CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206185Orig1s000

CLINICAL REVIEW(S)

Medical Officer's Review of Complete Response
Class 2 Resubmission

NDA 206185		
SDN-029	**Submission Date:**	May 7, 2018
	Receipt Date:	May 7, 2018
SDN-032	**Submission Date:**	June 7, 2018
	Receipt Date:	June 7, 2018
SDN-035	**Submission Date:**	July 31, 2018
	Receipt Date:	July 31, 2018
	Review Date:	August 1, 2018

Applicant: Sun Pharma Global FZE
P.O. Box 122304
Office #43, Block Y, SAIF Zone
Sharjah, UAE

Authorized US Agent Jeffrey Yuan, Associate VP, Global Regulatory Affairs
Sun Pharmaceuticals Industries, Inc.
2 Independence Way
Princeton, NJ 08540

Drug: Xelpros™ (latanoprost ophthalmic emulsion), 0.005%

Pharmacologic Category: prostaglandin analog

Submitted:
Reference is made to the new drug application (NDA) for Xelpros (latanoprost ophthalmic Emulsion), 0.005% for the reduction of elevated intraocular pressure in patients with open- angle glaucoma or ocular hypertension, submitted by Sun Pharma Advanced Research Company, Ltd. (SPARC) on January 31, 2014.

Further reference is made to the Complete Response letter dated July 30, 2015, and the July 28, 2016 resubmission. Reference is also made to the FDA's December 19, 2016, Complete Response letter and to the applicant's November 30, 2017, letter requesting an extension of the time to resubmit the NDA. Finally, on April 12, 2018, a change in NDA sponsorship was made from SPARC to Sun Pharma Global FZE (SUN FZE) by their US agent, Sun Pharmaceutical Industries, Inc. (SUN).

Reference is made to the May 7, 2018, Complete Response submission to the issues identified in the Agency's December 19, 2016 Complete Response letter. Reference is also made to the June 7 and July 31, 2018, submissions amending the Complete Response with the requested clean container mock up and proposed final package insert. The Safety Update Report is reviewed here. Refer to the Team Leader review for the most recent draft labeling.

SAFETY UPDATE REPORT

This safety update for Sun Pharma Global FZE (SUN) Ltd.'s latanoprost ophthalmic emulsion, 0.005% product (tentatively named Xelpros), NDA 206185, is provided in accordance with 21 CFR 314.50(d)(5)(vi)(b), and as requested by FDA in the Agency's "Complete Response" letter dated December 19, 2016.

No clinical studies are ongoing and no new clinical studies have been initiated with latanoprost ophthalmic emulsion, 0.005% (Xelpros) since the submission of NDA 206185 on January 31, 2014.

SUN is not marketing latanoprost ophthalmic emulsion, 0.005% (Xelpros) in any foreign countries.

Patient Discontinuations and Deaths

There have not been any new or ongoing clinical trials with latanoprost ophthalmic emulsion, 0.005% (Xelpros) since submission of NDA 206185. There is no new Xelpros-specific safety information on adverse events (AEs) or deaths to update NDA 206185.

Clinical Literature Search

The applicant performed clinical and nonclinical literature searches described below.

The clinical literature search for this safety update report in support of NDA 206185 latanoprost ophthalmic emulsion, 0.005% (Xelpros) was conducted using the following methodology and databases.

- PUBMED® (1946 to present): Consists of over 27 million references including the 24 million references from the MEDLINE database. MEDLINE includes citations from over 5,600 journals. Additionally, PubMed includes journals deposited into PubMed Central and the National Center for Biotechnology Information (NCBI) Bookshelf.

The specific clinical literature search strategy is detailed below. No restrictions were placed on language. Duplicate citations were removed. The search was conducted on April 23, 2018 and included all manuscripts published on and after July 9, 2016, when the previous literature search was conducted for the July 28, 2016 Complete Response.

Clinical Literature Search Strategy

Connector	Restriction Category	Specific Terms Used	Fields Searched
--	Drug name	latanoprost OR 130209-82-4 OR glaucostat OR klonaprost OR latanoflax OR louten OR ocuprost OR paraiop OR tanamof OR xalatan OR solusin OR unilat OR xaloptic ORgaax OR latof OR gaap ofteno OR latsol OR laprost OR latanopress	All fields
AND	Clinical	clinical OR human OR man OR men OR woman OR woman OR patient OR subject OR volunteer OR participant OR pediatric OR geriatric OR child OR children OR infant OR adolescent OR teen OR teenager OR youth OR baby OR babies OR elderly OR adults	All fields

Using this search criteria, 89 citations were identified, of which 8 were thoroughly analyzed for new clinical safety information on the use of latanoprost. No new safety signals were found.

Reviewer's Comment:
The Safety Update does not raise any new safety signals. No safety-related revisions to the current proposed labeling are recommended.

Labeling Review

Following is the applicant's proposed labeling submitted on July 31, 2018.

Applicant suggested revisions to the Agency's draft are identified by the retained Applicant comments.

Reviewer proposed additions are note by underline and deletions by.

14 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Reviewer's Comments:

Multiple editorial revisions have been made to the package insert. Some of these revisions were made to be consistent with the XALATAN package insert approved on January 24, 2018.

Section 6.2 Postmarketing Experience has been revised to include adverse reactions reported with topical latanoprost products to be consistent with the approved Xalatan prescribing information.

Section 7 DRUG INTERACTIONS has been deleted; information located here is redundant and already adequately expressed in Section 2 DOSAGE AND ADMINISTRATION.

The PLR format for Sections 8.1 Pregnancy and 8.3 Nursing Mothers is being maintained until appropriate PLLR language is agreed upon for the Xalatan labeling supplement currently under review.

For all container labels:

1. *The established name should be revised on the carton labels to a prominence commensurate with the proprietary name, as stated in 21 CFR 201.10(g)(2).*
2. *As space permits, increase the prominence of the statement, "For topical use in the eye."*
3. *We recommend you consider using a different NDC package code for the professional sample and 1-pack trade configurations to help prevent confusion.*

For all cartons:

1. *The established name should be revised on the carton labels to a prominence commensurate with the proprietary name, as stated in 21 CFR 201.10(g)(2).*
2. *Remove the statement, "(b) (4)."*
3. *Remove the statement, "(b) (4)."*
4. *It is recommended that the two sentences in the Storage statement be separated for readability.*
5. *As space permits, increase the prominence of the statement, "For topical use in the eye."*
6. *Regarding the 2.5 mL sample, we recommend you remove the (b) (4).*

Recommendations:

From a clinical perspective, NDA 206185 for Xelpros (latanoprost ophthalmic emulsion) 0.005% is recommended for approval with the labeling revisions contained in this review.

Rhea A. Lloyd, MD
Medical Officer

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

RHEA A LLOYD
08/01/2018

WILLIAM M BOYD
08/01/2018

Summary Review #3 for Regulatory Action

Date	(electronic stamp)
From	Renata Albrecht, MD
Subject	Division Director Summary Review
NDA/BLA # **Supplement #**	NDA 206185 N/A
Related IND	IND 102842
Applicant Name	Sun Pharma Advanced Research Company (SPARC) Limited
Agent for Applicant	Ora, Inc.
Application Type	505(b)(2)
Date of Submission	1/31/2014 (standard review)
PDUFA Goal Date	11/30/2014
Complete Response Letter	11/24/2014
Resubmission, Class 2	4/9/2015
PDUFA Goal Date	10/9/2015
Complete Response Letter #2	7/30/2015
Resubmission, Class 2	7/28/2016
PDUFA Goal Date	1/28/2017
Proprietary Name / **Established (USAN) Name**	XELPROS latanoprost ophthalmic emulsion
Dosage Forms / Strength	emulsion / 0.005%
Preservative	Potassium sorbate 0.47%
Route of Administration	Topical ophthalmic
Therapeutic Class	Prostaglandin
Proposed Indication(s)	Reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension
Dosage Regimen	One drop (1.5 µg latanorprost) in the affected eye(s) once daily in the evening
How Supplied	latanoprost 0.005% emulsion (50 µg/mL) will be supplied as a 2.5 mL emulsion in a 5 mL clear low density polyethylene (LDPE) bottle with a clear LDPE dropper tip and high-density polyethylene (HDPE) (b) (4) screw cap.
Action/Recommended	*Complete Response – Manufacturing facilities*

Review #2 was CDTL countersigned review dated 7/30/3015

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Rhea Lloyd, William Boyd 11/3/2014, 11/18/2014, 7/20/2015, 12/13/2016
CDTL Review	William Boyd, Wiley Chambers 11/20/2014 (2), 7/30/2015, 12/16/2016
Deputy Director Review	Wiley Chambers 11/20/2014
Statistical Review	Solomon Chefo, Yan Wang 10/14/2014
Pharmacology Toxicology Review	Maria Rivera, Lori Kotch 10/17/2014, 10/24/2014
Product Quality Review Drug Substance	#1 Milton Sloane, Mariappan Chelliah, Balajee Shanmugam, Rapti Madurawe 10/24/2014 #2 Chunchun Zhang 7/27/2015 #3 Chunchun Zhang 12/16/2016
Quality Microbiology Review	Robert Mello, Neal Sweeney 9/26/2014
Biopharmaceutics Review	Banu Zolnik, Okponanabofa Eradiri 10/17/2014
Office of Compliance	Withhold 11/19/2014, 7/17/2015, 12/13/2016
Clinical Pharmacology Review	Yongheng Zhang, Philip Colangelo 9/30/2014
OPDP/DPDP	Christine Corser 11/14/2014 Carrie Newcomer 12/13/2016
OSI/DGCPC	Roy Blay, Janice Pohlman, Kassa Ayalew 9/17/2014
OSE/DMEPA Proprietary Name Letter Proprietary Name Letter Proprietary Name Letter	Rachna Kappor, Yelena Maslov 5/14/2014 Kellie Taylor 5/19/2014 Sarah Vee, Yelena Maslov 7/14/2015 Todd Bridges 7/16/2015 Lissa Owens, Mishale Mistry 9/28/2016 Todd Bridges 10/3/2016
OSE/DMEPA	Rachna Kapoor, Yelena Maslov 9/15/2014 Madhuri Patel, Mishale Mistry 12/13/2016
Project Manager	Diana Willard

OND=Office of New Drugs
CDTL=Cross-Discipline Team Leader
OSI/DGCPC=Office of Scientific Investigations/Division of Good Clinical Practice Compliance
OPDP/DPDP=Office of Prescription Drug Promotion/Division of Prescription Drug Promotion
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DDRE= Division of Drug Risk Evaluation
DRISK=Division of Risk Management

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Signatory Authority Review Template

1. Introduction

Sun Pharma Advanced Research Company Limited (Sun Pharma or SPARC) has submitted NDA 206185 for Xelpros (latanoprost ophthalmic emulsion) 0.005%, as a 505(b)(2) application. Xelpros represents a new dosage form of latanoprost, which is currently marketed as Xalatan® (latanoprost ophthalmic solution) 0.005%, NDA 20597, approved June 5, 1996, for the reduction of elevated IOP in patients with open-angle glaucoma or ocular hypertension. Xelpros was studied for the same dosage regimen (1 drop or 1.5 µg latanoprost once daily in the evening) as the approved Xalatan® product. There are currently multiple generic formulations of latanoprost ophthalmic solution marketed.

NDA 206185 for Xelpros was submitted on January 31, 2014, and given a standard review. The applicant proposed their product was a (b) (4); however, it was determined that this represented a new dosage form, an ophthalmic emulsion (microemulsion).

Support for the efficacy and safety of Xelpros was based on four studies:

- Phase 3 efficacy and safety study (Study CLR_09_12) 12 weeks QD, conducted in the US
- Phase 3 safety study (Study CLR_09_13, an extension of CLR_09_12) also conducted in the U.S.
- Phase 3 efficacy and safety study (Study CLR_08_01) 4 weeks QD, conducted in India
- Pilot safety study (Study CLR_10_01) 8 weeks QD, also conducted in India.

Only Phase 3 Study CLR_09_12 is considered an adequate and well-controlled study in support of the application because the design and analysis provides adequate information on the efficacy and safety results of the Xelpros product. The other studies are of shorter duration and small sample size (CLR_08_01) or not controlled and not designed to evaluate efficacy (CLR-09-13, CLR_10_01) and therefore provide only supportive information.

Study CLR_09_12 comparing Xelpros (latanoprost ophthalmic emulsion) 0.005% and Xalatan did not establish equivalence with the preplanned clinical endpoint of change from baseline in intraocular pressure. The decrease in mean intraocular pressure in Xelpros-treated patients was 5 – 6 mmHg approximately 0.5 mmHg less than Xalatan treated patients (See Section 7).

Unlike Xalatan®, Xelpros does not contain the preservative benzalkonium chloride (BAC), but uses potassium sorbate 0.47% as a preservative. The applicant indicated that BAC is a commonly used preservative in eye drops and has been shown to exhibit inflammatory and toxic ocular effects. As a result, the applicant suggests BAC-free Xelpros may provide a safer alternative to existing marketed BAC-containing latanoprost products. However, the results of the safety analysis did not support a benefit in terms of adverse reactions, and the rate of eye pain was higher in the Xelpros (64%) compared to the Xalatan (47%) arm in the Phase 3 Study CLR_09_12.

Xelpros also contains an excipient, (b) (4) that has not been previously approved in an ophthalmic product in the United States, but is qualified (See Section 4).

