivary gland in high-dose males and in the heart, kidney, spleen (also mid-dose females; non-dose dependent), and thymus in high-dose females. Except for one high-dose male with elevated thymus weight and one high-dose female with elevated spleen weight, these differences were not observed in recovery animals. There was no microscopic correlate in any of these organs. These changes are considered unlikely related to the test article.

Histopathology (All animals)

Adequate Battery - Yes

Peer Review - No

Histological Findings - There were no test article-related microscopic findings in the ocular tissues. Meibomian gland inflammation (minimal to slight) and mononuclear cell infiltrate (minimal) in the lacrimal glands were noted in one or both eyes in control as well as test-article treated eyes without a dose-response. Systemically, granulomatous inflammation (minimal) of the tongue was noted in one high-dose male and one high-dose female at the end of the dosing phase.

At recovery sacrifice, mononuclear cell infiltrate (minimal) was noted in the lacrimal gland of one high-dose female, atrophy (minimal) of the nictitating gland in the left eye of one high-dose male, granulomatous inflammation (minimal) of the tongue in one high-dose female, inflammation/degeneration of the seminiferous tubules (slight, bilateral) and aspermia in one high-dose male, and mononuclear cell infiltration in the choroid plexus of the 4th ventricle of the brain (slight) and brainstem (minimal) in one high-dose female.

The sponsor claims that the findings in the tongue, testis, and choroid plexus are known spontaneous changes in beagles. This statement is supported by the following facts:

1. These findings (except for those in the tongue) were not observed during treatment in the current study.
2. The incidence of mononuclear cell infiltration in the choroid plexus (Table 9) was in general similar or higher at the end of dosing in control groups compared to test article-treated groups in the 13-week ocular toxicity study (Study # D6335M-SPD606).

Table 9: Microscopic Findings in the Tongue and Brain – 13-Week Ocular Toxicity Study in Dogs

Controls from group(s): 1		-- Animals --				Affected --			
Tissues With Diagnoses	Animal sex:	Males		Females		Males		Females	
	Dosage group: No. in group:	Ctls	2	3	4	Ctls	2	3	4
Tongue		3	0	0	3	3	0	0	3
Number examined:		3	0	0	3	3	0	0	3
Unremarkable:		2	0	0	2	1	0	0	1
Degeneration/Regeneration, Muscle		0	0	0	0	1	0	0	0
Infiltrate, Lymphocytes/Macrophages, Skeletal Muscle		1	0	0	1	1	0	0	1
Infiltrate, Neutrophils		0	0	0	0	0	0	0	1
Brain		3	0	0	3	3	0	0	3
Number examined:		3	0	0	3	3	0	0	3
Unremarkable:		0	0	0	1	2	0	0	3
Chromatolysis, Neurons		0	0	0	0	0	0	0	0
Hematopoiesis, Extramedullary, Choroid Plexus		1	0	0	1	0	0	0	0
Infiltrate, Lymphocytes/Macrophages, -Perivascular/Meninges/Choroid Plexus		2	0	0	1	1	0	0	0

However, granulomatous inflammation of the tongue was not previously reported. Based on the tongue findings in the rabbit (See Study # L6329M-SPD606), this reviewer believes that a test article-related effect cannot be ruled out.

Toxicokinetics

Plasma (Days 1, 129, and 269 of the dosing phase at predose and approximately 0.25, 1, 2, 4 (prior to 2nd daily dose), 6, and 24 hours after the first daily dose based on the last eye dosed/animal) - Systemic exposure to SAR 1118 was observed in all animals following topical ocular instillation. The increase in C_{max} or AUC was generally less than dose proportional. At Week 39, C_{max} and AUC were lower at the high-dose compared to the mid-dose. There was no substantial accumulation with repeated dosing. The sponsor concluded that there were no consistent sex-related differences in plasma SAR 1118 exposure. However, the data showed females tended toward higher mean plasma concentrations (≤ 3.8 -fold) at the low dose (all time points) and mid-dose (≤ 4.5 -fold; Day 1 only). Mean T_{max} was observed generally at 0.25 hours; mean T_{last} was generally 6 hours. Gender combined mean plasma exposure data is shown in the table below.

Table 10: Combined Mean (Standard Deviation) Plasma SAR 1118 Exposure in Male and Females Beagle Dogs – 39-Week Topical Ocular Instillation Study

Dose (mg/eye TID)	Day 1		Week 19		Week 39	
	C_{max}^a (ng/mL)	AUC_{last}^b (hr·ng/mL)	C_{max}^a (ng/mL)	AUC_{last}^b (hr·ng/mL)	C_{max}^a (ng/mL)	AUC_{last}^b (hr·ng/mL)
0.35	5.78 (5.01)	2.97 (3.94)	4.25 (2.76)	2.21 (1.94)	6.68 (3.60)	2.97 (2.92)
1.05	9.12 (5.16)	5.75 (5.42)	5.31 (1.83)	4.12 (2.22)	15.9 (7.49)	9.88 (9.41)
1.75	13.2 (12.6)	8.37 (9.75)	9.27 (4.55)	6.89 (6.27)	12.9 (10.1)	7.49 (6.33)

AUC=area under the concentration versus time curve; C_{max} =maximum concentration; TID=three times a day

^a Maximum plasma lifitegrast concentration during the first daily dose interval.

^b Plasma lifitegrast AUC_{last} during the first daily dose interval.

Tears (collected from nonfasted animals using dye-free Tear Flo Test [TFT] strips on Days 1, 129, and 269 of the dosing phase at predose, 0.125 [+ 1 minute] and 0.25 (+ 4 minute) hours after the first daily dose; and approximately 1, 2, 4 [prior to 2nd daily dose], 6, and 24 hours after the first daily dose based on the last eye dosed/animal) - Exposure to SAR 1118 was detected in tear fluid of all animals in the SAR 1118-dosed groups. The increase in C_{max} or AUC was generally less than dose proportional. There was no substantial accumulation with repeated dosing. No consistent sex-related differences in tear fluid SAR 1118 exposure were observed. There were no consistent differences in mean tear fluid SAR 1118 exposure parameters for the right eye versus the left eye. The T_{max} was observed generally at 0.125 hours; T_{last} was generally 4 hours. Gender combined mean tear exposure data is shown in the table below.

Table 11: Combined Mean (Standard Deviation) Tear SAR 1118 Exposure in Male and Females Beagle Dogs – 39-Week Topical Ocular Instillation Study**A. Right Eye**

Dose (mg/eye TID)	Day 1		Week 19		Week 39	
	C_{max}^a ($\mu\text{g/mL}$)	AUC_{last}^b ($\text{hr}\cdot\mu\text{g/mL}$)	C_{max}^a ($\mu\text{g/mL}$)	AUC_{last}^b ($\text{hr}\cdot\mu\text{g/mL}$)	C_{max}^a ($\mu\text{g/mL}$)	AUC_{last}^b ($\text{hr}\cdot\mu\text{g/mL}$)
0.35	658 (171)	145 (62.5)	762 (415)	204 (94.9)	694 (522)	152 (73.5)
1.05	2695 (2484)	674 (609)	1093 (544)	300 (175)	1714 (882)	509 (285)
1.75	1792 (640)	534 (287)	1541 (1239)	492 (435)	2211 (1344)	584 (464)

AUC=area under the concentration versus time curve; C_{max} =maximum concentration; TID=three times a day

^a Maximum tear lifitegrast concentration during the first daily dose interval.

^b Tear lifitegrast AUC_{last} during the first daily dose interval.

B. Left Eye

Dose (mg/eye TID)	Day 1		Week 19		Week 39	
	C_{max}^a ($\mu\text{g/mL}$)	AUC_{last}^b ($\text{hr}\cdot\mu\text{g/mL}$)	C_{max}^a ($\mu\text{g/mL}$)	AUC_{last}^b ($\text{hr}\cdot\mu\text{g/mL}$)	C_{max}^a ($\mu\text{g/mL}$)	AUC_{last}^b ($\text{hr}\cdot\mu\text{g/mL}$)
0.35	586 (408)	131 (123)	1012 (581)	214 (138)	969 (983)	216 (216)
1.05	1459 (1547)	553 (474)	982 (354)	229 (86.6)	1658 (1652)	435 (521)
1.75	1294 (952)	367 (214)	1636 (1200)	430 (325)	2056 (1490)	524 (410)

AUC=area under the concentration versus time curve; C_{max} =maximum concentration; TID=three times a day

^a Maximum tear lifitegrast concentration during the first daily dose interval.

^b Tear lifitegrast AUC_{last} during the first daily dose interval.

Vitreous (samples collected from all animals at scheduled sacrifices) - Only four eyes from 3 animals in the active dose groups showed quantifiable concentrations of SAR 1118 at the dosing phase sacrifice. Vitreous concentrations were below the lower limit of assay quantitation (0.500 ng/mL) in all other samples.

- Mid-dose male H05841: 0.525 ng/mL (left eye) and 0.850 ng/mL (right eye)
- High-dose male H05843: 0.604 ng/mL (left eye) and <0.500 ng/mL (right eye)
- High-dose male H05845: <0.500 ng/mL (left eye) and was 0.686 ng/mL (right eye)

Dosing Solution Analysis

Results from formulations sampled on Week 1, Week 13, Week 26, and Week 39 were 97.4-110.1% of nominal.

Study title: 39-Week Topical Ocular Instillation Toxicity and Toxicokinetic Study with SAR 1118 in Rabbits with a 13-Week Recovery Phase

Study no.: L6329M-SPD606 (Sponsor Ref # 7898-125)

Study report location: EDR Module 4.2.3.2

Conducting laboratory and location:

(b) (4)

(b) (4)
Date of study initiation: February 4, 2009
GLP compliance: Yes
QA statement: Yes
Drug, lot #, and % purity: SAR 1118 (b) (4) lot #
(b) (4), 98.9% pure

(b) (4)
(b) (4) A (b) (4)
(w/v) (b) (4) solution (b) (4)
was prepared using a vehicle of sodium bicarbonate and SWFI.

Dosing formulations were prepared every 2 weeks. The stock solution (b) (4) was diluted with the vehicle control article to the appropriate concentrations for dosing.

Key Study Findings

- A dose-dependent irritation response characterized by blinking and squinting was noted in test-article treated animals shortly postdose. However, findings were very mild and transient and did not result in any abnormal ocular observations.
- An increase incidence/severity of myofiber regeneration of the tongue was observed at all dose levels.
- SAR 1118 was detected at very low levels in the vitreous of only 3 animals, suggesting limited distribution to posterior eye structures. The levels were >4000-fold lower those observed in tears.
- The high-dose level of 5% 3x/day (5.25 mg/eye/day) is considered the NOAEL, which corresponds to a plasma level of C_{max} of 20.2 ng/mL and an AUC_{last} of 22.4 ng•hr/mL following 39 weeks of topical instillation of SAR 1118.