The review team recommends that adequate information has been submitted to support that the product is effective and safe. Labeling has been submitted in PLR format but needed extensive revisions, mainly intended to align the text with class labeling and the Xalatan package insert, currently undergoing PLR conversion review. The Office of Compliance has issued a recommendation of Withhold regarding approval of the application. The CDTL and Deputy Director Reviews provide an overall summary of the application, and further details are provided in the primary reviews for this NDA.

Reviewer Comment:
Although Xelpros was shown to be effective in terms of reducing the IOP by 5-6 mmHg in the clinical development program, there was a notable difference in the rate of eye pain reported: 64% in Xelpros and 47% in Xalatan treated patients in Phase 3 randomized, controlled, masked CLR_09_12. Based on further consideration of the benefit (clinically significant reduction of IOP by 5-6 mmHg) and the specific nature of the adverse reaction (transient stinging in the eye as recorded in patient diaries), the application can be approved from a clinical perspective and results of the Phase 3 clinical trial reflected in labeling for this 505(b)(2) product.

2. Background

Glaucoma is a life-long progressive disease that is characterized by irreversible damage to the optic nerve and corresponding loss of visual field. One of the primary risk factors is elevated intraocular pressure (IOP). The reduction and control of elevated IOP in open-angle glaucoma and ocular hypertension is usually managed by chronic, long-term topical ocular therapy.

There are currently multiple topical products in several classes available for the reduction of IOP, including beta-adrenergic antagonists (beta-blockers), alpha-adrenergic agonists, parasympathomimetic (miotic) agents, carbonic anhydrase inhibitors, prostaglandin analogs, and some combination products. A complete list is included in the Medical Officer's Review and CDTL Review.

The listed drug, Xalatan® (latanoprost ophthalmic solution) 0.005%, NDA 20597 was approved June 5, 1996 and indicated "for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma and ocular hypertension who are intolerant of other intraocular pressure lowering medications or insufficiently responsive (failed to achieve target IOP determined after multiple measurements over time) to another intraocular pressure lowering medication. The limitation was based on the reported adverse reactions of iris pigmentation changes, given the uncertainly of the long-term consequences of these findings (skin/eyelid pigmentation and eyelash changes were also noted). On December 20, 2002, the indication was revised to remove these limitations based on NDA 20597/S010, which contained follow up data of latanoprost-treated patients for multiple years showing the eyelash changes could be reversible while iris pigmentation was not. The follow-up and post-marketing information did not identify reports of pigmentary glaucoma or melanoma, which had been a potential concern.

Latanoprost is a prostaglandin analog, F2-α receptor agonist. Latanoprost is absorbed through the cornea where the isopropyl ester prodrug is hydrolyzed to latanoprost acid a derivative of prostaglandin F2-α which is biologically active. It is believed that latanoprost reduces intraocular pressure by increasing uveoscleral aqueous outflow from the eye.

Sun Pharma submitted their pre-IND 102842 on June 26, 2008, and a meeting was held on September 16, 2008, to discuss the development plan for their latanoprost product, including discussion of CMC recommendations and guidance documents, discussion of non-clinical studies including the need for 6-month systemic and ocular studies, and discussion of clinical pharmacology and clinical issues.

Sun Pharma submitted IND 102842 on August 19, 2009, and included protocols for Study CLR_09_12, a Phase 3 study designed to demonstrate equivalence[1] between the SPARC product and Xalatan and Study CLR_09_13, an open label extension study of Study CLR-09-12 to collect safety data for 6 months, and measure endothelial cell counts.

Sun Pharma met with the Division on February 20, 2013 for a pre-NDA meeting. The results of Study CLR_09_12 showed that while all IOP measurements were within the <1.5 mmHg margin, the majority were outside the <1 mm Hg margin; the applicant was told this was problematic and would be review issue. The recommendation that safety data be available for at least 100 patients treated for at least 6 months was not met; only 73 patients had adequate follow up. The applicant was advised this could become a potential filing issue. There was discussion that SPARC's proposed claim that their product is a safer alternative to Xalatan would need to be supported by data from adequate and well controlled studies. The Division provided advice on submitting the proprietary name and on the importance of clearly labeling the proposed different storage conditions for their product.

3. CMC

For details, see the CMC, Quality Microbiology and Biopharmaceutic reviews. The following summaries are excerpted from the CMC reviews.

3.1 CMC review dated October 24, 2014:

This application is not recommended for approval from Chemistry, Manufacturing, and Controls (CMC). The Office of Compliance has issued a recommendation of Withhold for this NDA. The applicant has been requested to update NDA with the correct dosage form of emulsion and the revised acceptance criteria. The final Biopharmaceutics review dated October 17, 2014 and Quality Microbiology review dated September 26, 2014 recommend approval.

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[1]From the January 26, 2009 meeting minutes:
Latanoprost ophthalmic (b) (4) *administered once a day in the evening is an acceptable positive control agent for IOP lowering studies. To establish equivalence, the two sided, 95% confidence interval should be within 1.5 mmHg for all IOP measurement time points and within 1.0 mmHg for the majority of IOP measurement time points. IOP measurements should be evaluated at 8am, 10am and 4pm at baseline, Week 1, Week 6 and Week 12. Each time point should be evaluated separately. It is expected that a comparison of the mean IOP at each time point will be evaluated.*

Xelpros® is an emulsion composed of [redacted] ([redacted] Water for Injection (WFI), boric acid, sodium borate, edentate disodium, and potassium sorbate) and [redacted] ([redacted] castor oil, latanoprost, and [redacted]). The formulation has a different composition than the reference drug Xalatan®. Xelpros® is described as an off-white, translucent, isotonic, sterile emulsion. It is buffered to [redacted] and is preserved using potassium sorbate, NF. As such, SPARC's formulation of latanoprost ophthalmic emulsion is not preserved with benzalkonium chloride, in contrast to the RLD. The applicant has described the proposed drug product as a "microemulsion." "Microemulsion" is not a recognized dosage form. The ONDQA CMC review has determined that the proposed drug product is an emulsion.

Latanoprost ophthalmic emulsion, 0.005% w/v, 2.5 ml will be manufactured, processed, packaged, labeled and held by Sun Pharmaceutical Industries Ltd.–Halol. Testing to assure the identity, quality, purity and stability of the finish dosage form will be performed by Sun Pharmaceutical Industries Ltd.–Halol.

The drug product is sterilized by [redacted] manufacturing aspects were found adequate. SPARC has also conducted a microbial challenge test to evaluate the integrity of the selected container closure system components. Samples of sterile media (soybean casein digest medium) were packaged in the proposed container closure system, and incubated for 14 days. At the end of the study, no growth was observed in the test container compared to the positive control.

The container closure was qualified and evaluated on results of the extractable study, drop count study, weight loss study, and photostability study. The container closure system was found suitable per USP <87>. The drop size and drug content of each drop of latanoprost ophthalmic emulsion drug product is approximately [redacted] µg and 1.51µg respectively.

The proposed 24-month tentative expiration-dating period to be assigned to latanoprost ophthalmic emulsion 0.005% w/v when stored [redacted] is acceptable based on the stability data provided. The stability results show that the opening of the proposed container and use of the dropper does not affect the quality of the proposed drug product up to 45 days.

[redacted] polyoxyl 15 hydroxystearate, and [redacted] is supplied by [redacted] and used in the proposed formulation as [redacted]. [redacted] is not listed by FDA as an inactive ingredient in approved drugs; as such, it is considered a "novel" excipient. However, this excipient is contained in approved drug products in Canada [redacted] and Argentina [redacted], a diclofenac sodium product). Data exist regarding its safety in animals including repeated dose intravenous toxicity studies in rats and dogs of 3-month and 1-month duration, respectively. The animal safety data generated with the proposed ophthalmic emulsion are presented and discussed in the NDA and IND 102842 Pharmacology/Toxicology Reviews. [redacted] does not cause direct ocular toxicity but does have the potential to cause sensitization reactions.

The sponsor submitted a request for BA/BE waiver and was found acceptable based on the Biopharmaceutics Review.

The Office of Compliance has issued a recommendation of Withhold for this NDA. The following CMC comments will be included in the Complete Response Letter:

1. Please update the NDA submission in all appropriate sections to indicate the correct dosage form of ophthalmic emulsion. This can be accomplished by submission of an "Erratum" page with a statement that throughout the NDA the product name was corrected from "latanoprost ophthalmic (b) (4)" to "latanoprost ophthalmic emulsion."

2. The release and stability data indicate that the proposed acceptance limits for (b) (4) (specified identified impurity) and highest unspecified impurity can be tightened. Please revise the limits to the above referenced impurities to NMT (b) (4)% for release and stability.

3.2 CMC Review dated July 27, 2015:

3.2.1 FDA requested that release and stability data indicate that the proposed acceptance limits for (b) (4) (specified identified impurity) and highest unspecified impurity can be tightened to NMT (b) (4)% for release and stability. SPARC replied that the highest unspecified impurity was below quantification limit (BQL) at all the stability conditions for related substances method I and method II. Release and stability specification for highest unspecified impurity (method I and II) has been tightened to not more than (b) (4)%. FDA agreed the applicant's revised acceptance limits are justified and are acceptable.

3.2.2. FDA requested that the NDA submission indicate the correct dosage form (emulsion) in all appropriate sections and include the revised acceptance criteria; FDA agreed the applicant's response in the resubmission was acceptable.

3.2.3. On July 17, 2015, the Office of Process and Facilities issued an overall recommendation of Withhold for facilities.

The following text was included in the second Complete Response letter dated 7/30/2015:

> During a recent inspection of the Sun Pharmaceutical Industries, Ltd, Halol, India manufacturing facility for this application, our field investigators conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

3.3 CMC Review dated December 16, 2016:

The Office of Process and Facilities issued an overall "Withhold" recommendation for facilities on this NDA during the current review cycle. Therefore, the NDA is not recommended for approval from Product Quality perspective. Complete Response Letters dated November 24, 2014, and July 30, 2015, were previously issued to SPARC.

In response to the July 30, 2015 CR, SPARC provided a resubmission on July 28, 2016. However, the outcome of the most recent inspection of drug product manufacturing facility Sun Pharmaceutical Industries Ltd., FEI# 3002809586 (Halol site) has resulted in the Office of Process and Facilities recommending "Withhold" as documented in the NDA-206185-ORIG-1-RESUB-22 project.

The following text will be included in the third Complete Response letter:

> During a recent inspection of the Sun Pharmaceutical Industries Ltd., FEI# 3002809586, manufacturing facility for this application, our field investigators conveyed deficiencies to the representatives of this facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

Comment:
This application is not recommended for approval from Chemistry, Manufacturing, and Controls (CMC) for the third time. The final inspection recommendation is OAI and the Office of Compliance has issued a Withhold recommendation for this NDA. Comments requesting the NDA be updated with the correct name of the product (latanoprost ophthalmic emulsion) and revised acceptance criteria were sent to the applicant in the second Complete Response letter and the applicant's responses were acceptable. No new CMC information was included in the current submission, therefore only a brief Product Quality Assessment review was drafted by the Assessment Team Lead.

4. Nonclinical Pharmacology/Toxicology

For details, see the Pharmacology/Toxicology Review. A brief summary it provided below.

SPARC is relying on FDA's prior findings of efficacy and safety of latanoprost, as summarized in the most current labeling (revised August 2012) for the active pharmaceutical product. In addition, SPARC performed repeated-dose ocular toxicity studies of up to 180-day duration in dogs and rabbits to evaluate the systemic and local ocular toxicities of the new formulation. To provide information on the safety of (b) (4), SPARC provided full study reports of (b) (4)-conducted studies.

In dogs, findings included an increased incidence of mild to moderate scleral congestion compared to controls (saline, placebo, and (b) (4)) and miosis at all latanoprost doses (QD, BID, and QID). The miosis was an expected pharmacological effect. These findings reversed during the recovery period. There was no ocular NOAEL. No adverse systemic findings were observed in any of the latanoprost dose groups or (b) (4) alone arm (0.25% QID).

In rabbits, mild lacrimation and redness in the conjunctiva were observed at the latanoprost high dose (QID). These findings reversed during the recovery period. There were no adverse systemic findings. The NOAEL was the mid dose (BID). No ocular or adverse systemic findings were observed in the (b) (4) alone arm (0.25% QID). The ocular findings observed in the nonclinical studies are consistent with those observed in the clinical trials. Ocular findings in the clinic included ocular hyperemia, conjunctival hyperemia, and eye

discharge. The sensitivity for the occurrence of miosis appears to be species dependent. Its occurrence in human following treatment with latanoprost is not common.

To evaluate the ocular safety of (b) (4), the above studies included an additional arm using this excipient. Systemic safety of (b) (4) was evaluated in repeated-dose oral toxicity studies in rats of up to 180- day duration. Intravenous administration of (b) (4) 0.25% to rats resulted in lipid accumulation in the sinus endothelial cells in the liver and spleen and an increase in the number and size of small granulomas (containing lipid droplets with brown pigment granules) in the liver. The lipid deposits were presumed to represent denaturation products of stearic acid.

Intravenous administration of (b) (4) to beagle dogs resulted in signs of an allergic reaction (pruritus, erythema, wheals) at doses ≥50 mg/kg which resolved within 15-60 min postdose.

In an embryofetal development toxicity study in rabbits, there was a significant increase (2.4-fold) in the number of resorptions and post-implantation loss and a decrease in live fetuses at the high (b) (4) dose of 464 mg/kg/day IV administered during organogenesis. In addition, fetal incidences of misaligned sternebrae and total skeletal variations were increased at this dose.

The exposure margins (based on mg/m^2) for systemic toxicities observed after IV dosing with (b) (4) are over 1,600X; those for the observed embryotoxicity are over 27,000X. The magnitude of the exposure margins indicate that similar findings are unlikely to be observed in the clinic at the intended clinical dosing regimen.

SPARC conducted a comparative plasma and ocular tissue distribution study of Xelpros and Xalatan®. The main differences in ocular tissue distribution include higher levels of latanoprost in the vitreous, optic nerve, and retina and lower levels in the conjunctiva, iris/ciliary body, and lens observed in Xelpros 0.005% compared to Xalatan®. Latanoprost free acid plasma levels were low for both formulations. The observed differences did not translate into differences observed in the general toxicity studies.

The nonclinical studies presented provide adequate safety information to support the intended dosing regimen of Latanoprost Ophthalmic (b) (4) 0.005% in humans. Approval is recommended.

Comment:
I concur with the conclusions reached by the pharmacology/toxicology reviewers to recommend approval. Labeling revisions have been incorporated in labeling.

5. Clinical Pharmacology/Biopharmaceutics

The following excerpts are from the Clinical Pharmacology Review:

Latanoprost is a prodrug analog of prostaglandin F2α; upon absorption into the cornea, it is

converted to the active moiety, latanoprost acid, which has high affinity and selectivity for the FP subtype of prostanoid receptors. Latanoprost is believed to reduce intraocular pressure (IOP) by increasing uveoscleral aqueous humor outflow, thereby reducing the pressure within the eye and reducing the risk of nerve damage and blindness.

The sponsor submitted a request for BA/BE waiver, which is acceptable based on the consideration that the differences in formulation between Xalatan and the proposed SPARC latanoprost ophthalmic (b) (4) 0.005% are not expected to influence the limited systemic exposure to latanoprost/latanoprost acid following topical ocular administration.

In conclusion, no labeling revisions (with respect to Section 12.3 Pharmacokinetics) are needed for this NDA from a clinical pharmacology perspective. NDA 206185 for latanoprost ophthalmic (b) (4) 0.005% is recommended for approval from a clinical pharmacology perspective.

Comment:
I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewers to recommend approval. There are no outstanding clinical pharmacology issues.

6. Clinical Microbiology

Not applicable

7. Clinical/Statistical-Efficacy

For details, see the Clinical and Statistical reviews. A brief summary is provided below. Four clinical studies were submitted, two controlled Phase 3 studies were reviewed for efficacy while an extension study CLR_09 _13 and pilot study CLR_10_01 were only evaluated for safety.

Table 1: Summary of Studies Reviewed

Study Number / Study Phase	**Study Objective**	**Study Design**	**Treatment groups (Number of Subjects)**	**Duration of Treatment/ Primary Efficacy endpoint**	**Study Population**
CLR_09_12 (U.S.) / Phase 3	Test the non-inferiority of Xelpros relative to Xalatan® for the reduction of IOP	Multicenter, assessor-masked, randomized, active-controlled, parallel group, non-inferiority study. Visits on Days -35, -7, 0, 7, 28, 56, and 84.	Xelpros (N = 289) Xalatan® (N = 289)	Once daily for 12 weeks / Change from baseline in intraocular pressure (IOP)	Patients diagnosed with open angle glaucoma or ocular hypertension and had un-medicated IOP ≥ 22 mmHg at the eligibility visit

CLR_08_01 (India)/ Phase 3	Compare the efficacy and safety of Xelpros with Xalatan® in subjects with OAG or OH	Multicenter, open label, randomized, active-controlled, parallel group. Visits on Days -7, 0, 8, 15, and 29.	Xelpros (N = 53) Xalatan® (N = 51)	Once daily for 4 Weeks / Reduction of IOP compared to baseline	Patients diagnosed with open angle glaucoma or ocular hypertension and screening IOP≥22.

Source: Table 2.7.3-1 of Applicant's Summary of Clinical Efficacy
Note: Study CLR_09_13 was an extension of Study CLR_09_12 designed for safety follow-up and Study CLR_10_01 was a Pilot study.

Source Statistical review, page 7

Study CLR_09_12 was a multicenter, assessor-masked, Phase 3, active-controlled, parallel group, randomized study of 12 week duration designed to evaluate the safety and IOP lowering efficacy of Xelpros relative to Xalatan® in adult patients with open angle glaucoma and ocular hypertension. In the study, a total of 578 subjects were randomized in a 1:1 ratio to receive either Xelpros (n=289) or Xalatan® (n=289) once daily at 8 PM.

At each investigational center, subjects were stratified by the eligibility visit IOP group (Low: 22-28 mmHg versus High: 29-35 mmHg group) in the study eye. According to the study protocol, the study eye was defined as the eye with higher IOP at the eligibility visit or if equal, subjects with an even randomization number were assigned the left eye and with an odd number the right eye.

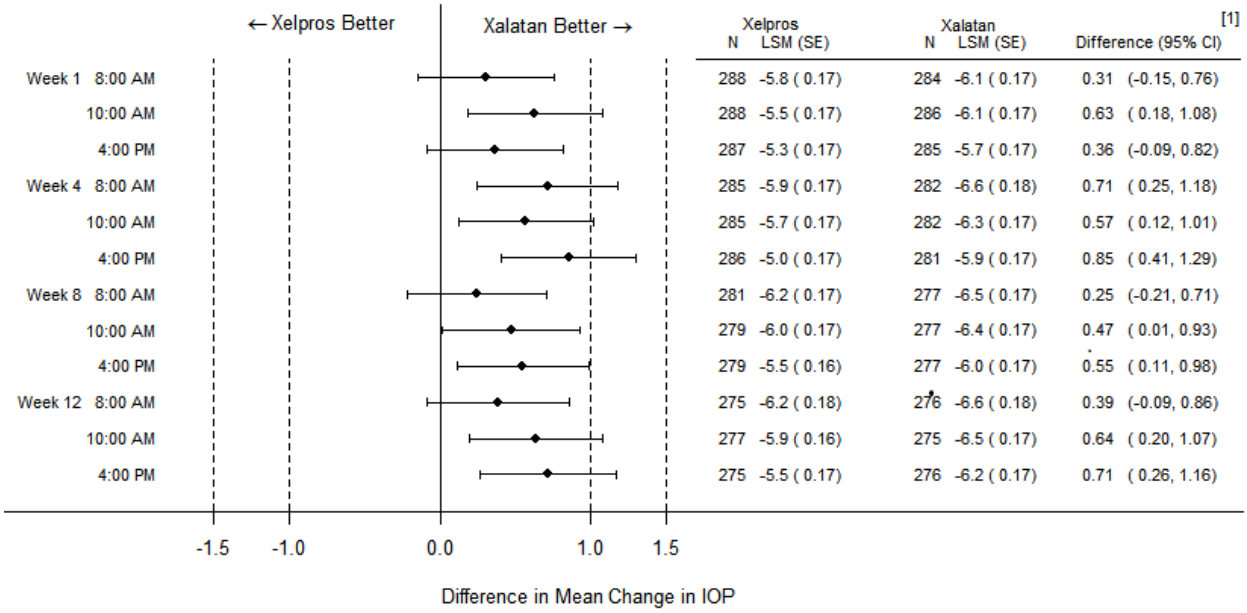
The primary efficacy endpoint of the study was the change in IOP from baseline evaluated at 8 AM, 10 AM, and 4 PM at the following visits: week 1, week 4, week 8, and week 12. The primary efficacy analysis of the study was based on the intent-to-treat (ITT) analysis population, and used the change from baseline in IOP as the primary efficacy variable. Analysis of covariance (ANCOVA) methodology with the change from baseline in IOP as the response variable and treatment, site, and baseline IOP as covariates was used in the statistical reviewer's primary efficacy analysis. The difference in the mean change in IOP between the treatment groups (Xelpros minus Xalatan®) was determined based the least square means using the ANCOVA model. Based on the model, non-inferiority of Xelpros to Xalatan® was established if the upper limit of the 95% CI for the difference in the mean change in IOP was <1.5 mmHg throughout the study (Statistical Criterion) and was < 1 mmHg at the majority of time points (Clinical Criterion).

Within the ITT analysis population, the majority of subjects in the study were white (68%) and female (63%). The average age of patients in the study was 65 years (range 27 to 88 years), about 53% of patients in the Xelpros group and 44% of patients in the Xalatan® group were ≥ 65 years of age. No marked difference between the treatment groups was observed in terms of the demographic characteristics.

The Medical Officer reports that for the Difference in Mean Change in IOP from Baseline for the ITT population without LOCF, the 95% confidence interval is within 1.5 mmHg for all time points, and the within 1.0 mmHg for 4 of 12 time points. Thus, SPARC latanoprost 0.005% has not demonstrated equivalence with Xalatan (latanoprost ophthalmic solution) 0.005%. For the Difference in Mean Change in IOP from Baseline – ANCOVA, for the ITT

population Observed Cases, the 95% confidence interval is within 1.5 mmHg for all time points and the within 1.0 mmHg for 6 of 12 time points. Thus, SPARC latanoprost 0.005% has demonstrated equivalence with Xalatan (latanoprost ophthalmic solution) 0.005% using the division's definition for this population.

Figure 1: Difference in Mean Change in IOP (mmHg) – ANCOVA Using Baseline IOP (CLR_09_12) (ITT Analysis Population, Observed Cases)



Source: Statistical review page 5.

Sensitivity Analyses were performed to assess the effect of missing data on the primary efficacy endpoint. Non-inferiority was not established for the ITT population analyzed with last observation carried forward, the ITT population with baseline observation carried forward or the ITT population with multiple imputations. The conclusions for these analyses were consistent with the primary analysis without imputations. (Source: MOR page 37)

The treatment and covariate adjusted mean IOP reductions from baseline throughout the study ranged from 5.0 to 6.2 mmHg in the Xelpros group and from 5.7 to 6.6 mmHg in the Xalatan® group. The test drug, Xelpros, demonstrated significant IOP reductions from baseline throughout the study; however, it was less effective compared to the active-control, Xalatan®, by about 0.3 to 0.9 mmHg units. (Source: Statistical Review, page 15)

The adjusted mean IOP ranged from 17.7 to 18.4 mmHg in the Xelpros group and from 17.0 to 18.1 mmHg in the Xalatan group. The mean IOP at each time point of each visit was lower in the Xalatan group. Xelpros was less effective in lowering IOP compared to Xalatan by about 0.5 mmHg. (Source: MO Review page 38)

The percentage of subjects who achieved IOP level of < 18 mmHg and the percent reduction in IOP of ≥ 30%, respectively, ranged from 47% to 56% and 26% to 38% in the Xelpros group and from 48% to 61% and 30% to 44% in the Xalatan® group. In both efficacy measures,

subjects in the Xalatan® group performed slightly better at all visits and time points compared to subjects in the Xelpros group. (Source: Statistical Review, page 18)

Miscoding of Data

Regarding the miscoding of patients and study visits, please see the MO Review page 9-10 and Statistical Review, page 8. This issue was identified and communicated to the applicant on June 5, 2014; the Statistical Reviewer was not able to reproduce the applicant's primary efficacy results as presented in the study report. The applicant responded that the ADaM dataset was correct but the study report was generated using an intermediate dataset. A second issue communicated on July 15, 2014, was that the link between visits 1, 2, 3 and 4 and week 1, 4, 8, and 12, respectively, resulted in the end-of-study visit linked to the week 12 visit even for early terminated subject. However, the amended Clinical Study Report and updated dateset submitted on September 3, 3014, still did not resolve the discrepancies. The Statistical Reviewer was initially unable to reproduce the primary efficacy results due to the difference in ADaM dataset which rounded the IOP data up (0.5 or greater) or down (0.49 or lower) to the nearest integers versus the updated dataset which used the actual IOP value used. The results were finally reproduced when the unrounded IOP data were used. Although there was no issue with the applicant using either the rounded or unrounded IOP data to produce the primary efficacy results, the applicant should have clearly communicated all the changes made when the updated dataset was submitted to the Agency.

Study CLR_08_01 was a multicenter, open label, Phase 3, active-controlled, parallel group, randomized study designed to evaluate the safety and IOP lowering efficacy of Xelpros relative to Xalatan® in adult patients with open angle glaucoma or ocular hypertension, conducted at eleven centers in India.

A total of 104 subjects 18 years or older with IOP ≥ 22 mmHg in one or both eyes, with no more than 5 mmHg inter-eye difference at the screen visit were enrolled in the study and randomized to Xelpros n=53 or Xalatan n=51. The study duration was four weeks and included five visits: screen (day -7 to -1), randomization (Day 0), and three follow-up visits: Days 8 to 10 (Visit 3), Days 15 to 17 (Visit 4), and Days 29 to 31 (Visit 5). Eye drops were given once daily in the evening for four weeks in one or both eyes as affected. The study eye was the eye with higher IOP at enrollment or if equal, subjects with an even randomization number were assigned the left eye and an odd number the right eye. IOP was measured twice at each study visit, − before administration of drug in the evening (trough effect) and 12-18 hours after administration of drug product in the following morning (peak effect).