Methods

Doses: 0, 0.3, 1, or 5% (0.105, 0.35, and 1.75 mg/eye/dose or 0, 0.315, 1.05, and 5.25 mg/eye/day, respectively)

Frequency of dosing: 3x/day (4 to 4.5 hours apart)

Route of administration: Topical ocular instillation to both eyes

Dose volume: 35 µL

Formulation/Vehicle: Methylparaben (b) (4)%, propylparaben (b) (4)%, (b) (4), sodium chloride (b) (4)%, sodium phosphate monobasic (b) (4)%, sodium phosphate dibasic (b) (4)%, sterile water for injection (q.s. to final volume)

Note: *This formulation is not the intended clinical formulation. The intended clinical formulation contains sodium chloride, sodium phosphate dibasic, sodium thiosulfate pentahydrate, sodium hydroxide/hydrochloric acid, and water for injection as excipients.*

Species/Strain: Hra:(NZW)SPF rabbits

Number/Sex/Group: 6/sex/group in control and high-dose groups; 4/sex/group in low and mid-dose groups

Two rabbits/sex/group in control and high-dose groups underwent a 13-week recovery phase.

Age: 13 weeks old

Weight: 2089 to 2462 g for males; 2136 to 2452 g for females

Satellite groups: An additional 2 rabbits/sex/group were used for TK analysis.

Unique study design: None

Deviation from study protocol: None with an impact in the interpretation of the data

Observations and Results**Mortality (2x/day)**

One mid-dose female (# F19802) died following blood sample collection on Day 266. Shortly after blood collection, this animal showed clinical signs of sternal recumbency, yellow nasal discharge, pale eyes, irregular respiration, and cold to touch and was diagnosed as having a possible spinal fracture. This animal showed no clinical signs of toxicity prior to Day 266 of the dosing phase. The death was considered due to a handling accident.

Clinical Signs (Daily cageside observations; weekly detailed observations)

Red conjunctiva was observed in one low-dose male and mid-dose male on Day 271; squinted eye was also observed in the mid-dose male on Day 271. The single occurrence and lack of a dose response suggest these findings are not test article related.

Body Weights (Daily)

No test article-related effects

Feed Consumption (Daily, qualitatively)

No test article-related effects

Ocular Squinting (Following each dose beginning with the 1st daily dose on Day 1 and continuing through the 3rd daily dose on Day 7; once weekly following each of the 3 daily doses during the dosing phase starting on Day 8)

Squinting or blinking was observed in test article-treated animals in a dose-related manner. The findings were noted on only a few occasions in animals given 0 or 0.315 mg/eye/day, but on 14 occasions in less than half of the animals given 1.05 mg/eye/day and on 143 occasions in all 12 animals given 5.25 mg/eye/day. The frequency of blinking or squinting lasting for ≥ 60 seconds also increased with increasing dose (i.e., not observed in control or low-dose groups, 2 occasions in mid-dose group and 43 occasions in high-dose group). The frequency and/or duration of the blinking or squinting diminished with repeated administration of the test article.

Ophthalmoscopy (Slit lamp and indirect ophthalmoscopy predose, on Days 1 [slit lamp only] and 4, and Weeks 13, 26, and 39 of the dosing phase [at least 30 minutes after the 1st daily dose], and Weeks 1, 7, and 13 of the recovery phase; ocular irritation conducted in conjunction with the slit lamp observations; findings scored using a modified McDonald-Shadduck scoring system)

Conjunctival congestion (slight) was observed sporadically in control as well as test article-treated eyes. The finding was not considered test article related. The finding was not present in recovery evaluations.

Intraocular pressure (Predose, on Day 4, and Weeks 13, 26, and 39 of the dosing phase, and on Weeks 1, 7, and 13 of the recovery phase at least 30 minutes after the 1st daily dose)

No test article-related effects

Pachymetry (Predose, on Day 4, and Weeks 13, 26, and 39 of the dosing phase, and on Weeks 1, 7, and 13 of the recovery phase)

No test article-related effects

Electroretinography (Predose and during Weeks 19 and 39 of the dosing phase; scotopic conditions only)

No test article-related effects were observed. As a note, a-wave amplitude measurements had a high within-group variability to allow the capture of subtle changes.

Hematology and Coagulation (Predose, on Weeks 19 and 39 of the dosing phase, and on Week 13 of the recovery phase)

No test article-related effects

Clinical Chemistry (Predose, on Weeks 19 and 39 of the dosing phase, and on Week 13 of the recovery phase)

No test article-related effects

Gross Pathology (Week 39 of the dosing phase and Week 13 of the recovery phase)

No test article-related findings

Organ Weights (Adrenals, brain, epididymis, heart, kidney, liver/gall bladder, lung, ovary, pituitary gland, prostate/seminal vesicles, mandibular salivary gland, spleen, testis, thymus, thyroid/parathyroid, uterus)

No test article-related effects

Histopathology (Ocular tissues of each animal [eyes, eyelids, conjunctivae, Harderian glands, lacrimal glands, nictitating membrane, and optic nerves]; systemic tissues from each animal in the control and high-dose groups and the animal sacrificed at an unscheduled interval, macroscopic lesions, thymus, and tongue from each animal in the low- and mid-dose groups for dosing phase sacrifice; macroscopic lesions, thymus, and tongue from each animal from the recovery phase sacrifice)

Adequate Battery - Yes

Peer Review - No

Histological Findings – No test article-related microscopic findings were noted in the ocular or systemic tissues. Sporadic, mild conjunctival hyperemia was seen infrequently in all groups including controls, but this did not follow a dose-responsive pattern and therefore was not attributed to SAR 1118.

Thymic atrophy and regeneration of muscle fibers in the tongue were observed in control as well as test article-treated animals at the dosing phase necropsy (Table 12). Thymic atrophy was also present in all recovery animals (i.e., control and high dose) but with higher severity in control animals (moderate in both male and female control

animals vs. one slight and one moderate each in high-dose male and high-dose female animals). Therefore, this reviewer agrees with the sponsor’s assessment that there was not a clear dose-relationship in incidence and severity to suggest the thymic findings were related to the test article.

Males given 0.35 or 1.75 mg/eye 3x/day had an increase in the severity score assigned to regeneration of muscle fibers in the tongue (from minimal-slight in controls to minimal-marked in the SAR 1118-treated animals). However, 2 female controls also had moderate severity of this finding. The tongue finding was not present in recovery animals.

Table 12: Incidence and Severity of Thymic Atrophy and Tongue Myofiber Regeneration - 39-Week Topical Ocular Instillation Study in Rabbits

Controls from group(s): 1		-- Animals --				Affected --			
		Males		Females		Males		Females	
Tissues With Diagnoses	Animal sex: Dosage group: No. in group:	Ctls	2	3	4	Ctls	2	3	4
Thymus	Number examined:	4	4	4	4	4	4	3	4
Atrophy	->	0	0	0	0	1	0	0	1
	2>	1	0	1	0	0	3	2	0
	3>	2	3	3	2	2	1	1	1
	4>	1	1	0	2	1	0	0	2
	Total Incidence of Finding Observed:	4	4	4	4	3	4	3	3
Tongue	Number examined:	4	4	4	4	4	4	3	4
Regeneration, Myofiber	->	2	1	0	0	1	0	0	1
	1>	1	1	1	0	1	1	2	0
	2>	1	2	0	0	0	2	0	0
	3>	0	0	2	4	2	0	0	3
	4>	0	0	1	0	0	1	1	0
	Total Incidence of Finding Observed:	2	3	4	4	3	4	3	3

When the incidence/severity of male and females is combined, a test article related effect is now apparent at all dose levels (Table 13). However, as noted by the applicant, regeneration is considered an indication of healing from a prior injury (e.g. infection, inflammation), rather than severe or ongoing tissue injury.

Table 13: Incidence and Severity of Tongue Myofiber Regeneration- Male and Female Combined

Tongue, regeneration, myofiber	0	0.315 mg/eye	1.05 mg/eye	5.25 mg/eye
1	2	2	3	0
2	1	4	0	0
3	2	0	2	7
4	0	1	2	0
Total	5	7	7	7

Note: Shading indicates values with increased incidence compared to controls.

Toxicokinetics

Plasma (Days 1, Weeks 19 and 39 of the dosing phase at predose and approximately 0.25, 1, 2, 4 [prior to 2nd daily dose], 6, and 24 hours following administration of the 1st daily dose)

Systemic exposure to SAR 1118 was observed in all animals following topical ocular instillation. Dose linearity was not observed for either plasma C_{max} or AUC_{0-n} . Some accumulation of SAR 1118 was observed in plasma on Week 19 but not on Week 39. At Week 39, C_{max} and AUC at the mid-dose were similar or lower than those at the low-dose. Plasma exposure data are shown in the following table. There were no consistent sex-related differences in plasma SAR1118 exposure. T_{max} was observed generally 0.25 hours; T_{last} was generally 6 hours. Gender combined mean plasma exposure data is shown in the table below.

Table 14: Combined Mean (Standard Deviation) Plasma SAR 1118 Exposure in Male and Females Rabbits – 39-Week Topical Ocular Instillation Study

Dose (mg/eye TID)	Day 1		Week 19		Week 39	
	C_{max}^a (ng/mL)	AUC_{0-n}^b (hr·ng/mL)	C_{max}^a (ng/mL)	AUC_{0-n}^b (hr·ng/mL)	C_{max}^a (ng/mL)	AUC_{0-n}^b (hr·ng/mL)
0.105	5.56 (0.539)	3.10 (2.14)	9.08 (2.88)	9.44 (3.51)	3.19 (1.40)	3.36 (2.69)
0.35	9.19 (9.86)	5.46 (5.56)	16.5 (6.94)	14.0 (2.91)	3.16 (0.957)	1.90 (1.47)
1.75	62.0 (16.2)	42.9 (8.14)	52.1 (12.5)	62.7 (4.95)	20.2 (10.2)	22.4 (10.7)

AUC=area under the concentration versus time curve; C_{max} =maximum concentration; TID=three times a day

^a Maximum plasma lifitegrast concentration during the first daily dose interval.

^b Plasma lifitegrast AUC_{0-n} during the first daily dose interval.

SAR 1118 was also detected in 4 control samples (4 different animals) at concentrations ranging from 0.902 to 4.33 ng/mL. However, because these occurred at a single time point, they are not expected to have a significant impact in the interpretation of the data.

Tears (collected from nonfasted animals using dye-free Tear Flo Test (TFT) strips on Days 1, Weeks 19 and 39 of the dosing phase at predose, and approximately 0.25, 1, 2, 4 [prior to 2nd daily dose], 6, and 24 hours following administration of the 1st daily dose)

Exposure to SAR 1118 was detected in tear fluid of all eyes at Week 19 and 39. On Day 1, exposure was observed in both eyes of all high-dose animals, but not in all eyes in the low- and mid-dose groups. Dose-linearity was not observed for C_{max} or AUC_{last} . Accumulation seems to have occurred at Week 19. However, there was high within group variability in C_{max} or AUC_{last} values that precludes an accurate assessment. No consistent sex-related differences were observed. The T_{max} was observed generally 0.25 hours; T_{last} was generally 6 or 24 hours (last timepoint measured). Gender combined mean tear exposure data is shown in the table below.

Table 15: Combined Mean (Standard Deviation) Tear SAR 1118 Exposure in Male and Females Rabbits – 39-Week Topical Ocular Instillation Study**A. Right Eye**

Dose (mg/eye TID)	Day 1		Week 19		Week 39	
	C _{max} ^a (µg/mL)	AUC _{0-n} ^b (hr·µg/mL)	C _{max} ^a (µg/mL)	AUC _{0-n} ^b (hr·µg/mL)	C _{max} ^a (µg/mL)	AUC _{0-n} ^b (hr·µg/mL)
0.105	13.2 ^c	4.84 ^c	60.5 (57.2)	65.4 (61.4)	10.0 (5.33)	18.7 (12.1)
0.35	16.2 (16.3)	10.3 (9.39)	230 (305)	216 (264)	26.0 (37.7)	18.5 (19.8)
1.75	1377 (2132)	758 (1127)	657 (472)	478 (283)	99.7 (77.9)	142 (93.5)

AUC=area under the concentration versus time curve; C_{max}=maximum concentration; TID=three times a day

^a Maximum tear lifitegrast concentration during the first daily dose interval.