The primary objective of study CL_08_01 was to demonstrate equivalence in IOP lowering efficacy of Xelpros to Xalatan® at the through and peak effect of the treatment. The primary endpoint of the study was the change in IOP from baseline during the morning and evening time points of each study visits at Day 8, Day 15, and Day 29. The applicant used the two samples independent T-test for the primary efficacy analysis, and the difference in the mean change in IOP between the treatment groups was determined based on the t-test. In the applicant's primary analysis, missing observations were imputed by LOCF method.

This study demonstrated a statistically significant change in mean IOP from baseline to both

time points at each study visit for both the Xelpros and Xalatan ($p<0.0001$) treatment groups. Although Xelpros demonstrated significant IOP reductions throughout the study, it was less effective compared to Xalatan® at the majority of time points during the study. However, the study did not meet both the statistical and clinical criteria for equivalence since at the majority of time points the two-sided 95% CIs were not within ± 1.5 mmHg. The reason for this may be due to the small sample size.

Comment:
In summary, study 12 met the pre-defined criteria for efficacy based on one analysis, but efficacy for Xelpros was less than for Xalatan; the latter lowered IOP by approximately 0.3 to 0.9 mmHg more compared to Xelpros. The results of study 08 support the finding of efficacy but did not meet the statistical and clinical criteria for equivalence, possibly due to the small sample size.

8. Safety

For further details, the Clinical and Statistical Reviews should be consulted. A brief summary is provided below. Four studies were reviewed for safety information, and are tabulated below:

Study Number / Study Phase	Study Design	Treatment Groups (Numbers of Subjects Treated)	Duration of Treatment / Age
Study CLR_08_01 (India) Phase 3	Multicenter, open-label, randomized, active-controlled, parallel group. Visits on Days -7, 0, 8, 15, and 29.	SPARC latanoprost (N=53) Xalatan (N=51)	Once daily for 4 weeks Age ≥ 18 years
Study CLR_10_01 (India) Pilot	Multicenter, open-label, Single arm, pilot Visits on Days 0, 28, and 56.	Subjects previously treated with Xalatan® were switched over to BAK-free SPARC latanoprost (N=25 subjects, 46 eyes)	Once daily for 8 weeks Age ≥ 18 years
Study CLR_09_12 (US, IND 102,842) Phase 3	Multicenter, assessor-masked, randomized, active-controlled, parallel group, non-inferiority study. Visits on Days -35, -7, 0, 7, 28, 56, and 84	SPARC latanoprost (N=289) Xalatan® (N=289)	Once daily for 12 weeks Age ≥ 18 years
Study CLR_09_13 (US, IND 102,842) Phase 3	Multicenter, open-label, non-randomized, uncontrolled, single group assignment. Visits at Weeks 1, 4, 8, 12, 16, 20, 24, 28, 32, and 36.	Single group, all subjects received SPARC latanoprost (open label extension of prior Study CLR_09_12) (N=161)	Once daily for 36 weeks Age ≥ 18 years

Note: SPARC latanoprost 0.005% is the name used by the applicant during product development. SPARC latanoprost 0.005%
and Xelpros (latanoprost ophthalmic emulsion) are interchangeable terms.
Adapted from applicant Table 2.5.1-1 and MO Review, page 44.

Based on the pooled analysis of the four studies, there were 448 patients treated with Xelpros and 340 treated with Xalatan/reference drug. The vast majority of patients received at least 12 weeks of treatment. There were no deaths reported in these studies. Serious adverse events were reported in 2% Xelpros and 1% Xalatan patients. Discontinuation from the study was reported in 25% of Zelpros and 5% Xalatan patients.

Subject Disposition	**Treatment Group [1]**		
	Xelpros 0.005%	**Xalatan 0.005%**	**Total**
Subjects screened	---	---	867
Screening failures	---	---	160
Subjects randomized	---	---	707
Subjects not treated	---	---	0
Subjects Included in ISS Analysis Set	448	340	707
Subjects with ≥ 1 dose study drug [2]	448	340	707
Subjects completed study	334 (74.6%)	324 (95.3%)	577 (81.6%)
Subjects discontinued from the study	114 (25.4%)	16 (4.7%)	130 (18.4%)
Reasons for Discontinuation			
Withdrawal of Consent	76 (17.0%)	7 (2.1%)	83 (11.7%)
Protocol Violation	7 (1.6%)	1 (0.3%)	8 (1.1%)
Adverse Event	5 (1.1%)	2 (0.6%)	7 (1.0%)
Withdrawal of Subject by Investigator	10 (2.2%)	1 (0.3%)	11 (1.6%)
Lost to follow up	6 (1.3%)	2 (0.6%)	8 (1.1%)
Study Terminated by Sponsor	7 (1.6%)	2 (0.6%)	9 (1.3%)
Study Medication Failure	3 (0.7%)	1 (0.3%)	4 (0.6%)

1 81 subjects switched therapy from the Reference drug in Study CLR_09_12 to the Test drug in Study CLR_09_13. They both contributed data to both treatment groups. All subjects were counted once in the Total column.
2 Percentage was calculated based on the number of subjects treated with ≥ 1 dose of study drug in each group.
Source: ISS Table 14.1.1.1

Source: MO Review, page 50

Eye pain was reported in 55% or Xelpros subjects and 40% of Xalatan patients in the pooled analysis of the four studies. Other ocular adverse reactions appeared to be reported at fairly comparable rates. (Source: Application Module 5.3.5.3.2-Integrated Summary of Safety, Table 3 Summary of disposition-all screened subjects; and Table 10, TEAE's by preferred term occurring in >1% of subjects).

Because of the imbalances in discontinuation in the pooled analysis of the efficacy and safety studies, controlled and uncontrolled studies, the results of Study CLR_09_12 were examined separately since this represents an adequate and well controlled study of design and duration recommended by the Division.

In Study CLR_09_12, 95% of patients received greater than 70 days of treatment. The safety profiles between Xelpros and Xalatan® in Study CLR_09_12 showed that approximately 80% of subjects experienced at least one AE, and at least 1.4% of subjects in the study experienced

at least one serious AE. The most frequently reported AEs in each treatment group was eye pain, it was reported by 64% of Xelpros patients and 47% Xalatan patients. Other adverse events were reported in fairly comparable rates.

Table 10: Treatment-Emergent AEs occurring in ≥1% of subjects in any treatment group (CLR_09_12) (Safety Analysis Population)

System Organ Class/ Preferred Term	Xelpros (N = 289)	Xalatan (N = 289)
Eye disorders	**238 (82.4%)**	**231 (79.9%)**
Eye pain	185 (64.0%)	136 (47.1%)
Ocular hyperaemia	135 (46.7%)	143 (49.5%)
Conjunctival hyperaemia	58 (20.1%)	55 (19.0%)
Eye discharge	39 (13.5%)	41 (14.2%)
Growth of eyelashes	27 (9.3%)	36 (12.5%)
Eyelash thickening	15 (5.2%)	17 (5.9%)
Eye pruritus	16 (5.5%)	14 (4.8%)
Visual acuity reduced	11 (3.8%)	12 (4.2%)
Erythema of eyelid	9 (3.1%)	13 (4.5%)
Dry eye	12 (4.2%)	5 (1.7%)
Foreign body sensation in eyes	6 (2.1%)	5 (1.7%)
Punctate keratitis	1 (0.3%)	9 (3.1%)
Vision blurred	3 (1.0%)	7 (2.4%)
Chalazion	2 (0.7%)	7 (2.4%)
Blepharitis	3 (1.0%)	4 (1.4%)
Eyelash discolouration	5 (1.7%)	2 (0.7%)
Lacrimation increased	2 (0.7%)	4 (1.4%)
Meibomianitis	3 (1.0%)	3 (1.0%)
Eyelid margin crusting	4 (1.4%)	1 (0.3%)
Eyelid oedema	5 (1.7%)	0 (0.0%)
Conjunctival oedema	3 (1.0%)	1 (0.3%)
Conjunctival haemorrhage	0 (0.0%)	3 (1.0%)
Infections and infestations	**20 (6.9%)**	**12 (4.2%)**
Upper respiratory tract infection	8 (2.8%)	0 (0.0%)
Sinusitis	4 (1.4%)	0 (0.0%)
Nasopharyngitis	0 (0.0%)	3 (1.0%)
Investigations	**4 (1.4%)**	**5 (1.7%)**
Corneal staining	1 (0.3%)	3 (1.0%)
Musculoskeletal and connective tissue	**7 (2.4%)**	**2 (0.7%)**
Rotator cuff syndrome	3 (1.0%)	0 (0.0%)
Nervous system disorders	**4 (1.4%)**	**7 (2.4%)**
Headache	3 (1.0%)	5 (1.7%)
Psychiatric disorders	**2 (0.7%)**	**4 (1.4%)**
Anxiety	2 (0.7%)	3 (1.0%)
Skin and subcutaneous tissue disorders	**10 (3.5%)**	**5 (1.7%)**
Rash	3 (1.0%)	0 (0.0%)
Vascular disorders	**1 (0.3%)**	**6 (2.1%)**
Hypertension	1 (0.3%)	6 (2.1%)

Source: Adapted from Section 2.7.4, Table 2.7.4-10 of submission and statistical Review, page 25

Reviewer Comment:
Based on further review of the application, the Medical Officer located information on the mapping of preferred terms and literal terms used in the diary reported by patients (Source: NDA 206185, Table 14.3.1.2.1.2, pages 309 of 510, CLR_09_12) The literal terms that were mapped to "Eye Pain" included transient stinging, stinging, ocular stinging, transient ocular

stinging and mild ocular stinging. The information on stinging associated with the instillation of the medication will be included in labeling.

In CLR_08_01, there was an imbalance in the subjects who discontinued (page 40/72 MOR): Xelpros 8/53 (15%) vs. Xalatan 3/51 (6%). Adverse reactions reporting was overall much lower than in the US study, with approximately 14% of subjects reporting ocular adverse reactions. Eye pain was reported by one Xalatan patient, eye irritation was reported by four Xelpros patients. (Source: Module 5.3.5.1, CLR_08_01 study report)

Study Disposition of Randomized Subjects

	Total N (%)	Number (%) of Subjects	
		Test	Reference
Randomized	104	53	51
Received study medication	104(100)	53(100)	51(100)
Completed study	93(89.42)	45(84.91)	48(94.12)
Discontinued	11(10.58)	8(15.09)	3(5.88)
Major Protocol Violation	2(1.92)	1(1.89)	1(1.96)
Consent Withdrawn	2(1.92)	2(3.77)	0(0)
Subject Lost to Follow-up	6(5.77)	4(7.55)	2(3.92)
Failure of study medication	1(0.96)	1(1.89)	0(0)
Analyzed for efficacy	104(100)	53(100)	51(100)
Analyzed for safety	104(100)	53(100)	51(100)

Source: Table D1, D4

MedDRA System Organ Class / Preferred Term	Test n=53 n (%)	Reference n=51 n (%)
OCULAR		
Eye Disorders	8(15.09)	6(11.76)
Conjunctivitis	2(3.77)	0(0)
Dry eye	0(0)	1(1.96)
Eye discharge	0(0)	1(1.96)
Eye irritation	4(7.55)	0(0)
Eye pain	0(0)	1(1.96)
Eye pruritus	1(1.89)	3(5.88)
Eyelid disorder	1(1.89)	0(0)
Eyelid oedema	0(0)	1(1.96)
Foreign body sensation in eyes	0(0)	1(1.96)
Keratitis	0(0)	1(1.96)
Lacrimation increased	0(0)	2(3.92)
Meibomianitis	1(1.89)	0(0)
Ocular hyperaemia	1(1.89)	2(3.92)
Retinal vein occlusion	1(1.89)	0(0)
Vision blurred	0(0)	1(1.96)
Vitreous floaters	1(1.89)	0(0)
NON OCULAR		
Body as a Whole	4(7.55)	2(3.92)
Ear and labyrinth disorders	1(1.89)	0(0)
Vertigo	1(1.89)	0(0)
Gastrointestinal disorders	0(0)	1(1.96)
Epigastric discomfort	0(0)	1(1.96)
Infections and infestations	1(1.89)	0(0)
Urinary tract infection	1(1.89)	0(0)
Musculoskeletal and connective tissue disorders	1(1.89)	0(0)
Pain in extremity	1(1.89)	0(0)
Nervous system disorders	2(3.77)	1(1.96)
Headache	2(3.77)	0(0)
Migraine	0(0)	1(1.96)

Source: Table S2.3.1

In Study CLR_09_13, the extension study, 153 subjects were followed for 36 weeks.

In their 2015 and 2016 resubmissions, SPARC included safety updates and stated there have been no ongoing or new clinical studies with Xelpros, and the product is not marketed in any foreign countries. Therefore, there is no new safety information submitted to the NDA. The applicant conducted a literature search for the previous year, from March 2014 to March 2015, and again in July 2016, respectively. The Medical Officer concluded that no new safety issues were identified and the proposed labeling did not need to be revised.

In addition, there was discussion with the applicant regarding the cap-closure system specifically that the breakaway plastic ring attached to the cap can fall off when the bottle is inverted over the eye. The applicant made revisions to the closure which were judged acceptable.

Comment:
SPARC stated their development of this new emulsion formulation containing a new stabilizer and using potassium sorbate instead of benzalkonium chloride as preservative was intended to create a formulation that had less toxicity. However, while the adverse reaction profile of Xelpros is fairly comparable to Xalatan for most ocular adverse reactions, there is a notably higher percentage of patients reporting eye pain with Xelprox than Xalatan. Overall, in this Phase 3 trial this adverse reaction was not associated with more discontinuation on the Xelpros arm than Xalatan arm.

9. Advisory Committee Meeting

This is a new dosage form (emulsion) of a marketed product. The application did not identify scientific issues for presentation and discussion at the Advisory Committee meeting.

10. Pediatrics

The Pediatric Review Committee agreed on August 13, 2014, with the applicant's proposal that pediatric studies be waived because the necessary studies would be impossible or highly impracticable because there are too few children with glaucoma to study.

11. Other Relevant Regulatory Issues

Office of Compliance Facility Inspections
Manufacturing facilities are not acceptable, the recommendation from compliance is Withhold approval for the third time.

Office of Scientific Investigation (OSI) Audits
Inspections of three investigators were completed; two were not issued Form FDA 483s, and the final classification of these inspections was No Action Indicated (NAI). One clinical site was issued a Form FDA 483, and the final classification of this inspection was Voluntary Action Indicated (VAI). OSI recommended that the data generated by these clinical sites appear adequate.

Financial Disclosure

(b) (4) has adequately disclosed financial arrangements with the clinical investigators who participated in the clinical development program for latanoprost 0.005%. None of the investigators had financial arrangements or interests to disclose.

Other Regulatory Issues

This is a 505(b)(2) application relying on the non-clinical information from Xalatan. The application was evaluated in this cycle, and the regulatory action cleared by the 505(b)(2) committee on 12/19/2016.

12. Labeling

- Labeling was not reviewed during the current review cycle given the ongoing manufacturing deficiencies.
- The proprietary name Xelpros for latanoprost ophthalmic emulsion 0.005% was found acceptable and the applicant notified via letter on 5/19/2014, 7/16/2015, and 10/3/2016. It will need to be reviewed again before an approval action.
- Physician labeling (PLR) has been submitted and input from the reviewers and consultants was discussed and incorporated as applicable. The labeling has been updated to make it consistent with Xalatan.
- Carton and immediate container labels have been reviewed during the previous cycle; input from reviewers and consultants was discussed and changes incorporated as applicable. The most recent labeling consult was sent 12/13/2016 and not considered in this review cycle because of the manufacturing deficiencies (given that in the next resubmission the applicant may again change their labeling.
- Patient labeling/Medication guide – these are not proposed for the current product

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action

NDA 206185 will receive a *Complete Response* letter for this third review cycle due to manufacturing facility deficiencies. Labeling was not finalized with the applicant during this cycle, given the facility inspection deficiencies. The labeling submitted is in PLR. The Division will not include revised labeling (package insert, carton and container labels) with the CR letter.

- Risk Benefit Assessment

Glaucoma is a life-long progressive disease that is characterized by irreversible damage to the optic nerve and corresponding loss of visual field. One of the primary risk factors is elevated intraocular pressure (IOP). The reduction and control of elevated IOP in open angle glaucoma and ocular hypertension is usually managed by chronic, long-term topical ocular therapy.

There are currently multiple topical products in several classes available for the reduction of IOP, including beta-adrenergic antagonists (beta-blockers), alpha-adrenergic agonists,

parasympathomimetic (miotic) agents, carbonic anhydrase inhibitors, prostaglandin analogs, and some combination products. A complete list is included in the Medical Officer's Review and CDTL Review.

One controlled, randomized, single-masked clinical trial of 12 week duration was submitted that compared Xelpros to Xalatan (latanoprost ophthalmic solution) 0.005% . The results showed that Xelpros was within a 1.5 mmHg margin, but was not clinically equivalent at the 1 mmHg level. Xelpros reduced IOP about 0.5 mmHg less than Xalatan and was not as effective as Xalatan. Study CR_01_08 providing supportive evidence of efficacy, but failed to meet either the 1.5 mmHg or 1 mmHg margin, possibly due to sample size. Xelpros reduced IOP by 5-6 mmHg, about 0.5 mmHg less effective than Xalatan.

In study CLR_09_12, the rates of discontinuation and adverse events for most ocular adverse reactions were comparable; with the exception of eye pain. The rate of eye pain was 64% on Xelpros and 47% on Xalatan.

Although Xelpros is approximately 10% less effective than Xalatan the reduction of IOP by 5-6 mmHg is clinically significant and clearly effective in lowering intraocular pressure. The incidence of eye pain was reported in 64% on Xelpros and 47% on Xalatan treated patients. The literal terms were mapped to the preferred term "Eye Pain" included transient stinging, stinging, ocular stinging, transient ocular stinging and mild ocular stinging. The stinging associated with the instillation of the medication will be included in labeling. Of note, there was no difference to the rate of discontinuation due to stinging on installation.

There are differences in the two formulations; Xelpros is an emulsion that contains potassium sorbate while Xalatan has benzalkonium chloride as the preservative. The formulation differences may in part account for the difference in irritation. Xelpros can provide another option in the treatment of patients with open angle glaucoma and ocular hypertension; patient and physician decisions to use this product may be based on various factors, including the anticipated benefit and risk of adverse reactions.

Manufacturing facility deficiencies need to be resolved. Two pending chemistry information requests regarding correction of the name (ophthalmic emulsion, not (b) (4)) and revision of acceptance criteria need to be submitted.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

None at this time

- Recommendation for other Postmarketing Requirements and Commitments

None at this time

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/s/

RENATA ALBRECHT
12/19/2016

Cross-Discipline Team Leader Review

Date	December 16, 2016
From	William M. Boyd, M.D.
Subject	Cross-Discipline Team Leader Review
NDA #	206185
Applicant	Sun Pharm Advanced Research Company Ltd. U.S Representative: Ora., Inc.
Date of Submission	7/28/16
PDUFA Goal Date	1/28/17
Type of Application	505(b)(2)
Name	Xelpros (latanoprost ophthalmic emulsion) 0.005%
Dosage forms / Strength	Topical ophthalmic emulsion
Proposed Indication(s)	Reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension
Recommended:	Not Recommended for Approval

1. Introduction

This application received a Complete Response letter dated November 24, 2014. The letter requested that the applicant:

1. Update the NDA submission in all appropriate sections to indicate the correct dosage form of ophthalmic emulsion.
2. Tighten the proposed acceptance limits for (b) (4) and the highest unspecified impurity to no more than (b) (4)%.
3. Revise the draft prescribing information.
4. Revise the carton and container labeling.
5. Resolve the deficiencies noted during the inspection of the manufacturing facility located in Halol, India.

An April 9, 2015, submission to the new drug application served as a complete, class 2 response to the November 24, 2014, action letter. This application received a second Complete Response letter dated July 30, 2015. The letter requested that the applicant:

1. Resolve the deficiencies noted during the inspection of the manufacturing facility located in Halol, India.
2. Revise the draft prescribing information and the carton and container labeling.

A July 28, 2016, submission to the new drug application served as a complete, class 2 response to the July 30, 2015, action letter.

2. Background

There are many ophthalmic drug products approved for lowering intraocular pressure in patients with open-angle glaucoma and ocular hypertension. These treatments include beta-adrenergic antagonists (beta-blockers), alpha-adrenergic agonists, parasympathomimetic (miotic) agents, carbonic anhydrase inhibitors, and prostaglandin analogs.

Drug Products with Approved NDAs

Pharmacologic Class/ Applicant	**Trade Name**	**Established Name**
Alpha-2 agonists		
Allergan, Inc.	Alphagan/ Alphagan P	brimonidine tartrate
Beta-adrenergic antagonists		
Alcon	Betoptic/ Betoptic S	betaxolol hydrochloride
Novartis	Ocupress	carteolol hydrochloride
Allergan	Betagan	levobutanol hydrochloride
Bausch & Lomb	Optipranolol	Metipranolol
Vistakon	Betimol	timolol hemihydrate
Aton Pharma	Timoptic	timolol maleate
Ista	Istalol	timolol maleate
Aton Pharma	Timoptic XE	timolol maleate gel forming solution
Carbonic Anhydrase Inhibitors		
Duramed Pharamaceuticals	Diamox	Acetazolamide
Sandoz, Inc.	N/A	Methazolamide
Topical Carbonic Anhydrase Inhibitors		
Alcon	Azopt	Brinzolamide
Merck	Trusopt	dorzolamide hydrochloride
Cholinergic agonist		
Alcon	Pilopine HS	pilocarpine hydrochloride gel
Alcon	Isopto Carpine	pilocarpine hydrochloride
Prostaglandin Analogues		
Allergan	Lumigan	Bimatoprost
Pharmacia	Xalatan	Latanoprost
Alcon	Travatan	Travoprost
Alcon	Travatan Z	Travoprost
Merck	Zioptan	Tafluprost
Alcon	Izba	Travoprost

Pharmacologic Class/ Applicant	Trade Name	Established Name
Sympathomimetics		
Allergan	Propine	dipivefrin hydrochloride
Combination Products		
Merck	Cosopt	dorzolamide hydrochloride/timolol maleate
Merck	Cosopt PF	dorzolamide hydrochloride/timolol maleate
Allergan	Combigan	brimonidine tartrate/timolol maleate
Alcon	BetopticPilo	betaxolol hydrochloride/pilocarpine hydrochloride
Alcon	Simbrinza	Carbonic anhydrase inhibitor/alpha-agonist
Other		
Sucampo Pharma Americas, Inc.	Rescula	unoprostone isopropyl

3. CMC

From the Product Quality Review finalized 12/16/16:

NDA 206-185, Xelpros (latanoprost ophthalmic emulsion) 0.005% was submitted by Sun Pharma Advanced Research Company, Ltd. (SPARC) on January 31, 2014, and a resubmission on April 09, 2015, following the first cycle CR action. The Office of Process and Facilities issued an overall "Withhold" recommendation for facilities on this NDA. Therefore, this application was not recommended for approval from Product Quality perspective. A Complete Response Letter dated November 24, 2014, and subsequently on July 30, 2015 was issued to SPARC.

In response to the July 30, 2015, CR, SPARC submitted a resubmission on July 28, 2016. However, the outcome of the most recent inspection of drug product manufacturing facility Sun Pharmaceutical Industries Ltd., FEI# 3002809586 (Halol site) has resulted in Office of Process and Facilities recommending "Withhold" as documented in the NDA-206185-ORIG-1-RESUB-22 project (see screenshots attached). Therefore, NDA 206185 is recommended for a Complete Response from the Product Quality perspective.

Labeling recommendations from the Product Quality perspective will be provided to the OND PM for consideration during final labeling. No new or updated Product Quality information was submitted in the resubmission and therefore a separate Product Quality review will not be written. This Addendum covers the Product Quality aspect of the resubmission.

Manufacturing Facility Status

Project Overall Manufacturing Facility Statuses

Overall Status	Completion Date	Submission Status	Project Name
Withhold	12/16/2016	Pending	NDA-206185-ORIG-1-RESUB-22
Withhold	6/17/2015	Complete Response	NDA-206185-ORIG-1-RESUB-18
Withhold	11/13/2014	Complete Response	NDA-206185-ORIG-1

Current pOAI alert for Sun Pharmaceutical Industries Ltd. (FEI 3002809586)

Program Manufacturing Facilities

Facility Status	Completion Date	Project Name	FEI	DUNS	Facility ID	Facility Name	Profile Code	Association (per 356h)	Alert
Withhold Approval	11/14/2014	NDA-206185-ORIG-1	3002809586	719638124	110002606	SUN PHARMACEUTICAL INDUSTRIES LIMITED	SLQ STERILE LIQUID (EXCLUDE S...		Potential Official Action Indicated as of
Approve Facility	10/7/2014	NDA-206185-ORIG-1	(b) (4)				CSN NON-STERILE API BY CHEMIC...		None
Approve Facility	5/12/2015	NDA-206185-ORIG-1-RESUB-18					CSN NON-STERILE API BY CHEMIC...		None
No Further Evaluation	4/28/2015	NDA-206185-ORIG-1-RESUB-18					CTL CONTROL TESTING LABORATOR...	PENDING	None
Approve Facility	4/28/2015	NDA-206185-ORIG-1-RESUB-18	3007512695	676162401	110003680	SUN PHARMA ADVANCED RESEARCH COMPANY LIM...	CTL CONTROL TESTING LABORATOR...	ACTIVE	None
No Further Evaluation	4/28/2015	NDA-206185-ORIG-1-RESUB-18	(b) (4)				CTL CONTROL TESTING LABORATOR...	PENDING	None
Withhold Approval	6/17/2015	NDA-206185-ORIG-1-RESUB-18	3002809586	725959238	110002606	SUN PHARMACEUTICAL INDUSTRIES LTD.	SLQ STERILE LIQUID (EXCLUDE S...	ACTIVE	Potential Official Action Indicated as of
No Further Evaluation	4/28/2015	NDA-206185-ORIG-1-RESUB-18	3002809586	719638124	110002606	SUN PHARMACEUTICAL INDUSTRIES LIMITED	SLQ STERILE LIQUID (EXCLUDE S...		Potential Official Action Indicated as of
No Further Evaluation	5/12/2015	NDA-206185-ORIG-1-RESUB-18	(b) (4)				CTL CONTROL TESTING LABORATOR...	ACTIVE	None
Withhold Approval	12/16/2016	NDA-206185-ORIG-1-RESUB-22	3002809586	725959238	110002606	SUN PHARMACEUTICAL INDUSTRIES LTD	SLQ STERILE LIQUID (EXCLUDE S...		Potential Official Action Indicated as of