^b Tear lifitegrast AUC_{0-n} during the first daily dose interval.

^c Standard deviation was not calculated as the number of animals for which tear concentrations were above the lower limit of assay quantitation (0.500 µg/mL) was <3.

B. Left Eye

Dose (mg/eye TID)	Day 1		Week 19		Week 39	
	C _{max} ^a (µg/mL)	AUC _{0-n} ^b (hr·µg/mL)	C _{max} ^a (µg/mL)	AUC _{0-n} ^b (hr·µg/mL)	C _{max} ^a (µg/mL)	AUC _{0-n} ^b (hr·µg/mL)
0.105	9.88 (4.32)	4.15 (4.87)	15.7 (4.04)	20.2 (5.56)	8.74 (6.58)	12.2 (17.3)
0.35	70.0 (49.6)	35.8 (42.8)	119 (122)	138 (84.5)	26.9 (16.1)	35.2 (17.6)
1.75	762 (985)	420 (552)	389 (232)	501 (179)	192 (150)	415 (342)

AUC=area under the concentration versus time curve; C_{max}=maximum concentration; TID=three times a day

^a Maximum tear lifitegrast concentration during the first daily dose interval.

^b Tear lifitegrast AUC_{0-n} during the first daily dose interval.

SAR 1118 was also detected in some control samples at concentrations ranging from 1.23 to 17.3 µg/mL. As these were generally observed in 2 or more consecutive timepoints, they are expected to have an impact in the interpretation of the data.

Vitreous (Samples collected from all animals at scheduled sacrifices)

Only four eyes from 3 animals in the active dose groups showed quantifiable concentrations of SAR 1118 at the dosing phase sacrifice. Vitreous concentrations were below the lower limit of assay quantitation (0.500 to 1.25 ng/mL) in all other samples.

- Mid-dose female F19799: 0.658 ng/mL (left eye)
- High-dose male F19778: 32.8 ng/mL (right eye) and 18.0 ng/mL (left eye)
- High-dose female F19805: 1.62 ng/mL (right eye) and 2.45 ng/mL (left eye)

Dosing Solution Analysis

Results from formulations sampled on Week 1, Week 13, Week 26, and Week 39 were 95.2-106% of nominal.

Shorter term ocular toxicity studies were conducted in rabbits and dogs (Tables 16 and 17). The doses used were similar or lower than those used in the 39-week studies. No new findings were identified in these studies. Except for Study # L6332M-SPD606, these studies were previously reviewed by Dr. Zhou Chen under the initial IND.

Table 16: List of Short-term Repeat-Dose Ocular Toxicity Studies in Rabbits

Test System	Duration/ Route	Formulation	Dose ^a (Number/ Group)	Results	GLP Status	Study Report Number
New Zealand White Rabbit	2-week/ topical ocular instillation	1) (b)(4) lifitegrast in vehicle control article 1 ^b 2) (b)(4) lifitegrast in vehicle control article 2 ^c	Vehicle 1 + lifitegrast: 0, <u>1.75</u> mg/eye TID (0%, 5.0%) Vehicle 2 + lifitegrast: 0, <u>1.75</u> mg/eye TID (0%, 5.0%) (4/sex/dose)	No lifitegrast- related effects were observed on any of the parameters measured.	GLP	L6332M- SPD606 (SAR- 1118-TOX- 1101)
New Zealand White Rabbit	13-week/ topical ocular instillation	(b)(4) lifitegrast in vehicle control containing methylparaben, propylparaben, (b)(4) sodium chloride, mono- and di-basic phosphates, and SWFI	0, 0.105, 0.35, <u>1.05</u> mg/eye TID (0%, 0.3%, 1.0%, 3.0%) (4/sex/dose + 2/sex/dose recovery for control and high dose)	Lifitegrast-related squinting observed sporadically in 1.05 mg/eye animals (≤100 seconds).	GLP	L6333M- SPD606 (7898-103)

TID=three times a day

^aUnderlined, bold indicates No Observable Adverse Effect Level (NOAEL)

Table 17: List of Short-term Repeat-Dose Ocular Toxicity Studies in Dogs

Test System	Duration/ Route	Formulation	Dose ^a (Number/ Group)	Results	GLP Status	Study Report Number
Beagle Dog	dose escalation/ topical ocular instillation	(b) (4) lifitegrast in sterile water for injection, USP	0.35, 1.05, <u>3.5</u> mg/eye TID (1.0%, 3.0%, 10.0%) (3 males)	Non-adverse squinting and tearing was observed at 1.05 and 3.5 mg/eye animals (<60 seconds).	Non- GLP	D6330M- SPD606 (7898-100)
Beagle Dog	13-week/ topical ocular instillation	(b) (4) lifitegrast in vehicle control containing methylparaben, propylparaben, (b) (4) sodium chloride, mono- and di-basic phosphates, and SWFI	0, 0.11, 0.35, <u>1.05</u> mg/eye TID (0%, 0.3%, 1.0%, 3.0%) (3/sex/dose + 2/sex/dose recovery for control and high dose)	Lifitegrast-related blinking and squinting in 1.05 mg/eye animals.	GLP	D6335M- SPD606 (7898-104)

TID=three times a day

^aUnderlined, bold indicates No Observable Adverse Effect Level (NOAEL)

Systemic Route Repeat-Dose Toxicology Studies

Table 18 shows the IV repeat-dose toxicity studies conducted in dogs (7 days and 4 weeks) and rats (13 weeks). These studies were previously reviewed by Dr. Zhou Chen under the initial IND.

Table 18: List of Short-term Repeat-Dose Systemic Toxicity Studies in Dogs and Rats

Species	Duration/ Route	Formulation	Dose ^a [N/Group]	Results	GLP Status	Study Report Number
Beagle Dog	dose escalation and 7-day/ IV	(b) (4) lifitegrast in PBS	Dose escalation: 1, 3, 10 mg/kg [1/sex]; 7- day: 0, 3, 10 mg/kg/day [1/sex/dose]	No lifitegrast- related findings were noted	Non- GLP	D6331M- SPD606 (7898-119)
Beagle Dog	4-week/ IV	(b) (4) lifitegrast in PBS	0, 3, 10, 30 mg/kg/day [3/sex/dose + 2/sex/dose recovery for control and high dose]	No lifitegrast- related findings were noted	GLP	D6338M- SPD606 (7898-106)
Sprague- Dawley Rat	13-week/ IV	(b) (4) lifitegrast in phosphate buffered saline (PBS)	0, 3, 10, or 30 mg/kg/day [10/sex/dose + 5/sex/dose recovery for control and high dose]	Non-adverse effects included lifitegrast-related decrease in food consumption in 10 or 30 mg/kg/day females during the dosing phase and lifitegrast- related decrease in aspartate aminotransferase for 30 mg/kg/day males and females	GLP	R6337M- SPD606 (7898-105)

^aUnderlined, bold indicates No Observable Adverse Effect Level (NOAEL)

Regarding the 13-week IV rat study, additional findings of unclear relationship to treatment include the following.

Clinical Signs: One high-dose male (# B51965) was observed with a mass. This finding was noted during the dosing phase (Days 85, 92-93) and recovery phase (Days 7, 14, 21, 28 and 29). The applicant considered this as an incidental and/or spontaneous finding. There were no additional details about location or nature of the mass. This animal did not present any toxicologically relevant microscopic findings.

Body weights: Consistent with the decrease in food consumption, high-dose females showed a trend toward decreased body weight during the dosing phase with a 10% decrease (not statistically significant) in mean body weight gain for the overall Day 1 to Day 92 dosing interval.

Hematology and Coagulation - The applicant indicated there were no test article-related findings. However, there was a slight increase in mean neutrophil (41%) and % neutrophil (17%) compared to control in high-dose males on Day 93 (not statistically significant). The increase was related to 3 high-dose males (# B51952, B51956, and B51963) with elevated neutrophils (3.01-4.47 E3/ μ L vs 0.66-2.80 E3/ μ L in controls) and % neutrophils (25-32% vs 6.4-24% in controls). Male # B51963 was kept for the recovery period; levels were within control range for this animal at recovery.

Clinical Chemistry - There were minimal, but statistically significant, lower (~18%) aspartate aminotransferase values for high-dose males and females. The applicant considered this finding as test article related. However, to this reviewer knowledge, no toxicological relevance is given to decreased AST levels.

Histopathology - No findings were considered test article-related by the applicant. There were some findings observed at Week 13 with a higher incidence and/or severity at the high dose compared to controls. These findings are shown in the table below.

Table 19: Microscopic Findings – 13-Week IV Repeat-Dose Toxicity Study in Rats

Finding	Severity	Males ^a		Females ^a	
		Control	High dose	Control	High dose
Thymus					
Hyperplasia, epithelium	1	2	1	2	6
	2	0	0	1	1
	Total	2	1	3	7
Kidney^b					
Pyelonephritis	3	0	1	0	0
	Total	0	1	0	0
Hyperplasia, epithelium, pelvis	1	0	1	0	0
	Total				
Urinary bladder^b					
Hyperplasia, epithelial with acute inflammation	4	0	1	0	0
	Total	0	1	0	0
Ureter^b					
Hyperplasia, transitional cell	1	0	1	0	0
	Total	0	1	0	0
Testis^c					
Hypoplasia, Inflammation - chronic active/abscesses	3	0	1		
	Total	0	1		
Epididymis^c					
hypospermia, hypoplasia	3	0	1		
	Total	0	1		

^an= 10 animals/sex at each group

^bFindings were present in the same animal.

^cFindings were present in the same animal (all of moderate severity); the testicular inflammation was bilateral; all other findings were unilateral.

The microscopic renal findings (kidney and urinary bladder) occurred in the same male (# B51956) and the microscopic testicular/epididymal findings occurred in a second male (# B51952). These findings were considered by the applicant to be isolated incidental disease processes in these animals and unrelated to the test article. As cell adhesion plays a critical role in immunological function, there is a potential for immunosuppressive effects that may lead to increase susceptibility to infections. However, in this same study, there were no test article related effects in blood immunophenotyping.

Based on the renal and reproductive findings in the 2 high-dose males and the thymic findings in high-dose females, the NOAEL is considered to be the mid-dose, 10 mg/kg/day. The mean plasma C_{max} and AUC at this dose are shown in the table below.

Table 20: Mean Plasma Exposure Parameters – 13-Week IV Repeat-Dose Toxicity Study in Rats

	Dose= 3 mg/kg		Dose= 10 mg/kg		Dose= 30 mg/kg	
	C_{max} , ng/mL ¹	AUC _{0-n} , hr*ng/mL ²	C_{max} , ng/mL ¹	AUC _{0-n} , hr*ng/mL ²	C_{max} , ng/mL ¹	AUC _{0-n} , hr*ng/mL ²
Day 1	305.2	148.3	1045.3	535.6	5117.3	2345.5
Week 13	377.5	241.4	1691.5	907.1	16932.8	7471.5

¹Maximum observed plasma SAR1118 concentration during the dose interval.