4. Nonclinical Pharmacology/Toxicology

From the original Pharmacology/Toxicology Review finalized 10/17/14:

SPARC seeks approval of Latanoprost Ophthalmic Emulsion, 0.005%, which is intended for the same dosage (1 drop QD or 1.5 µg/day) and administration (once daily in the evening) as that of the approved Listed Drug (LD) Xalatan (NDA 20-597), for the reduction of elevated IOP in patients with open-angle glaucoma or ocular hypertension. The new formulation contains an excipient, (b) (4) which has not been previously approved in an ophthalmic product in the United States. SPARC is relying on FDA's prior findings of the efficacy and safety of latanoprost, as summarized in the most current Xalatan labeling (revised August 2012). In addition, SPARC performed repeated-dose ocular

toxicity studies of up to 180-day duration in dogs and rabbits to evaluate the systemic and local ocular toxicities of the new formulation. To evaluate the ocular safety of (b) (4) these studies included an additional arm(s) using this excipient. Systemic safety of (b) (4) was evaluated in repeated-dose oral toxicity studies of (b) (4) in rats of up to 180-day duration. In addition, SPARC used the extensive battery of systemic toxicity studies conducted by (b) (4)

5. Clinical Pharmacology/Biopharmaceutics

From the original Clinical Pharmacology Review finalized 9/30/14:

The applicant (Sun Pharmaceutical Industries, Ltd; SPARC) has submitted this current NDA for a different formulation of latanoprost ophthalmic emulsion 0.005%. The proposed SPARC latanoprost formulation differs from Xalatan in several ways: SPARC latanoprost includes (b) (4) as a (b) (4), and potassium sorbate as a preservative. Xalatan contains 0.02% w/v benzalkonium chloride (BKC) as a preservative. The submitted latanoprost product is an emulsion, (b) (4) (b) (4). The applicant submitted a request for an *in vivo* bioavailability (BA) or bioequivalence (BE) waiver, which is acceptable based on the consideration that the differences in formulation between Xalatan and the proposed SPARC latanoprost ophthalmic emulsion 0.005% are not expected to influence the limited systemic exposure to latanoprost/latanoprost acid following topical ocular administration.

From the Biopharmaceutics Review dated 10/17/14:

Based on 21 CFR § 320.22 (e), Biopharmaceutics is of the opinion that for good cause, the requirement for the submission of evidence of in vivo bioavailability or bioequivalence can be waived, because the proposed drug product is an ophthalmic product intended only for local therapeutic effect. Therefore, the biowaiver request is granted.

The ONDQA-Biopharmaceutics team has reviewed NDA 206185 and its amendments (Seq. 0008 and Seq.0014) submitted on May 23, and July 19, 2014. From the Biopharmaceutics perspective, NDA 206185 Xelpros (latanoprost) ophthalmic emulsion, 0.005% w/v is recommended for **APPROVAL.**

6. Sterility Assurance

From the original Product Quality Microbiology Review finalized 9/26/14:

There are no microbiology deficiencies identified. Endotoxin specification of the drug product is (b) (4) EU/mL. The Applicant has demonstrated adequate controls over the manufacturing process to mitigate the sterility and pyrogenicity risks to the final drug product. (b) (4) There was also adequate primary container closure integrity study data supporting the sterility maintenance of the final

packaged product. The drug product is preserved and adequate preservative effectiveness testing was conducted during development. This testing is also a part of the long term stability program.

7. Clinical/Statistical - Efficacy

From the original Medical Officer Review dated 11/3/14:

Study CLR_09_12 was an adequate, well-controlled study designed with endpoints to evaluate the safety and efficacy of the intended indication, reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension. Studies CLR_09_13, CLR_08_01 and CLR_10_01 were open-label studies.

Efficacy Summary Statement
Study CLR_09_12 comparing Xelpros (latanoprost ophthalmic emulsion) 0.005% and Xalatan did not establish equivalence with the preplanned clinical endpoint of change from baseline in intraocular pressure. The decrease in mean intraocular pressure in Xelpros-treated patients was 5 – 6 mmHg approximately 0.5 mmHg less than Xalatan treated patients. The data obtained from other submitted open-label studies provides supportive information regarding the decrease from baseline in mean intraocular pressure.

Although inferior to Xalatan, the IOP reduction is a clinically significant reduction in IOP and represents a benefit over the potential risks of using the product.

For additional detail, see the Clinical Team Leader Memo dated November 20, 2014, from the original NDA review cycle.

8. Safety

From the original Medical Officer Reviews dated 11/3/14 and 11/18/14:

The following studies were included in the Integrated Summary of Safety (ISS) for Xelpros (latanoprost ophthalmic emulsion) 0.005%. The safety analysis dataset for the Integrated Safety Summary included all subjects that were included in the safety analyses in each study.

Table 7.1.1 Studies Used to Evaluate Safety

Study Number / Study Phase	Study Design	Treatment Groups (Numbers of Subjects Treated)	Duration of Treatment / Age
Study CLR_08_01 (India) Phase 3	Multicenter, open-label, randomized, active-controlled, parallel group. Visits on Days -7, 0, 8, 15, and 29.	SPARC latanoprost (N=53) Xalatan (N=51)	Once daily for 4 weeks Age ≥ 18 years
Study CLR_10_01 (India) Pilot	Multicenter, open-label, randomized, active-controlled, parallel group Visits on Days 0, 28, and 56.	Subjects previously treated with Xalatan were switched over to SPARC latanoprost (N=25 subjects, 46 eyes)	Once daily for 8 weeks Age ≥ 18 years
Study CLR_09_12 (US, IND 102,842) Phase 3	Multicenter, assessor-masked, randomized, active-controlled, parallel group, non-inferiority study. Visits on Days -35, -7, 0, 7, 28, 56, and 84	SPARC latanoprost (N=289) Xalatan (N=289)	Once daily for 12 weeks Age ≥ 18 years
Study CLR_09_13 (US, IND 102,842) Phase 3	Multicenter, open-label, non-randomized, uncontrolled, single group assignment. Visits at Weeks 1, 4, 8, 12, 16, 20, 24, 28, 32, and 36.	Single group, all subjects received SPARC latanoprost (open label extension of prior Study CLR_09_12) (N=161)	Once daily for 36 weeks Age ≥ 18 years

Note: SPARC latanoprost 0.005% is the name used by the applicant during product development. SPARC latanoprost 0.005% and Xelpros (latanoprost ophthalmic emulsion) are interchangeable terms.

Four-hundred and forty-eight subjects were exposed to SPARC latanoprost 0.005% ophthalmic emulsion for a mean of 131.2 days.

Safety Summary Statement
There is substantial evidence of safety consisting of an adequate and well controlled study and supportive evidence from three additional open-label studies which demonstrate that Xelpros dosed

once daily in the evening, is safe for the reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

Treatment-emergent adverse events which occurred in ≥ 5 % of subjects and more frequently in the Xelpros group compared to the Xalatan group were: eye pain (55%), eye discharge (13%), growth of eyelashes (12%) and eyelash thickening (9%).

9. Advisory Committee Meeting

No Advisory Committee Meeting was held. There were no new issues raised in the review of the application which were thought to benefit from an Advisory Committee Meeting.

10. Pediatrics

Safety and effectiveness in pediatric patients have not been established.

This application was presented at the Pediatric Regulatory Committee (PeRC) meeting on August 13, 2014. PeRC concurred with the recommendation to waive the assessment of pediatric patients for all pediatric age groups for this indication. Necessary studies would be impossible or highly impracticable because there are too few children with disease/condition to study. The prevalence and incidence of pediatric glaucoma is very low. The number of pediatric patients is very small and geographically dispersed.

11. Other Relevant Regulatory Issues

See the Clinical Team Leader Memo dated November 20, 2014, from the original NDA review cycle.

12. Labeling

It is recommended that the labeling for NDA 206185, Xelpros (latanoprost ophthalmic emulsion) 0.005% be revised consistent with the draft labeling found in the Appendix at the end of this CDTL review. The Agency reserves additional comment on the proposed labeling until the application is otherwise adequate.

13. Recommendations/Risk Benefit Assessment

RECOMMENDED REGULATORY ACTION:
NDA 206185, Xelpros (latanoprost ophthalmic emulsion) 0.005% is not recommended for approval for the reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

The Office of Process and Facilities has issued an overall withhold recommendation for facilities on this NDA (21CFR314.125(b)(13). See Section 3 of this review. The following language is recommended for the Complete Response letter:

> During a recent inspection of the Sun Pharmaceutical Industries Ltd., FEI# 3002809586, manufacturing facility for this application, our field investigators conveyed deficiencies to the representatives of this facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

Although inferior to Xalatan (latanoprost ophthalmic solution) 0.005%, the IOP reduction is a clinically significant reduction in IOP and represents a benefit over the potential risks of using the product. The decrease in mean intraocular pressure in Xelpros-treated patients was 5 – 6 mmHg approximately 0.5 mmHg less than Xalatan treated patients. The data obtained from other submitted open-label studies provides supportive information regarding the decrease from baseline in mean intraocular pressure.

There is substantial evidence of safety consisting of an adequate and well controlled study and supportive evidence from three additional open-label studies which demonstrate that Xelpros dosed once daily in the evening, is safe for the reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

Treatment-emergent adverse events which occurred in ≥ 5 % of subjects and more frequently in the Xelpros group compared to the Xalatan group were: eye pain (55%), eye discharge (13%), growth of eyelashes (12%) and eyelash thickening (9%).

RISK BENEFIT ASSESSMENT:

The efficacy endpoints chosen for the phase 3 study have been widely used in clinical studies of ophthalmic topical IOP-lowering products and are recognized as reliable, accurate, and relevant for evaluation of the efficacy and safety of investigational products.

Pharmacology/Toxicology, CMC, Biostatistics, Clinical, Clinical Pharmacology, and Microbiology have recommended approval for this application. Product Quality has not recommended approval until the overall recommendation from the Office of Process and Facilities is "Acceptable."

RECOMMENDATION FOR POSTMARKETING RISK MANAGEMENT ACTIVITIES:

There are no risk management activities recommended beyond the routine monitoring and reporting of all adverse events.

There are no recommended Postmarketing Requirements or Phase 4 Commitments.

Appendix

Updated carton/container and prescribing information were submitted in the July 28, 2016, complete response. It is recommended that the labeling for NDA 206185, Xelpros (latanoprost ophthalmic emulsion) 0.005% be revised consistent with the draft labeling found in the Appendix at the end of this CDTL review. The Agency reserves additional comment on the proposed labeling until the application is otherwise adequate.

13 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

2.5 mL Professional Sample Label

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

WILLIAM M BOYD
12/16/2016

WILEY A CHAMBERS
12/16/2016

Medical Officer's Review of Complete Response
Safety Update

NDA 206185	**Submission Date:**	July 28, 2016
SDN-022	**Receipt Date:**	July 28, 2016
	Review Date:	December 12, 2016

Applicant: Sun Pharm Advanced Research Company, Ltd.
Tandalja, Vadodara
Gujarat, India 390020

Applicant's Representative: Aron Shapiro, VP
Ora, Inc.
300 Brickstone Square
Andover, MA 01810

Drug: Xelpros™ (latanoprost ophthalmic emulsion), 0.005%

Pharmacologic Category: prostaglandin analog

Submitted:
Reference is made to the teleconference scheduled at the Agency's request on December 15, 2015, between Aron Shapiro, VP, Ora, Inc., SPARC's authorized US Representative, Jeffrey Coderre, Director, Regulatory Writing, Ora, and representatives of the Division of Transplant and Ophthalmology Products. During this teleconference, the Agency stated reports of problems with other ophthalmic products using the same cap closure system (same DMF number) as that used for Xelpros had been received. These reports indicated that the breakaway plastic ring attached to the cap can fall off when the bottle is inverted over the eye.

Ora on behalf of SPARC submitted a response on February 5, 2016, regarding the Xelpros cap closure system (CCS). In response, the Agency requested a teleconference with Ora on March 11, 2016. During this teleconference, the Agency stated that because of the reports that had been received, going forward, for any eye drop container with a break-away safety ring, changes to the CCS would be requested, if there was no existing ring retaining ridge on the bottle. The Agency also stated that they were willing to examine the actual Xelpros bottles; however, without a ridge on the bottle the Agency would probably consider it not acceptable.

Reference is also made to the SPARC June 3, 2016, submission to this NDA. That submission discussed revisions made to the CCS to address reports that the breakaway plastic ring attached to the cap could fall off when the bottle was inverted over the eye. Reference is also made to the General Advice correspondence received dated June 21, 2016 from the Agency indicating that it concurred with the proposed modifications to the CCS and that no additional stability testing would be required.

This July 28, 2016, submission represents a Complete Response to the FDA's Complete Response letter dated July 30, 2015. The Safety Update Report is reviewed here. Refer to the Team Leader review for the most recent draft labeling.

SAFETY UPDATE REPORT

This safety update for Sun Pharma Advanced Research Company (SPARC), Ltd.'s Latanoprost Ophthalmic Emulsion, 0.005% product (tentatively named Xelpros), NDA 206185, is provided in accordance with 21 CFR 314.50(d)(5)(vi)(b), and as requested by FDA in the Agency's "Complete Response" letter dated July 30, 2015.

No clinical studies are ongoing and no new clinical studies have been initiated with SPARC Latanoprost Ophthalmic Emulsion, 0.005% (Xelpros) since the submission of NDA 206185 on January 31, 2014.

Sun Pharma Advanced Research Company, Ltd. is not marketing Latanoprost Ophthalmic Emulsion, 0.005% (Xelpros) in any foreign countries.

Patient Discontinuations and Deaths

Because there have not been any new or ongoing SPARC Latanoprost Ophthalmic Emulsion, 0.005% (Xelpros) clinical trials since submission of NDA 206185, there is no new Xelpros-specific safety information on adverse events (AEs) or deaths to update NDA 206185.

Clinical Literature Search

The applicant performed clinical and nonclinical literature searches described below.

The clinical literature search for this safety update report in support of the SPARC Latanoprost Ophthalmic Emulsion 0.005% (Xelpros) NDA 206185 was conducted using the following methodology and databases.

- EMBASE® (1974 to present): Comprehensive index of the world's literature on human medicine and related disciplines. Includes citations from approximately 7,600 journals.
- MEDLINE® (1950 to present): Produced by the U.S. National Library of Medicine as a major source for biomedical literature. Includes citations from approximately 5,000 journals.
- BIOSIS Previews® (1926 to present): Coverage of research in life sciences including 1,500 biomedical meetings and patents and book contents not available in MEDLINE.

The specific clinical literature search strategy is detailed in Table 1 below. No restrictions were placed on language. Duplicate citations were programmatically removed. The search was conducted on July 8, 2016 and included all manuscripts published after March 2015, the month in which the last literature search was conducted for the submitted NDA.

Reviewer's Comment:
The Safety Update does not raise any new safety signals. No safety-related revisions to the current proposed labeling are recommended at this time.

Recommendations:

From a clinical perspective, NDA 206185 for Xelpros (latanoprost ophthalmic emulsion) 0.005% is recommended for approval. Refer to the Team Leader review for the most recent draft labeling.

Rhea A. Lloyd, MD
Medical Officer

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/s/

RHEA A LLOYD
12/13/2016

WILLIAM M BOYD
12/13/2016

Cross-Discipline Team Leader Review

Date	July 28, 2015
From	William M. Boyd, M.D.
Subject	Cross-Discipline Team Leader Review
NDA #	206185
Applicant	Sun Pharm Advanced Research Company Ltd. U.S Representative: Ora., Inc.
Date of Submission	April 9, 2015
PDUFA Goal Date	October 9, 2015
Type of Application	505(b)(2)
Name	Xelpros (latanoprost ophthalmic emulsion) 0.005%
Dosage forms / Strength	Topical ophthalmic emulsion
Proposed Indication(s)	Reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension
Recommended:	Not Recommended for Approval

1. Introduction

This application received a Complete Response letter dated November 24, 2014. The letter requested that the applicant:

1. Update the NDA submission in all appropriate sections to indicate the correct dosage form of ophthalmic emulsion.

2. Tighten the proposed acceptance limits for (b) (4) and the highest unspecified impurity to no more than (b) (4)%.

3. Revise the draft prescribing information.

4. Revise the carton and container labeling.

5. Resolve the deficiencies noted during the inspection of the manufacturing facility located in Halol, India.

An April 9, 2015, submission to the new drug application served as a complete, class 2 response to the November 24, 2014, action letter.

2. Background

There are many ophthalmic drug products approved for lowering intraocular pressure in patients with open-angle glaucoma and ocular hypertension. These treatments include beta-adrenergic antagonists (beta-blockers), alpha-adrenergic agonists, parasympathomimetic (miotic) agents, carbonic anhydrase inhibitors, and prostaglandin analogs.

Drug Products with Approved NDAs

Pharmacologic Class/ Applicant	Trade Name	Established Name
Alpha-2 agonists		
Allergan, Inc.	Alphagan/ Alphagan P	brimonidine tartrate
Beta-adrenergic antagonists		
Alcon	Betoptic/ Betoptic S	betaxolol hydrochloride
Novartis	Ocupress	carteolol hydrochloride
Allergan	Betagan	levobutanol hydrochloride
Bausch & Lomb	Optipranolol	metipranolol
Vistakon	Betimol	timolol hemihydrate
Aton Pharma	Timoptic	timolol maleate
Ista	Istalol	timolol maleate
Aton Pharma	Timoptic XE	timolol maleate gel forming solution
Carbonic Anhydrase Inhibitors		
Duramed Pharamaceuticals	Diamox	acetazolamide
Sandoz, Inc.	N/A	methazolamide
Topical Carbonic Anhydrase Inhibitors		
Alcon	Azopt	brinzolamide
Merck	Trusopt	dorzolamide hydrochloride
Cholinergic agonist		
Alcon	Pilopine HS	pilocarpine hydrochloride gel
Alcon	Isopto Carpine	pilocarpine hydrochloride
Prostaglandin Analogues		
Allergan	Lumigan	bimatoprost
Pharmacia	Xalatan	latanoprost
Alcon	Travatan	travoprost
Alcon	Travatan Z	travoprost
Merck	Zioptan	tafluprost
Alcon	Izba	travoprost
Sympathomimetics		
Allergan	Propine	dipivefrin hydrochloride
Combination Products		
Merck	Cosopt	dorzolamide hydrochloride/timolol maleate
Merck	Cosopt PF	dorzolamide

Pharmacologic Class/ Applicant	Trade Name	Established Name
		hydrochloride/timolol maleate
Allergan	Combigan	brimonidine tartrate/timolol maleate
Alcon	BetopticPilo	betaxolol hydrochloride/pilocarpine hydrochloride
Alcon	Simbrinza	Carbonic anhydrase inhibitor/alpha-agonist
Other		
Sucampo Pharma Americas, Inc.	Rescula	unoprostone isopropyl

3. CMC

From the Product Quality Review finalized 7/27/15:

1. The release and stability data indicate that the proposed acceptance limits for (b) (4) (specified identified impurity) and highest unspecified impurity can be tightened. Please revise the limits to the above referenced impurities to NMT (b) (4)% for release and stability.

SPARC Response
Please note that the drug product specification for related substance test have been tightened as per below table. The level of (b) (4) (specified identified impurity) at 18 month long-term stability station for the exhibit batch # JKK0537A was found to be (b) (4)%. (b) (4) (b) (4), the release and stability specification for (b) (4) (specified identified impurity) has been tightened to not more than (b) (4)% for release and stability.

Please also note that the highest unspecified impurity was below quantification limit (BQL) at all the stability conditions for related substances method I and method II. Release and stability specification for highest unspecified impurity (method I and II) has been tightened to not more than (b) (4)%.

Release and Stability Specification	
Previous Specification	**Proposed Specification**
Related substances method I	
Highest unspecified impurity: Not more than (b) (4)%	Highest unspecified impurity: Not more than (b) (4)%
Related Substances Method II	
(b) (4) impurity: Not more than (b) (4)%	(b) (4) impurity: Not more than (b) (4)%
Highest unspecified impurity: Not more than (b) (4)%	Highest unspecified impurity: Not more than (b) (4)%

Revised drug product release specification, test procedure and post-approval stability protocol with above proposed specifications has been provided herewith in *section 3.2.P.5.1, 3.2.P.5.2* and *3.2.P.8.2*.

Please also note that we have evaluated long-term stability data of exhibit batches obtained up to 24 months for related substance results. All the three exhibit batches comply with the above proposed specification for specified identified impurity ((b) (4)) and highest unspecified impurities.

Product Quality Reviewer Evaluation of Response:
The applicant has responded with proposed acceptance criteria as provided in the table above. The revised acceptance limits are justified and are acceptable.

Clinical Team Evaluation of Response:
The revised specifications are acceptable from a clinical prospective.

2. Please update the NDA submission in all appropriate sections to indicate the correct dosage form of emulsion and the revised acceptance criteria.

SPARC Response
Please note that in the revised *section 3.2.P.5.1, 3.2.P.5.2* and *3.2.P.8.2* dosage form of emulsion has been specified.

Please also note that in the *Module 1.11.4* provided herewith the response, we have included a statement indicating that the drug product name has been revised to "Latanoprost ophthalmic emulsion, 0.005%" from the previously submitted name of "Latanoprost ophthalmic (b) (4) 0.005%". Please note that the drug product labeling has also been updated to include the revised product name (refer SN0011 amendment dated July 09, 2014).

In addition to above, please also note that during the internal review of the stability data of the drug product typographical errors were observed in the particulate matter and latanoprost assay results for batch # JKK0537A. We apologize for the typographical errors. An erratum to the submitted stability data for batch # JKK0537A with the correct results has been provided herewith in *section 3.2.P.8.3*.

Evaluation of Response:
The applicant has revised the NDA submission to indicate the correct dosage form is an emulsion as recommended. The response is acceptable.

DESCRIPTION AND COMPOSITION OF THE DRUG PRODUCT:

3.2.P.1 Description and Composition of the Drug Product [Latanoprost ophthalmic emulsion, 0.005%, Sun Pharmaceutical Industries Limited]

Table 3.2.P.1-1. Components of Latanoprost ophthalmic emulsion, 0.005%

Component	Amount (per mL)	% w/v	Function	Reference to Quality Standards
Latanoprost	0.05	0.005	Active	In house
Potassium sorbate	4.70	0.47	Preservative	NF
Boric acid	(b) (4)	(b) (4)	(b) (4)	NF
Edetate disodium				USP
Castor oil				USP
(b) (4)				Ph.Eur.
Propylene glycol				USP
Sodium borate				NF
Hydrochloric acid				NF
Sodium hydroxide				NF
Water for injection				USP
(b) (4)				

The proposed drug product will be supplied as a 2.5-mL (b) (4) in a (b) (4) 5-mL low-density polyethylene bottle with a low-density polyethylene (LDPE) dropper tip, equipped with a high- density polyethylene (b) (4) screw cap.

PROPOSED REGULATORY SPECIFICATIONS:

Table 3.2.P.5.1-1 Specification for Latanoprost ophthalmic emulsion 0.005% W/V, 2.5 ml		
Test	**Acceptance Criterion**	**Analytical Procedure Reference**
Description	Off white to pale yellow translucent solution filled in LDPE bottle.	In house, *Section 3.2.P.5.2.1*
Identification		
Identification (By HPLC)	The retention time of the latanoprost peak in the chromatogram of the assay preparation corresponds to that of the standard preparation as obtained in the assay.	HPLC, *Section 3.2.P.5.2.2.1*
Identification (By HPLC)	The PDA spectrum, in the range of (b) (4) nm, of latanoprost peak in the sample preparation corresponds to that of latanoprost peak in standard preparation as obtained in the related substances method II.	HPLC, *Section 3.2.P.5.2.2.2*
pH	Between (b) (4)	In house, *Section 3.2.P.5.2.3*
Absorbance at 420 nm	Not more than (b) (4) AU.	In house, *Section 3.2.P.5.2.4*
Osmolality	(b) (4) mOsm	In house, *Section 3.2.P.5.2.5*
Volume in container	Between (b) (4) ml	USP, *Section 3.2.P.5.2.6*
Volume variation	Between (b) (4) ml	In house, *Section 3.2.P.5.2.7*
Viscosity	(b) (4) cp – (b) (4) cp	In house, *Section 3.2.P.5.2.8*
Particle size Distribution	D10: (b) (4) D50: D90:	In house, *Section 3.2.P.5.2.9*

Table 3.2.P.5.1-1 Specification for Latanoprost ophthalmic emulsion 0.005% W/V, 2.5 ml		
Test	**Acceptance Criterion**	**Analytical Procedure Reference**
Particulate Matter	Particles greater than or equal to (b) (4) µm NMT (b) (4) per ml Particles greater than or equal to (b) (4) µm NMT (b) (4) per ml Particles greater than or equal to (b) (4) µm NMT (b) (4) per ml	USP, *Section 3.2.P.5.2.10*
Sterility	(b) (4)	USP, *Section 3.2.P.5.2.11*
Bacterial Endotoxins	Not more than (b) (4) EU/ml	USP, *Section 3.2.P.5.2.12*
Related Substances (by HPLC)		
Method I		In house validated method *Section 3.2.P.5.2.13*
Unspecified Impurities		
Highest unspecified impurity	Not more than (b) (4) %	
Total Impurities	Not more than %	
Method II		In house validated method *Section 3.2.P.5.2.14*
Specified identified Impurities		
(b) (4)	Not more than (b) (4) %	
Unspecified Impurities		
Highest unspecified impurity	Not more than (b) (4) %	
Total Impurities	Not more than %	
Assay - content of potassium sorbate (by HPLC)	Not less than (b) (4) %	In house validated method *Section 3.2.P.5.2.15*
Assay - of EDTA	(b) (4) mg/ml	In house validated method *Section 3.2.P.5.2.16*
Assay - of Latanoprost (by HPLC)	(b) (4) % of Label claim.	In house validated method *Section 3.2.P.5.2.17*
Residual solvents	Should comply as per USP <467> (b) (4)	USP, *Section 3.2.P.5.2.18*

FACILITIES INSPECTIONS:
The Office of Process and Facilities has issued an overall recommendation of Withhold for facilities. Approval for this NDA is recommended only when all supporting sites have an acceptable recommendation.