²Plasma SAR1118 AUC_{0-n} during the dose interval.

³Estimated from mean plasma SAR1118 concentration versus time profile, n= 6 rats (3 male and 3 female) per timepoint.

7 Genetic Toxicology

These studies (Table 21) were previously reviewed by Dr. Zhou Chen under the initial IND. SAR 1118 was negative for mutagenicity or clastogenicity in the Ames test or in vivo micronuclei assay. However, SAR 1118 induced chromosomal aberrations at a single concentration (3500 µg/mL) in incubations without S9 mix (3-hour treatment). At this concentration, there was a 14% reduction in monolayer confluency and a 51% reduction in mitotic index indicating this was a toxic concentration and the results are not toxicologically relevant. In addition, SAR 1118 induced an increase in polyploidy and endoreduplication in incubations without S9 mix and in endoreduplication in incubations with S9 mix in the initial assay. These results were considered equivocal due to either a lack of a dose response (incubations without S9 mix) or similar results were not observed in the confirmatory assay (incubations with S9 mix).

Table 21: Genetic Toxicology Studies with SAR 1118

Study Type	Test System	Formulation	Dose [Number/ Group]	Results	GLP Status	Study Report Number
<i>Salmonella typhimurium</i> - <i>Escherichia coli</i> /Mammalian Reverse Mutation Assay with a Confirmatory Assay	<i>Salmonella typhimurium</i> / TA98, TA100, TA1535, and TA1537 <i>Escherichia coli</i> / WP2uvrA	(b) (4) lifitegrast in deionized water	(± S9) 33.3, 100, 333, 1000, 3330, and 5000 µg/plate	Lifitegrast was not genotoxic in any bacterial strain tested	GLP	V6322M-SPD606 [7898-109]
Chromosomal Aberrations in Chinese Hamster Ovary (CHO) Cells	Hamster/ Chinese hamster ovary cells	lifitegrast in cell culture grade water	Initial Assay: (-S9) 1200, 1720, 2450, 3500 µg/mL; (+S9) 840, 1200, 2450, 3500 µg/mL Confirmatory Assay: (-S9) 250, 500, 1000, 1200 µg/mL; (+S9) 2750, 3500, 4250, 5000 µg/mL	No lifitegrast-related structural chromosomal aberrations were observed (± S9) except at a single toxic dose (-S9) (3-hour treatment)	GLP	V6323M-SPD606 [7898-110]
In Vivo Mouse Bone Marrow Micronucleus Assay (IV Dosing)	Mouse/ CD-1®(ICR) BR	(b) (4) lifitegrast in PBS	0, 125, 250, 500 mg/kg [4-5 males/ dose]	At 500 mg/kg/day 1 of 5 animals died and signs of clinical toxicity were observed. No lifitegrast-related increases in micronucleated PCEs were observed and lifitegrast was not cytotoxic to the bone marrow	GLP	M6324M-SPD606 [7898-111]

GLP=Good Laboratory Practices; IV=intravenous; PBS=phosphate-buffered saline; PCE= polychromatic erythrocyte; S9=Aroclor 1254 induced rat liver post mitochondrial fraction

7.4 Other Genetic Toxicity Studies

The following bacterial reverse mutation study was conducted to qualify a potential genotoxic impurity, (b) (4) was flagged as a potential genotoxic impurity (b) (4) is present in the starting material (b) (4). The sponsor concluded that based on principles described in ICH M7, the negative results obtained with (b) (4) in this assay also applies to (b) (4) as the same structural alert is present in both compounds. This reviewer agrees that the applicant approach is consistent with recommendations in ICH M7.

Study title: SPD606: Bacterial Reverse Mutation Assay

Study no.: V6745M-SHP606
 Study report location: EDR Module 4.2.3.7.6
 Conducting laboratory and location: (b) (4)
 Date of study initiation: January 13, 2014
 GLP compliance: Yes (OECD and UK)
 QA statement: Yes
 Drug, lot #, and % purity: (b) (4)

(b) (4)

(product name), batch #
AL/C046/PBL05, 98.8% pure

Key Study Findings

(b) (4) was not mutagenic in any bacterial strain tested at concentrations up to 5000 µg/plate, under the conditions of this study.

Methods

Strains: *Salmonella typhimurium* tester strains TA98, TA100, TA102, TA1535, and TA1537

Concentrations in definitive study: 0, 5, 16, 50, 160, 500, 1600 and 5000 µg/plate ± S9 mix

Basis of concentration selection: Regulatory guidance with recommended high dose of 5000 µg/plate

Negative control: Dimethyl sulphoxide (DMSO)

Positive control:

Chemical ^a	Stock ^b Concentration (µg/mL)	Final Concentration (µg/plate)	Strain(s)	S-9
2-nitrofluorene (2NF)	50	5	TA98	-
Sodium azide (NaN ₃)	20	2	TA100, TA1535	-
9-aminoacridine (AAC)	500	50	TA1537	-
Mitomycin C (MMC)	2	0.2	TA102	-
Benzo[a]pyrene (B[a]P)	100	10	TA98	+
2-aminoanthracene (AAN)	50	5	TA100, TA1535, TA1537	+
	200	20	TA102	+

Formulation/Vehicle: DMSO

Incubation & sampling time: Plate incorporation method was used. After the overlay solidified, the plates were inverted and incubated for 3 days.

Study Validity – All formulations were within 91-99% of the nominal concentrations, with the exception of the highest concentration formulated (50 mg/mL) and one intermediate concentration (0.5 mg/mL) with mean concentrations were 86.7% and 88.3% of nominal, respectively. However, as toxicity was observed in all strains tested at 5000 µg/plate, a suitable maximum concentration was therefore achieved in the study and these results are not considered to have an impact in the interpretation of the data.

The values in negative and positive controls were within historical range.

Results – Evidence of toxicity in the form of a slight thinning of the background bacterial lawn, with or without a concurrent reduction in revertant numbers, was observed at 5000 µg/plate in all strains ± S9 mix. No precipitation was observed.

(b) (4) did not increase the number of revertant colonies/plate in any of the tester strains ± S9 mix compared to the negative control.

Genetic Toxicity Studies with Impurities

(b) (4)

(b) (4)

Impurities

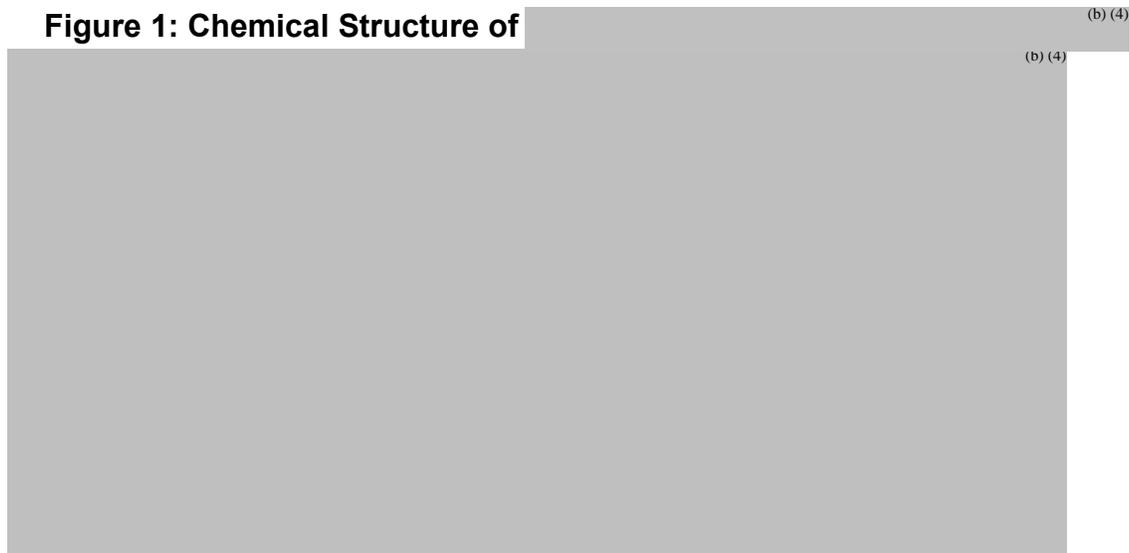
(b) (4)

were evaluated in GLP in vitro mutagenicity assays (Ames) and in GLP in vitro chromosomal aberration assays (Table 22). The 5 impurities contain the same structures of concern as the active pharmaceutical ingredient (b) (4). None of the impurities showed a positive response under the conditions of the assays.

Table 22: List of Genetic Toxicity Studies Conducted with Several Impurities

Test System	Method of Administration	Duration of Dosing	Dose	GLP Status ^a	Testing Facility	Study Report Number
Other Toxicity Studies–Impurities						
<i>Salmonella typhimurium</i> / TA98, TA100, TA1535, TA1537; <i>Escherichia coli</i> / WP2uvrA	In vitro incubation	52 ± 4 hours incubation	(±S9) 1.60, 5.00, 16.0, 50.0, 160, 500, 1600, 5000 µg/plate	GLP	(b) (4)	V6987M-SHP606 (8314535)
<i>Salmonella typhimurium</i> / TA98, TA100, TA1535, TA1537; <i>Escherichia coli</i> / WP2uvrA	In vitro incubation	52 ± 4 hours incubation	(±S9) 1.60, 5.00, 16.0, 50.0, 160, 500, 1600, 5000 µg/plate	GLP	(b) (4)	V6988M-SHP606 (8314536)
<i>Salmonella typhimurium</i> / TA98, TA100, TA1535, TA1537; <i>Escherichia coli</i> / WP2uvrA	In vitro incubation	52 ± 4 hours incubation	(±S9) 1.60, 5.00, 16.0, 50.0, 160, 500, 1600, 5000 µg/plate	GLP	(b) (4)	V6989M-SHP606 (8314537)
<i>Salmonella typhimurium</i> / TA98, TA100, TA1535, TA1537; <i>Escherichia coli</i> / WP2uvrA	In vitro incubation	52 ± 4 hours incubation	(±S9) 1.60, 5.00, 16.0, 50.0, 160, 500, 1600, 5000 µg/plate	GLP	(b) (4)	V6990M-SHP606 (8314538)
<i>Salmonella typhimurium</i> / TA98, TA100, TA1535, TA1537; <i>Escherichia coli</i> / WP2uvrA	In vitro incubation	52 ± 4 hours incubation	(±S9) 1.60, 5.00, 16.0, 50.0, 160, 500, 1600, 5000 µg/plate	GLP	(b) (4)	V6991M-SHP606 (8314539)

Toxicological Analysis of Extractables 1 and 2 using Derek Nexus for Carcinogenicity, Chromosome Damage, Genotoxicity, Mutagenicity and Rapid Prototypes: Chromosome Damage In Vitro (Study # V6321M-SPD606) - Extractables (b) (4) (Figure 1) were analyzed by Derek Nexus for carcinogenicity, chromosome damage, genotoxicity, mutagenicity and rapid prototypes: chromosome damage *in vitro* over a range of endpoints in a number of mammalian and bacterial species.

Figure 1: Chemical Structure of

The results section indicates that no alerts were triggered by either extractable for any of the endpoints evaluated. No raw data was provided. A consultation request was submitted to CDER Computational Toxicology Consulting Service to confirm these results. Four software programs were used: *Derek Nexus* 4.1.0 (DX), *Leadscope Model Applier* 2.0.3-1 (LMA), and *MC4PC* 2.4.1.4 (MC) or *CASE Ultra* 1.5.2.0 (CU).

The results obtained from the consult were consistent with those provided by the sponsor for (b) (4). It was predicted to be negative in the bacterial mutation, mouse lymphoma, *in vitro* chromosomal aberration, and *in vivo* micronucleus assays, as well as for carcinogenicity in male and female rats and in male and female mice.

(b) (4) was predicted to be positive for *in vitro* chromosome aberrations and negative in the bacterial mutation, mouse lymphoma, and *in vivo* micronucleus assays (Table 23).

Table 23: Genetic Toxicity for Predicting the ICH S2 Battery

Software	<i>Salmonella</i> Mutagenicity	<i>E. coli/TA102</i> Mutagenicity	Mouse Lymphoma	<i>In Vitro</i> Chromosome Aberrations	<i>In Vivo</i> Micronucleus
<i>Derek Nexus</i>	-*	-*	NSA	NSA	NSA
<i>Leadscope Model Applier</i>	-	-	-	+	-
<i>CASE Ultra/MC4PC</i>	-	-	-	-	-
Overall Software Prediction	-	-	-	+	-
Overall Expert Prediction	-	-	-	+	-

T
 + = positive; - = negative; -* = negative with unclassified features; Eqv = equivocal; NSA = no structural alerts are identified by DX (Derek Nexus cannot differentiate between a negative call and the inability to make a call because of no coverage); NC = test chemical features are not adequately represented in the model training data set, leading to a no call.

The *LMA* positive prediction by the CHL *in vitro* chromosome aberrations model is based on the presence of an alkylcarboxylate feature along with general structural properties and attributes. (b) (4) was predicted to be negative for carcinogenicity in male and female rats and in male and female mice.

According to ICH Guidance for Industry M7, a computational toxicology assessment should be performed using Quantitative Structure-Activity Relationship ([Q]SAR) methodologies that predict the outcome of a bacterial mutagenicity assay. As (b) (4) was negative for bacterial mutations, *in vivo* micronuclei formation, as well for carcinogenicity in rats and mice, the positive prediction for chromosome aberration is not considered of clinical concern.

8 Carcinogenicity

No studies were conducted.

9 Reproductive and Developmental Toxicology

9.1 Fertility and Early Embryonic Development

Study title: Intravenous Injection Combination Fertility/Embryofetal Development Study with SAR 1118 (b) (4) in Female Rats

Study no.: R6341M-SPD606
Study report location: EDR Module 4.2.3.5.1
Conducting laboratory and location: (b) (4)
Date of study initiation: July 26, 2012
GLP compliance: Yes, except for test article manufacturing, characterization, stability and dosing solution analysis
QA statement: Yes
Drug, lot #, and % purity: SAR 1118 (b) (4) lot # 12AK0083F, 99.5% pure

(b) (4)

Key Study Findings

- In high-dose males, findings included a slight decrease in food consumption, decreased prostate and seminal vesicle weights (trend toward decrease prostate weight in low and mid-dose males), and enlarged renal pelvis (2 males).
- Individual animal listings showed 2 dams in the low-dose, 3 in the mid-dose, and 2 in the high-dose groups had higher preimplantation loss compared to concurrent control range. The mean value at the high dose was above the

historical mean control value of 4.0%, suggesting a test article related effect at this dose.

- There were several minor skeletal variations and malformations limited to 1 – 2 fetuses and litters, particularly at the high dose. Collectively, an effect was apparent at this dose.
- The applicant concluded the NOAEL for fertility and embryofetal development was the high dose of 30 mg/kg. This reviewer agrees with this NOAEL for fertility endpoints. However, based on the increased preimplantation loss and the observation of minor skeletal variations and malformations at the high dose, this reviewer believes the embryofetal development NOAEL was the mid dose of 10 mg/kg.

Methods

Doses: 0, 3, 10, and 30 mg/kg/day
 Frequency of dosing: Once daily
 Dose volume: 1 mL/kg
 Route of administration: IV injection in a tail vein
 Formulation/Vehicle: PBS
 Species/Strain: Crl:CD(SD) rats
 Number/Sex/Group: 22
 Satellite groups: None
 Study design: Males were dosed for at least 28 days prior to mating, throughout the mating period and through the day prior to termination. Males were dosed for at least 10 weeks prior to sacrifice. Females were dosed for at least 14 days prior to mating, throughout the mating period, and through GD 17. Cesarean sections were performed on all surviving females on GD 21.

Deviation from study protocol: None with an impact in the interpretation of the data

Observations and Results

Mortality (2x/day)

None

Clinical Signs (Daily)

No test article-related effects

Body Weight (2x/week for males; 2x/week during pre-mating and mating period and on GD 0, 2, 4, 6, 8, 10, 12, 14, 16, 18, and 21 for females)

No test article-related effects

Feed Consumption (Weekly during the pre-mating and post-mating treatment period for males; weekly during pre-mating period and at gestation body weight intervals)

A slight statistically significant decrease (~ 9%) in food consumption was noted in high-dose males on Premating Day 21 – 28. The feed consumption in high-dose males also showed a trend towards lower values during the post-pairing intervals Days 0-7 (~4.5%) and Days 7-14 (~6%) but it was similar to control values afterwards. Therefore, this decrease was not considered adverse.

Toxicokinetics

Not performed

Dosing Solution Analysis

The concentrations ranged from 87.4 to 90.4% and 91.7 to 92.3% of nominal values on the first day and last day of dosing, respectively.

Necropsy (GD 21)

Large renal pelvis was observed in 2 high-dose males (unilateral in one male; bilateral in the second male). This finding was not considered test article-related by the applicant. However, based on findings from the 4-week (Study # R6706M-SHP606) and 13-week IV toxicity (Study # R6337M-SPD606) studies suggesting the kidney as a target, a contribution by the test article cannot be ruled out.

There was a dose-dependent decrease in absolute and adjusted mean prostate weight at all test-article doses compared to controls with statistical significance at the high dose (absolute values only). Based on absolute values, the decrease was approximately 5, 10, and 16% at the low, mid, and high dose, respectively. Although not acknowledged in the study report, there was a decrease of approximately 10% in mean absolute (~7% relative to body weight) seminal vesicle weight at the high dose (not statistically significant).

Fertility Parameters (Mating/Fertility Index, Corpora Lutea, Preimplantation Loss, etc.)

Males in the 10 mg/kg/day dose group exhibited reduced mean fertility index compared to control males (77% compared to 90% in controls). The reduced fertility index in males at 10 mg/kg/day corresponded with a lower mean fertility index seen in females at the same dose level (86% compared to 91% in controls). The applicant considered these effects were not treatment-related given that no effects on male/female reproductive indices were seen at the 30 mg/kg/day high-dose level with respect to the control groups. This reviewer agrees that based on the lack of a dose response, it is difficult to attribute this finding to the test article.

There was a dose-related trend toward increased number of mean preimplantation loss and mean % preimplantation loss (Table 24). None of the changes were statistically significant. The applicant noted the mean % preimplantation loss was within historical control range of 2.9 to 11.2% and therefore the finding was not considered test article related. However, the mean value at the high dose is above historical mean control value of 4.0% ((b) (4) Historical Database [2011-2013]).

Table 24: Summary of C-Section Data – Rat Fertility/Embryofetal Development Study in Rats

	Group	Control	3 mg/kg	10 mg/kg	30 mg/kg
Summary of Cesarean Section Data					
Number of females pregnant at cesarean section	(n)	20	22	18	20
Corpora Lutea	(n)	20	22	18	20
	Mean	15.0	16.2	16.1	15.2
	SD	3.61	2.47	1.83	2.46
Implantation Sites	(n)	20	22	18	20
	Mean	14.5	15.6	15.3	14.1
	SD	3.50	2.95	2.37	3.33
Preimplantation Loss	(n)	20	22	18	20
	Mean	0.5	0.6	0.8	1.1
	SD	0.83	1.30	1.63	2.31

Table 24 (cont.)

	Group	Control	3 mg/kg	10 mg/kg	30 mg/kg
Summary of Cesarean Section Data					
Preimplantation Loss (%)	(n)	20	22	18	20
	Mean	3.4	4.0	4.8	7.6
	SD	5.04	8.73	10.02	15.75
Early Resorptions	(n)	20	22	18	20
	Mean	0.6	0.8	0.4	0.4
	SD	1.10	1.66	0.62	0.60
Late Resorptions	(n)	20	22	18	20
	Mean	0.1	0.0	0.1	0.0
	SD	0.22	0.21	0.24	0.00
Total Resorptions	(n)	20	22	18	20
	Mean	0.6	0.8	0.5	0.4
	SD	1.23	1.65	0.62	0.60

Table 24 (cont.)

	Group	Control	3 mg/kg	10 mg/kg	30 mg/kg
Summary of Cesarean Section Data					
Dead Fetuses	(n)	20	22	18	20
	Mean	0.0	0.0	0.0	0.0
	SD	0.00	0.00	0.00	0.00
Postimplantation Loss	(n)	20	22	18	20
	Mean	0.6	0.8	0.5	0.4
	SD	1.23	1.65	0.62	0.60
Postimplantation Loss (%)	(n)	20	22	18	20
	Mean	6.3	7.3	3.1	3.4
	SD	14.51	18.87	3.84	5.71
Live Fetuses	(n)	20	22	18	20
	Mean	13.9	14.8	14.8	13.7
	SD	4.30	4.09	2.24	3.44

The study report acknowledged the increase observed in preimplantation loss at the high dose and attributed it mainly to two females in this dose group that exhibited a 54.5% and 50.0% preimplantation loss, respectively. In addition, there were 3 females in the low-dose and 2 in the mid-dose group with higher preimplantation loss compared to the range observed in control group (22.2, 25.0 and 27.3% at the low dose, 23.5 and 37.5% at the mid dose vs. $\leq 14.3\%$ in controls). Except for a litter of 1 in the low-dose female with 27.3% preimplantation loss (also had 87.5% postimplantation loss), the number of live fetuses in these females were within the range observed in controls (4-19 live fetuses in controls, 1, 11, and 13 in the low dose animals, 10 and 13 in the mid dose animals, and 4 and 9 in the high dose animals).

There were several skeletal variations that were limited to 1 or 2 fetuses and litters in the SAR 1118-023-treated groups including mild variations in ossification (incomplete, bipartite, asymmetric, increased or additional ossification sites in the skull bones, vertebrae or sternbrae) and the finding of a pre-sacral vertebra in the same high-dose fetus that exhibited the malformation of a fused thoracic centrum (Dam # B03220).

The sponsor concluded that given the low incidences of these skeletal variations compared to the large number that are typically observed in an embryo-fetal developmental study, these anomalies were considered to be spontaneous events unrelated to the test article. Historical control data to support this claim was not provided. Historical control data from (b) (4) showed these findings (when found in the database) occurred at low incidences (1-6 fetuses in a database of at least 672 litters). Therefore, it is difficult to definitely rule out the potential for a test article related effect, particularly at the high dose since the number of collective incidences is significantly greater than the control.

The litter and fetal incidence of these findings is shown in the table below.

Table 25: Incidence of Skeletal Variations and Malformations – Rat Fertility/ Embryofetal Development Study

Finding	Dose (mg/kg)	0	3	10	30	Historical control (range/study) ^a	Historical control (range/study) ^b
	# litter/fetus examined	19/130	22/164	18/133	20/136		
Skull							
Interparietal-incomplete ossification	Incidence litter/fetus	0/0	0/0	0/0	1/1	---	0-1/0-1
	%litter/%fetus per group	0/0.00	0/0.00	0/0.00	5/0.72	---	0-4.2/0-0.6
	Mean % litter/%fetus	1.7/0.23 ^c				---	0.15/0.02
Nasal/frontal-additional ossification site, between	Incidence litter/fetus	0/0	0/0	0/0	1/1	---	---
	%litter/%fetus per group	0/0.00	0/0.00	0/0.00	5/1.00	---	---
Parietal-incomplete ossification	Incidence litter/fetus	0/0	0/0	0/0	2/2	0-2/0-2	0-1/0-1
	%litter/%fetus per group	0/0.00	0/0.00	0/0.00	10/1.18	0-8.3/0-1.1	0-5.0/0-0.7
	Mean % litter/%fetus	3.33/0.46 ^c				0.66/0.09	0.89/0.12
Squamosal-incomplete ossification	Incidence litter/fetus	0/0	1/1	1/1	1/1	0-1/0-1	0-1/0-1
	%litter/%fetus per group	0/0.00	5/0.65	6/0.79	5/0.63	0-4/0-0.5	0-4.0/0-0.6
	Mean % litter/%fetus	5.3/0.69 ^c				0.13/0.02	0.45/0.06
Zygomatic arch – increased ossification	Incidence litter/fetus	0/0	0/0	0/0	1/1	---	0-1/0-1
	%litter/%fetus per group	0/0.00	0/0.00	0/0.00	5/0.63	---	0-4/0-0.6
	Mean % litter/%fetus	1.7/0.23 ^c				---	0.30/0.04
Vertebral column							
Pre-sacral vertebra	Incidence litter/fetus	0/0	0/0	0/0	1/1	---	---
	%litter/%fetus per group	0/0.00	0/0.00	0/0.00	5/0.72	---	---
Sternebrae							
Sternebra – additional ossification site, between	Incidence litter/fetus	0/0	0/0	0/0	1/1	---	---
	%litter/% fetus per group	0/0.00	0/0.00	0/0.00	5/0.72	---	---
Sternebra – asymmetric ossification	Incidence litter/fetus	0/0	1/1	1/1	1/1	0-1/0-1	0-1/0-1
	%litter/%fetus per group	0/0.00	5/0.57	6/0.93	5/0.50	0-4.8/0-0.6	0-5.0/0-0.7
	Mean %	5/0.69 ^c				0.40/0.06	0.74/0.10

	litter/%fetus						
Sternebra - bipartite ossification	Incidence litter/fetus	0/0	1/1	1/1	2/2	---	0-1/0-1
	%litter/% fetus per group	0/0.00	5/0.65	6/0.62	10/1.50	---	0-4.0/0-0.6
	Mean % litter/%fetus	6.7/0.92 ^c				---	0.30/0.04
Vertebra-thoracic centrum							
Thoracic centrum- fused	Incidence litter/fetus	0/0	0/0	0/0	1/1	0-1/0-1 ^d	0-1/0-1 ^e
	%litter/% fetus per group	0/0.00	0/0.00	0/0.00	5/0.72	0-10/0-1.4 ^d	0-4.2/0-0.6 ^e
	Mean % litter/%fetus	1.7/0.23 ^c				0.13/0.02 ^d	0.30/0.04 ^e
Rib							
Rib interrupted	Incidence litter/fetus	0/0	0/0	0/0	1/1	---	---
	%litter/% fetus per group	0/0.00	0/0.00	0/0.00	5/0.63	---	---
Ribs - fused	Incidence litter/fetus	0/0	0/0	0/0	1/1	0-1/0-1	0-1/0-1
	%litter/% fetus per group	0/0.00	0/0.00	0/0.00	5/0.72	0-5.0/0-0.7	0-4.2/0-0.6
	Mean % litter/%fetus	1.7/0.23 ^c				0.13/0.02	0.3/0.04

^a (b) (4) historical Database [2008-2010]

^b historical Database [2011-2013]

^c Sum of litter or fetal incidence in all 3 test article-treated groups/total number of litters or fetuses in all 3 test article-treated groups) x 100

^d Vertebra-thoracic centrum – Incidence from finding defined in the database as “arch fused to centrum”

^e Vertebra-thoracic centrum – Incidence from finding defined in the database as “arches fused”

Note: Shaded values indicate values above historical control.

9.2 Embryonic Fetal Development

Study title: Intravenous Injection Study for Effects on Embryofetal Development and Toxicokinetic with SAR 1118 (b) (4) in Rabbits

Study no.: L6340M-SPD606

Study report location: EDR Module 4.2.3.5.2

Conducting laboratory and location: (b) (4)

Date of study initiation: October 9, 2012

GLP compliance: Yes, except for test article manufacturing, characterization, stability and dosing solution analysis

QA statement: Yes

Drug, lot #, and % purity: SAR 1118 (b) (4), lot # 12AK0083F, 99.5% pure

Key Study Findings

- The applicant concluded there were no effects in maternal toxicity or embryofetal toxicity endpoints at doses up to 30 mg/kg/day.
- Omphalocele was noted in a single fetus at 3 and 30 mg/kg/day. Given the limited and non-dose dependent occurrence, this external anomaly was considered by the applicant to be unrelated to the test article. However, since the historical database shows that this finding is extremely rare, a test article-related effect in this study cannot be ruled out (overall % litter incidence of 3.33% vs. a mean of 0.09% in the historical database).
- There was an increase incidence in the mean value for supernumerary branches of the subclavian vein at the high dose.
- The incidence of sternebra bipartite ossification at the mid-dose and high-dose was higher than that in the historical control range, supporting a potential test article-related effect. However, this finding would likely not be adverse (expected to ossify as the animal continues growing).
- This reviewer agrees with the sponsor selection of the maternal NOAEL. However, based on the finding of omphalocele at the low dose and high dose, a fetal NOAEL was not identified in this study.

Methods

Doses:	0, 3, 10, and 30 mg/kg/day
Frequency of dosing:	Once daily
Dose volume:	1 mL/kg
Route of administration:	IV injection in an ear vein
Formulation/Vehicle:	PBS
Species/Strain:	Hra:(NZW)SPF rabbits
Number/Sex/Group:	22 females/group
Satellite groups:	None
Study design:	The females were mated at the supplier using males of the same strain. The day of confirmation was designated as GD 0 and the females were received prior to GD 4. Animals were dosed from GD 7 to GD 19 and euthanized on GD 29.
Deviation from study protocol:	None with an impact in the interpretation of the data

Observations and Results

Mortality (2x/day)

There were four early terminations (1 low dose, 1 mid-dose, and 2 high-dose females); none was considered test article-related. The low-dose female had red discharge (blood) and fetal material in the cage pan on GD 20, indicating an abortion, and was

subsequently sacrificed. Given that no abortions or developmental toxicities (i.e. increased resorptions or decreased fetal survival) occurred in the mid- or high-dose groups, this abortion was considered to be spontaneous and not treatment related.

Clinical Signs (Daily)

SAR1118-treated dams showed a higher incidence of few feces excretion throughout the study. However, the lack of a dose response and continued observation after the cessation of dosing (GD 20-29), suggest the finding was not test article related.

Body Weight (GD 0, 4, 7, 9, 11, 13, 15, 18, 21, 24, 27, and 29)

No test article-related effects

Feed Consumption (Daily from GD4 onward)

Mean food consumption showed a decrease in all groups, including the control, between the end of the dosing period (GD 19) and the end of the study (GD 29). The sponsor claims all mean food consumption values were within the normal range for pregnant rabbits.

Toxicokinetics (GD 7 and 19; predose and at ~0.25, 0.5, 1, 2, 4, 6, and 24 hours postdose)

The mean C_{max} and AUC_{0-t} are shown in the table below.

Table 26: Toxicokinetic Parameters (Mean ± SD) for SAR 1118 in the Rabbit Embryofetal Developmental Toxicity Study

Parameter	3 mg/kg	10 mg/kg	30 mg/kg
C_{max} (ng/mL)	449 ± 231	33052 ± 54379	11549 ± 8657
AUC_{0-t} (ng•hr/mL)	562 ± 281	111242 ± 189458	12922 ± 11362
T_{max} (hr)	0.25 ± 0.00	0.5 ± 0.43	0.25 ± 0.00

No dose relationship was observed in mean exposure values. However, one mid-dose and one high-dose female had C_{max} and AUC_{0-t} values much higher than those of the other 2 females in the group. C_{max} values were 1707, 1606, and **95844** at the mid dose and 8998, **21194**, and 4454 at the high dose. AUC_{0-t} values were 1812, 1905, **330009** ng•hr/mL in the mid dose and 8211, **25882**, and 4673 ng•hr/mL at the high dose.

Dosing Solution Analysis

The study report indicates that samples were collected from all dose formulations prepared on the first and last day of the dosing phase. However, the dosing solution analysis report only included the results for samples labeled Oct 19, 2012 (first day of dosing was Oct 15, 2012). The concentrations ranged from 87.2 to 91.0% of nominal values.

Necropsy (GD29)

No test article-related findings

Cesarean Section Data (Implantation Sites, Pre- and Post-Implantation Loss, etc.)

No test article-related effects

Offspring (Malformations, Variations, etc.)

Some findings with higher incidence at the mid and/or high dose are listed below.

Table 27: Incidence of Visceral Malformations/Variations or Skeletal Variations in Embryofetal Development Study in Rabbits

Finding	# litter/fetus examined	0	3	10	30	Historical control (range/study) ^a	Historical control ^b
		20/180	20/180	20/185	20/179		
Omphalocele							
	Incidence litter/fetus	0/0	1/1	0/0	1/1	0-2/0-2 ^c	2/2 ^d
	%litter/%fetus per group	0/0	5/0.56	0/0	5/0.56	0-4.5/0-0.6 ^c	0-5.56/0-0.87
	Mean % litter/%fetus	3.33/0.37 ^e				0.86/0.10 ^c	0.09/0.01
Blood vessel							
Subclavian vein – supernumerary branch	Incidence litter/fetus	2/2	1/1	1/3	4/6	---	---
	%litter/%fetus per group	10/1.04	5/0.56	5/2.14	20/2.78	---	---
Sternebrae							
Sternebra - bipartite ossification	Incidence litter/fetus	0/0	0/0	2/3	2/4	0-1/0-1 ^f	1/1 ^{d, g}
	%litter/%fetus per group	0/0.00	0/0.00	11/1.80	11/2.70	0-5.6/0-0.7 ^f	0-4.35/0-0.51 ^g
	Mean % litter/%fetus ^e	6.67/1.29 ^e				0.14/0.02 ^f	0.04/0.01 ^g

^a (b) (4) historical database [2008-2010]

^b (b) (4) historical database [1983-2013]

^c Incidence from finding reported as "Intestines-Protruded through umbilicus or abdominal wall"

^d Sum of the finding observed in all studies

^e Sum of litter or fetal incidence in all 3 test article-treated groups/total number of litters or fetuses in all 3 test article-treated groups) x 100

^f Sternebrae – Incidence from finding described in the database as 'duplicated'

^g Sternebrae – Incidence from finding described in the database as 'bifurcated'

Note: Shaded values indicate values above historical control.

Omphalocele was noted in a single fetus in the 3 and 30 mg/kg/day dose groups. Given the limited and non-dose dependent occurrence, this external anomaly was considered by the applicant to be unrelated to the test article. However, since the historical database (b) (4) 1983-2013) shows that this finding is extremely rare (i.e., noted in 1 fetus each in 2 litters from a total of 2237 litters), there is no basis to rule out a test article-related effect (overall % litter incidence of 3.33% vs. a mean of 0.09% [2/2237] in the historical database).

The study report indicates the incidence of supernumerary branches of the subclavian vein although slightly higher than control values, it was still within the range of historical control (applicant given values of mean %litter/%fetus: 7.42/1.15 and range: 0-37% and 0-6%, respectively), and were therefore not attributed to the test article. However, when the historical control mean value is considered, there was an increase incidence at the high dose.

The sternebra bipartite ossification appears test article-related, but likely would not be adverse (expected to ossify as the animal continues growing).

10 Special Toxicology Studies

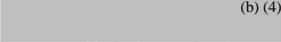
Study title: SHP606: 28 Day Intravenous (Bolus) Administration Toxicity Study in the Rat

Study no.: R6706M-SHP606
 Study report location: EDR Module 4.2.3.7.6
 Conducting laboratory and location:  (b) (4)

Date of study initiation: April 29, 2014
 GLP compliance: Yes (UK and OECD)
 QA statement: Yes
 Drug, lot #, and % purity: SHP606 (SAR 1118), lot # 13AK0148R, 99.8% pure

 (b) (4)
 (Impurity (b) (4)), lot # MDJ-E-11-4,
 (Impurity (b) (4)), lot # MDJ-E-49-6,
 (Impurity (b) (4)), lot # KBM-E-168-7,

Key Study Findings

- SHP606 at 30 mg/kg/day alone of spiked with impurities  (b) (4), was well tolerated.
- The kidney and urinary bladder were identified as potential targets.
- No findings could be attributed to the impurities, as similar targets have been observed in studies with SHP606 (SAR 1118) alone.

Methods

Doses: 0, 30 mg/kg/day SHP606, and 30 mg/kg/day SHP606/Impurities

Each impurity was spiked at a concentration of (b) (4) %.

Frequency of dosing: Once daily for 29 days
Route of administration: IV bolus into lateral caudal vein (tail)
Dose volume: 1.0 mL/kg
Formulation/Vehicle: PBS
Species/Strain: Crl:WI(Han) rats
Number/Sex/Group: 10
Age: ~10 weeks old
Weight: 237.2 to 321.9g for males; 133.8 to 199.8g for females
Satellite groups: 3 rats/sex in control and 6 rats/sex/group in test-articles-treated rats for TK evaluation
Unique study design: None
Deviation from study protocol: None with an impact in the interpretation of the data

Observations and Results

Mortality (2x/day)

None

Clinical Signs (Daily cageside observations; weekly detailed observations)

None test article related

Body Weights (2x/week)

No test article-related effects

Feed Consumption (2x/week)

No test article-related effects

Ophthalmoscopy (Pretreatment and on Week 4; indirect ophthalmoscopy)

No test article-related effects

Hematology and Coagulation (Day 25)

No test article-related changes

Clinical Chemistry (Day 25)

Statistically significant changes were noted in alkaline phosphatase (44% increase), triglycerides (37% decrease) and urea (11% increase) in females administered SHP606 co-spiked with the three impurities, compared to controls. The increase in blood urea is consistent with additional findings observed suggestive of an effect in the kidney.

Urinalysis (Day 28)

Reduced urinary volume (15-34%; not statistically significant) was observed in male and females given SHP606 alone or SHP606 co-spiked with the three impurities, compared to controls.

Gross Pathology (Day 28)

No test article-related findings

Organ Weights (Adrenals, brain, heart, kidney, liver, ovary, pituitary gland, prostate/seminal vesicles, spleen, testis/epididymis, thymus, thyroid/parathyroid, uterus)

No test article related effects

Histopathology

Adequate Battery - Yes

Peer Review - No

Histological Findings - Treatment-related microscopic observations were limited to the tail injection site (lateral caudal vein) in all groups including controls. However, in groups treated with either SHP606 alone co-spiked with the three impurities, there was increased incidence of some of the microscopic changes compared to controls. These included perivascular fibrosis and perivascular/vascular necrosis (minimal to marked), with inflammatory cell infiltration (minimal to moderate) around the vein and/or in the cutaneous/subcutaneous tail tissue.

A kidney cyst (moderate) and transitional cell hyperplasia (moderate) in the urinary bladder were noted in one male and one female given SHP606 co-spiked with impurities, respectively.

Toxicokinetics (Day 1 and 28 at approximately 0.25 and 0.5 hour postdose)

In general, plasma SHP606 concentrations were similar between Days 1 and 28. Plasma SHP606 concentrations were generally similar between the group administered SHP606 alone and the group administered SHP606 co-spiked with the three impurities. C_{max} was observed at 0.25 hour. Mean concentrations of SHP606 ranged between 11444 to 29174 ng/mL on Day 28 at C_{max} .

Dosing Solution Analysis

Results from formulations of SHP606 ± impurities and each individual impurity sampled on Week 1 and Week 4 were (b) (4) % of nominal.

In-Vitro Toxicity Evaluation of SAR1118 on Corneal Epithelial Cells (Study # V6325M-SPD606; GLP) –This study was previously reviewed by Dr. Zhou Chen under the initial IND. SAR1118 cytotoxic potential to human corneal epithelial cells was evaluated at concentrations of 0.001 to 3% at 1 hour, 4 hour and 24 hours incubations. SAR1118 caused cytotoxicity at concentrations $\geq 1.0\%$. The sponsor indicated it would be anticipated that if the test article were able to be maintained on the ocular surface for at least 1 hour, then toxic effects on the ocular surface would be observed. However, corneal toxicity was not observed in rabbits or dogs following topical ocular instillation for up to 39 weeks at concentrations up to 5.0% 3x/day.

Hemolytic Potential and Plasma Compatibility Testing with SAR1118 (b) (4) (Study # V6326M-SPD606; GLP) - This study was previously reviewed by Dr. Zhou Chen under the initial IND. SAR1118 (b) (4) was tested at concentrations of 1, 3, and 10%. Hemolysis was observed only in dog blood at concentrations of 3 and 10%. Plasma compatibility testing showed macroscopic (cloudiness) and microscopic changes (nonrefractive spheres) in the plasma of both dogs and humans at all concentrations. However, no signs of hemolysis or plasma incompatibility were observed in in vivo nonclinical studies, presumably due to the rapid dilution of lifitegrast in the bloodstream.

11 Integrated Summary and Safety Evaluation

Pharmacology studies have demonstrated that lifitegrast is a potent inhibitor of LFA-1/ICAM-1 interactions (EC_{50} of 3.69 nM or 2.27 ng/mL), with no clinically relevant signals for off-target and/or central nervous system, cardiovascular, or pulmonary actions observed under the conditions of the studies.

The PK/ADME studies showed that topical ocular instillation of lifitegrast results in adequate distribution to anterior ocular tissues known to be chronically inflamed in dry eye disease. Lifitegrast is absorbed into the eye with the highest exposure in the anterior ocular tissues (bulbar and palpebral conjunctiva, cornea, and iris/ciliary body), the site of action. Radioactivity in these anterior tissues was maximal at 0.5 hours postdose but substantial levels of radioactivity were still present at 24 hours postdose.

Compared to the levels of lifitegrast measured in the anterior ocular tissues, exposure in the posterior segment, including vitreous, was in general minimal and transient following topical ocular administration.

Systemic exposure to lifitegrast was observed following topical administration although at low levels (e.g., C_{max} of 12.9 ng/mL and 20.2 ng/mL and AUC_{last} of 7.49 ng•hr/mL and 22.4 ng•hr/mL in dogs and rabbits, respectively, after the first daily administration of 5% lifitegrast 3x/day for 39 weeks). Systemic exposure observed in the clinic after twice daily administration of 5% lifitegrast to each eye for 10 days was at least 10-fold lower (based on AUC) than that observed in the nonclinical studies (clinical C_{max} of 1.70 ng/mL and AUC_{0-8} of 0.69 ng•hr/mL after the first daily administration).

The distribution of radioactivity into systemic tissues following an ocular dose of [¹⁴C]-lifitegrast to rats and dogs showed the highest levels of radioactivity were associated with the gastrointestinal tract/contents and the tissues/fluids associated with excretion (liver, kidneys and bile [dog only]). The highest concentrations generally occurred at 0.5 hour postdose. High levels of radioactivity were noted in the nasal turbinates in the rat (no data presented for this tissue in the dog). The data support the view that following topical ocular instillation, lifitegrast passes from the eye, into the nasolacrimal drainage system, through the nasal turbinates, into the esophagus and is ultimately excreted through the gastrointestinal tract. As radioactivity was also noted in the bile (dog only), liver and kidneys, the data suggest that systemic absorption occurred from the gastrointestinal tract. The major route of elimination of lifitegrast by both the ocular and IV routes was determined to be the feces/bile, with minimal excretion via the kidneys.

Tissue distribution of lifitegrast in pigmented and albino rats was comparable and indicated that lifitegrast did not preferentially bind to melanin in vivo. In vitro, melanin binding was moderate, ranging from 35.2% to 60.4%. The extent of lifitegrast binding to plasma proteins in vitro ranged from 96.1% in the dog to 99.5% in rabbits. No preferential uptake of [¹⁴C]-lifitegrast derived radioactivity into red blood cells was seen in dogs and rats.

Four formulations of lifitegrast were used during the clinical development program. The formulations used in nonclinical studies appropriately mirrored those used in concurrent clinical trials, with the 39-week topical ocular instillation toxicity study in dogs using the intended commercial formulation.

Repeat-dose ocular toxicity studies of up to 39 week duration were conducted in dogs and rabbits at concentrations up to 5% administered 3x/day. Ocular findings were limited to transient blinking and squinting, indicating mild ocular irritation. The incidence and duration of this effect was dose related. The squinting and blinking was not associated with other signs of ocular surface irritation such as conjunctival hyperemia, increased ocular discharge, or conjunctival swelling (chemosis) or any adverse ocular finding. Therefore, the ocular NOAEL was the highest dose evaluated, 5% 3x/day (5.25 mg/eye/day).

The exposure margins from the ocular toxicity studies are shown in the following table (as presented by the applicant). A drop volume of 35 µL was used for rabbit and dogs total daily dose/eye calculations, whereas a drop volume of 50 µL was used for humans. Although the exposure margins are low, the mild and transient nature of the irritation observed does not represent a major clinical concern. Eye irritation and eye pain were adverse reactions reported in the clinical trials with an incidence of 16% and 15%, respectively.

Table 28: Exposure Margins from Nonclinical Repeat Dose Ocular Toxicity Studies Based on Total Ocular Daily Dose Administered

Study Type and Duration	Route of Administration	Species	Dose Levels ^a	Fold Compared to Human Dose ^b
Repeat-dose Toxicity				
13-week L6333M-SPD606 (7898-103)	topical ocular instillation	rabbit	0, 0.105, 0.35, <u>1.05</u> mg/eye/dose TID	0.63
39-week L6329M-SPD606 (7898-125)	topical ocular instillation	rabbit	0, 0.105, 0.35, <u>1.75</u> mg/eye/dose TID	1.05
13-week D6335M-SPD606 (7898-104)	topical ocular instillation	dog	0, 0.11, 0.35, <u>1.05</u> mg/eye/dose TID	0.63
39-week D6336M-SPD606 (SAR-1118-TOX- 1201)	topical ocular instillation	dog	0, 0.35, 1.05, <u>1.75</u> mg/eye/dose TID	1.05

TID=three times daily

^a Underlined bold indicates no observed adverse effect level (NOAEL)^b Maximum human clinical dose is 5.0 mg/eye/day (2.5 mg/eye/dose; dose volume approximately 50 µL; up to 2 doses per day). Refer to Module 2.5; Clinical Study Reports 1118-DRY-300 and 1118 DRY 400 (Phase 3 Studies).

The tongue was identified as a potential target in both dogs and rabbits in the 39-week ocular toxicity studies. In dogs, granulomatous inflammation (minimal) of the tongue was noted in one high-dose male and one high-dose female at the end of the dosing phase and one high-dose female at the end of the recovery phase. In rabbits, an increase in the incidence of animals with moderate to severe myofiber regeneration of the tongue was observed at all dose levels compared to controls. The finding was not present in recovery animals. As shown in the table below, the exposure margins for the tongue findings are <7.3-fold (rabbit) and 16-fold (dog). A 15% incidence of dysgeusia was reported in the clinical trials. It is unclear whether the tongue findings in the dogs and rabbits are related to clinically observed dysgeusia.

Table 29: Exposure Margins for the Tongue Findings in Repeat-Dose Ocular Toxicity Studies

Toxicity	Study	Species	NOAEL (mg/eye)	AUC (ng•hr/mL) ^a	Exposure Margin (AUC) ^b
Granulomatous inflammation of the tongue	39-week ocular toxicity	Dog	1.75	7.49	16.3
Myofiber regeneration of the tongue	39-week ocular toxicity	Rabbit	<0.105	<3.36	<7.30

^a Plasma SAR1118 AUC_{0-n} during the first daily dose interval. Tripled for 3x/day daily dosing to estimate exposure margin.^b AUC in human: Highest reported human plasma AUC₀₋₈ was 0.69±0.47 ng•hr/mL (first dosing interval) following administration of 5% lifitegrast to each eye twice daily for 10 days; doubled for twice daily dosing to estimate exposure margin.

No other systemic findings were observed in the repeat-dose ocular toxicity studies.

Intravenous toxicity studies were conducted in dogs (7 and 4 weeks) and rats (13 weeks) at doses up to 30 mg/kg/day. No adverse findings were observed in the dog studies. In the 13-week IV toxicity study in the rat, findings observed at the high dose included the following: a mass in one male (no details were provided about the nature of this mass), a slight decrease in body weight gain/food consumption in females (also mid-dose females), increased levels of blood neutrophils in 3 males, increased incidence of thymus epithelial hyperplasia (minimal to slight) in females, pyelonephritis (moderate), hyperplasia of the transitional epithelium in the urinary bladder (severe), and transitional cell hyperplasia in one male, and hypoplasia, chronic inflammation in the testis and hypospermia/hypoplasia in the epididymis of a second male. As cell adhesion plays a critical role in immunological function, there is a potential for immunosuppressive effects that may lead to increase susceptibility to infections. However, in this same study, there were no test article related effects in peripheral blood immunophenotyping. Based on the urinary and reproductive organs findings in the 2 high-dose males and the thymic findings in high-dose females, the NOAEL is considered to be the mid-dose, 10 mg/kg/day. At this dose, the exposure margin is 657-fold (Table 30); indicating no clinical concern at the intended topical ocular dosing regimen.

No effects on hematology, serum chemistry, peripheral blood immunophenotyping and macroscopic and microscopic evaluation of immune tissues were noted in the 4-week IV dog toxicity study at doses up to 30 mg/kg.

In addition to the renal findings noted above in the rat, there were some findings in other repeat-dose toxicology studies in rats that support the kidney as a target of the test article. In the rat fertility study, two males treated with 30 mg/kg IV males had an enlarged renal pelvis. In a 28-day IV toxicity study in rats where the test article (30 mg/kg) was spiked with 3 impurities (each at a level of (b) (4) %), a slight increase in mean blood urea (11%) was noted in females, reduce urinary volume was noted in males and females, a moderate kidney cyst was noted in one male, and moderate transitional cell hyperplasia was noted in the urinary bladder in one female.

Lifitegrast was negative for mutagenicity in the Ames test or clastogenicity in the in vivo micronuclei assay. However, lifitegrast induced chromosomal aberrations in CHO cells at a single concentration (3500 µg/mL) in incubations without S9 mix (3-hour treatment). This was a toxic concentration reflected by a 14% reduction in monolayer confluency and a 51% reduction in mitotic index. According to recommendations in ICH S2(R1) Guidance for Industry, if a positive response in only seen at a toxic concentration with lack of a positive effect in vivo, the weight of evidence indicates a lack of genotoxic potential. Lifitegrast induced an increase in polyploidy and endoreduplication. These results were considered equivocal due to either a lack of a dose response or similar results were not observed in the confirmatory assay.

The reproductive and developmental toxicity of lifitegrast was investigated in rats and rabbits. In male rats, there was a slight decrease in prostate and seminal vesicle weights at 30 mg/kg/day IV, but no effects were noted in fertility index. A fetal effect emerged at the high dose in rats, as reflected by an increase in mean preimplantation loss and increased incidence of several minor skeletal variations and malformations limited to 1 or 2 fetuses and litters. Based on the increased preimplantation loss and the observation of minor skeletal variations and malformations at the high dose, the embryofetal development NOAEL was the mid dose of 10 mg/kg/day IV. Based on AUC, the exposure margin for the fetal findings is 460-fold (Table 30), indicating minimal clinical concern. The NOAEL for male and female fertility was the high dose of 30 mg/kg/day ($AUC_{0-n} = 7471.5 \text{ ng}\cdot\text{hr/mL}$ [Study # R6337M-SPD606]; 5414-fold the clinical exposure).

In the rabbit, omphalocele was noted in a single fetus at 3 and 30 mg/kg/day IV, in addition to an increase incidence subclavian vein supernumerary branch at the high dose and bipartite ossification of the sternebra at the mid dose and high dose. Regarding the finding of omphalocele, the historical database ((b) (4) 1983-2013) shows that this finding is extremely rare (i.e., noted in 1 fetus each in 2 litters from a total of 2237 litters). As 2 litters had an affected fetus in the current study, a test article related effect cannot be ruled out. The bipartite sternal ossification appears test article-related, but likely would not be adverse (expected to ossify as the animal continues growing). Based on the finding of omphalocele at the low dose and high dose, a fetal NOAEL was not identified in this study. Based on AUC, the exposure margin at the low dose of 3 mg/kg/day IV is 407-fold (Table 30), indicating minimal clinical concern.

The maximum UV absorbance for lifitegrast is at a wavelength of 256 nm. Therefore, lifitegrast is not expected to absorb light within the range of natural sunlight (290 nm to 700 nm). Therefore, phototoxicity studies were not conducted with lifitegrast.

The sponsor has been asked to reduce the specification for (b) (4) a potentially genotoxic impurity, to as low as reasonably possible (see Section 2.5 Comments on Impurities/Degradants of Concern). In addition, 3 leachables were found in developmental stability batch 3P80 and primary stability batches 4F14-2 and 4F90-2 at levels above (b) (4) ppm. The sponsor has been asked to identify these leachables and provide safety/qualification data to support these levels.

A summary of the exposure margins for systemic effects is shown in the following table. These systemic adverse effects occurred at systemic exposures well in excess of the plasma exposure observed in humans. Based on the exposure margins, the nonclinical data presented in this NDA provides adequate safety support for the intended dosing regimen of 5% lifitegrast 2x/day (2.5 mg/eye) in the treatment of the signs and symptoms of dry eye. Approval of the NDA is recommended, pending resolution of impurity issues. A pending request was communicated to the Sponsor stating that specifications for (b) (4) should be reduced to as low as reasonably possible, and that adequate safety data should be provided to support the levels of 3 leachables.

Table 30 Exposure Margins for Systemic Effects Observed in the Repeat –Dose Intravenous Toxicity Study and Reproductive Toxicity Studies

Toxicity	Study	Species	NOAEL (mg/kg) M/F	AUC (ng•hr/mL)	Exposure Margin (AUC) ^a
↑ blood neutrophils, ↑ incidence of thymus epithelial hyperplasia in females, urinary organs findings in males, reproductive organs findings in males	13-Week IV toxicity	Rat	10	907	657
↑ preimplantation loss, ↑ incidence of several minor skeletal variations	Fertility/embryofetal development	Rat	10	632 ^b	460
↑ incidence of omphalocele	Embryofetal development	Rabbit	< 3	562 ^c	<407
↑ incidence subclavian vein supernumerary branch,			10	6570 ^c	4760
↑ incidence of bipartite sternebra ossification			3	562	407

^a AUC in human: Highest reported human plasma AUC₀₋₈ was 0.69±0.47 ng•hr/mL, which was doubled for twice daily dosing to determine exposure margin (Module 2.7.2).

^b Value from non-pregnant rats (same strain) at Week 13 (Study # R6337M-SPD606)

^c Mean excludes one extremely high value.

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/s/

MARIA I RIVERA
07/31/2015

LORI E KOTCH
07/31/2015

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 208073 Applicant: Shire Development LLC Stamp Date: Feb. 25, 2015

Drug Name: Xiidra (lifitegrast ophthalmic solution) 5.0% NDA/BLA Type: Commercial

On **initial** overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	X		
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	X		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	X		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	X		<p>The applicant indicated that carcinogenicity studies were not conducted as there was low systemic exposure of lifitegrast after topical ocular application, lifitegrast was not mutagenic or clastogenic in the battery of genetic toxicity assays (except for positive result at the highest concentration without S9 fraction in the CHO cells chromosomal aberration assay), and there were no preneoplastic findings in any of the in vivo toxicity studies.</p> <p>A carcinogenicity waiver was not submitted to the Division. According to the minutes from the Type B meeting held on Dec. 15, 2010 (filed in DARRTs on Jan 10, 2011), the sponsor asked if the Agency agreed that a carcinogenicity program is not indicated for this product. The Division agreed. Submission of a waiver was not requested.</p>
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).	X		<p>Four formulations of lifitegrast have been used during clinical development. A repeat-dose toxicity study, as well as a PK and ocular distribution study in rabbits, were conducted to determine how changes in formulation might affect the tolerability or the PK parameters.</p> <p>The 39-week topical ocular instillation toxicity study in dogs used the intended commercial formulation.</p>

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement
010908

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	Comment
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant <u>submitted</u> a rationale to justify the alternative route?	X		
7	Has the applicant <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?	X		
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X		
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m ² or comparative serum/plasma levels) and in accordance with 201.57?	X		
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	X		
11	Has the applicant addressed any abuse potential issues in the submission?	X		The applicant indicated that abuse liability studies were not conducted because: <ul style="list-style-type: none"> • No significant interaction was observed in a panel of 139 targets to identify secondary pharmacology activity. • CNS safety pharmacology study and repeat-dose toxicity studies did not indicate CNS activity.
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			N/A

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? Yes

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Please submit a carcinogenicity waiver to the IND.

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement
010908

**PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR
NDA/BLA or Supplement**

Reviewing Pharmacologist

Date

Team Leader/Supervisor

Date

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/s/

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03/13/2015

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03/13/2015