Facility Alerts

This report displays the Alerts associated with facilities on the selected applications
Time run: 7/17/2015 12:10:31 PM

Facility FEI	Facility DUNS	Issue Name	Alert Type	Status	Entry Date	Entered By
3002809586	719638124	OAI/POAI Alert: SUN PHARMACEUTICAL INDUSTRIES LIMITED	Official Action Indicated	NEW	10/2/2014	DARRTS MIGRATION
3002809586	725959238	OAI/POAI Alert: SUN PHARMACEUTICAL INDUSTRIES LIMITED	Official Action Indicated	NEW	2/24/2015	DARRTS MIGRATION

Facility Status View for NDA 206185 Original 1

Displays information for the facilities that are associated to NDA 206185 Original 1. It also shows the Overall Manufacturing Inspection Recommendation for the application and the associated OPF Facility Recommendations.
Time run: 7/17/2015 12:10:32 PM

Overall Manufacturing Inspection Recommendations for NDA 206185 Original 1

Project Name	Sponsor Name	Overall Manufacturing Inspection Recommendation	Overall Manufacturing Inspection Re-Evaluation Date	Overall Manufacturing Inspection Task Status	Overall Manufacturing Inspection Recommendation Task Completion Date
NDA 206185-Orig1-New/NDA(1)	SUN PHARMA ADVANCED RESEARCH CO LTD	Withhold	03/01/2015	Complete	11/13/2014
NDA 206185-Orig1-Resubmission/Class 2(18)	SUN PHARMA ADVANCED RESEARCH CO LTD	Withhold	09/30/2015	Complete	6/17/2015

OPF Facility Recommendations for Facilities on NDA 206185 Original 1

Project Name	FEI	DUNS	Facility Name	Profile	OPF Facility Recommendation	OPF Facility Re-Evaluation Date	OPF Facility Recommendation Task Status	OPF Facility Recommendation Task Completion Date
NDA 206185-Orig1-Resubmission/Class 2(18)	3007512695	676162401	SUN PHARMA ADVANCED RESEARCH COMPANY LIMITED	CTL CONTROL TESTING LABORATORY	Approve Facility	07/31/2015	Complete	4/28/2015
NDA 206185-Orig1-Resubmission/Class 2(18)	(b) (4)			CTL CONTROL TESTING LABORATORY			Cancelled	5/12/2015
NDA 206185-Orig1-Resubmission/Class 2(18)				CTL CONTROL TESTING LABORATORY			Cancelled	4/28/2015
NDA 206185-Orig1-Resubmission/Class 2(18)				CTL CONTROL TESTING LABORATORY			Cancelled	4/28/2015

Data refreshed on: 07/17/15 08:37:01 AM

4. Nonclinical Pharmacology/Toxicology

From the original Pharmacology/Toxicology Review finalized 10/17/14:

SPARC seeks approval of Latanoprost Ophthalmic Emulsion, 0.005%, which is intended for the same dosage (1 drop QD or 1.5 µg/day) and administration (once daily in the evening) as that of the approved Listed Drug (LD) Xalatan (NDA 20-597), for the reduction of elevated IOP in patients with open-angle glaucoma or ocular hypertension. The new formulation contains an excipient, (b) (4) which has not been previously approved in an ophthalmic product in the United States. SPARC is relying on FDA's prior findings of the efficacy and safety of latanoprost, as summarized in the most current Xalatan labeling (revised August 2012). In addition, SPARC performed repeated-dose ocular toxicity studies of up to 180-day duration in dogs and rabbits to evaluate the systemic and local ocular toxicities of the new formulation. To evaluate the ocular safety of (b) (4) these studies included an additional arm(s) using this excipient. Systemic safety of (b) (4) was evaluated in repeated-dose oral toxicity studies of (b) (4) in rats of up to 180-day duration. In addition, SPARC used the extensive battery of systemic toxicity studies conducted by (b) (4)

5. Clinical Pharmacology/Biopharmaceutics

From the original Clinical Pharmacology Review finalized 9/30/14:

The applicant (Sun Pharmaceutical Industries, Ltd; SPARC) has submitted this current NDA for a different formulation of latanoprost ophthalmic emulsion 0.005%. The proposed SPARC latanoprost formulation differs from Xalatan in several ways: SPARC latanoprost includes (b) (4) as a (b) (4), and potassium sorbate as a preservative. Xalatan contains 0.02% w/v benzalkonium chloride (BKC) as a preservative. The submitted latanoprost product is an emulsion, (b) (4) (b) (4). The applicant submitted a request for an *in vivo* bioavailability (BA) or bioequivalence (BE) waiver, which is acceptable based on the consideration that the differences in formulation between Xalatan and the proposed SPARC latanoprost ophthalmic emulsion 0.005% are not expected to influence the limited systemic exposure to latanoprost/latanoprost acid following topical ocular administration.

From the Biopharmaceutics Review dated 10/17/14:

Based on 21 CFR § 320.22 (e), Biopharmaceutics is of the opinion that for good cause, the requirement for the submission of evidence of in vivo bioavailability or bioequivalence can be waived, because the proposed drug product is an ophthalmic product intended only for local therapeutic effect. Therefore, the biowaiver request is granted.

The ONDQA-Biopharmaceutics team has reviewed NDA 206185 and its amendments (Seq. 0008 and Seq.0014) submitted on May 23, and July 19, 2014. From the Biopharmaceutics perspective, NDA 206185 Xelpros (latanoprost) ophthalmic emulsion, 0.005% w/v is recommended for **APPROVAL.**

6. Sterility Assurance

From the original Product Quality Microbiology Review finalized 9/26/14:

There are no microbiology deficiencies identified. Endotoxin specification of the drug product is (b) (4) EU/mL. The Applicant has demonstrated adequate controls over the manufacturing process to mitigate the sterility and pyrogenicity risks to the final drug product. (b) (4) There was also adequate primary container closure integrity study data supporting the sterility maintenance of the final packaged product. The drug product is preserved and adequate preservative effectiveness testing was conducted during development. This testing is also a part of the long term stability program.

7. Clinical/Statistical - Efficacy

From the original Medical Officer Review dated 11/3/14:

Study CLR_09_12 was an adequate, well-controlled study designed with endpoints to evaluate the safety and efficacy of the intended indication, reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension. Studies CLR_09_13, CLR_08_01 and CLR_10_01 were open-label studies.

Efficacy Summary Statement
Study CLR_09_12 comparing Xelpros (latanoprost ophthalmic emulsion) 0.005% and Xalatan did not establish equivalence with the preplanned clinical endpoint of change from baseline in intraocular pressure. The decrease in mean intraocular pressure in Xelpros-treated patients was 5 – 6 mmHg approximately 0.5 mmHg less than Xalatan treated patients. The data obtained from other submitted open-label studies provides supportive information regarding the decrease from baseline in mean intraocular pressure.

Although inferior to Xalatan, the IOP reduction is a clinically significant reduction in IOP and represents a benefit over the potential risks of using the product.

For additional detail, see the Clinical Team Leader Memo dated November 20, 2014, from the original NDA review cycle.

8. Safety

From the original Medical Officer Reviews dated 11/3/14 and 11/18/14:

The following studies were included in the Integrated Summary of Safety (ISS) for Xelpros (latanoprost ophthalmic emulsion) 0.005%. The safety analysis dataset for the Integrated Safety Summary included all subjects that were included in the safety analyses in each study.

Table 7.1.1 Studies Used to Evaluate Safety

Study Number / Study Phase	Study Design	Treatment Groups (Numbers of Subjects Treated)	Duration of Treatment / Age
Study CLR_08_01 (India) Phase 3	Multicenter, open-label, randomized, active-controlled, parallel group. Visits on Days -7, 0, 8, 15, and 29.	SPARC latanoprost (N=53) Xalatan (N=51)	Once daily for 4 weeks Age ≥ 18 years
Study CLR_10_01 (India) Pilot	Multicenter, open-label, randomized, active-controlled, parallel group Visits on Days 0, 28, and 56.	Subjects previously treated with Xalatan were switched over to SPARC latanoprost (N=25 subjects, 46 eyes)	Once daily for 8 weeks Age ≥ 18 years
Study CLR_09_12 (US, IND 102,842) Phase 3	Multicenter, assessor-masked, randomized, active-controlled, parallel group, non-inferiority study. Visits on Days -35, -7, 0, 7, 28, 56, and 84	SPARC latanoprost (N=289) Xalatan (N=289)	Once daily for 12 weeks Age ≥ 18 years
Study CLR_09_13 (US, IND 102,842) Phase 3	Multicenter, open-label, non-randomized, uncontrolled, single group assignment. Visits at Weeks 1, 4, 8, 12, 16, 20, 24, 28, 32, and 36.	Single group, all subjects received SPARC latanoprost (open label extension of prior Study CLR_09_12) (N=161)	Once daily for 36 weeks Age ≥ 18 years

Note: SPARC latanoprost 0.005% is the name used by the applicant during product development. SPARC latanoprost 0.005% and Xelpros (latanoprost ophthalmic emulsion) are interchangeable terms.

Four-hundred and forty-eight subjects were exposed to SPARC latanoprost 0.005% ophthalmic emulsion for a mean of 131.2 days.

Safety Summary Statement
There is substantial evidence of safety consisting of an adequate and well controlled study and supportive evidence from three additional open-label studies which demonstrate that Xelpros dosed

once daily in the evening, is safe for the reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

Treatment-emergent adverse events which occurred in ≥ 5 % of subjects and more frequently in the Xelpros group compared to the Xalatan group were: eye pain (55%), eye discharge (13%), growth of eyelashes (12%) and eyelash thickening (9%).

Since the submission of the NDA 206185 on January 31, 2014, there have been no ongoing or new clinical studies initiated with Xelpros (latanoprost ophthalmic emulsion), 0.005%. Sun Pharm Advanced Research Company, Ltd. (SPARC) is not marketing latanoprost ophthalmic emulsion, 0.005% in any foreign countries. Since there have been no ongoing or new clinical trials, there is no new Xelpros-specific safety information on adverse events (AEs) with which to update the NDA. There has been no new information regarding Xelpros-specific deaths associated with NDA 206185. For additional detail, see the Clinical Team Leader Memo dated November 20, 2014, from the original NDA review cycle.

9. Advisory Committee Meeting

No Advisory Committee Meeting was held. There were no new issues raised in the review of the application which were thought to benefit from an Advisory Committee Meeting.

10. Pediatrics

Safety and effectiveness in pediatric patients have not been established.

This application was presented at the Pediatric Regulatory Committee (PeRC) meeting on August 13, 2014. PeRC concurred with the recommendation to waive the assessment of pediatric patients for all pediatric age groups for this indication. Necessary studies would be impossible or highly impracticable because there are too few children with disease/condition to study. The prevalence and incidence of pediatric glaucoma is very low. The number of pediatric patients is very small and geographically dispersed.

11. Other Relevant Regulatory Issues

See the Clinical Team Leader Memo dated November 20, 2014, from the original NDA review cycle.

12. Labeling

It is recommended that the labeling for NDA 206185, Xelpros (latanoprost ophthalmic emulsion) 0.005% be revised to match the draft labeling found in the Appendix at the end of this CDTL review. The proposed revisions are minor editorial changes identified by tracked changes.

13. Recommendations/Risk Benefit Assessment

RECOMMENDED REGULATORY ACTION:
NDA 206185, Xelpros (latanoprost ophthalmic emulsion) 0.005% is not recommended for approval for the reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension. The Office of Process and Facilities has issued an overall withhold recommendation for facilities on this NDA (21CFR314.125(b)(13). See Section 3 of this review.

Although inferior to Xalatan (latanoprost ophthalmic solution) 0.005%, the IOP reduction is a clinically significant reduction in IOP and represents a benefit over the potential risks of using the product. The decrease in mean intraocular pressure in Xelpros-treated patients was 5 – 6 mmHg approximately 0.5 mmHg less than Xalatan treated patients. The data obtained from other submitted open-label studies provides supportive information regarding the decrease from baseline in mean intraocular pressure.

There is substantial evidence of safety consisting of an adequate and well controlled study and supportive evidence from three additional open-label studies which demonstrate that Xelpros dosed once daily in the evening, is safe for the reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

Treatment-emergent adverse events which occurred in ≥ 5 % of subjects and more frequently in the Xelpros group compared to the Xalatan group were: eye pain (55%), eye discharge (13%), growth of eyelashes (12%) and eyelash thickening (9%).

RISK BENEFIT ASSESSMENT:
The efficacy endpoints chosen for the phase 3 study have been widely used in clinical studies of ophthalmic topical IOP-lowering products and are recognized as reliable, accurate, and relevant for evaluation of the efficacy and safety of investigational products.

Pharmacology/Toxicology, CMC, Biostatistics, Clinical, Clinical Pharmacology, and Microbiology have recommended approval for this application. Product Quality has not recommended approval until the overall recommendation from the Office of Process and Facilities is "Acceptable."

RECOMMENDATION FOR POSTMARKETING RISK MANAGEMENT ACTIVITIES:
There are no risk management activities recommended beyond the routine monitoring and reporting of all adverse events.

There are no recommended Postmarketing Requirements or Phase 4 Commitments.

Appendix

Updated carton/container and prescribing information were submitted in the November 9, 2014, complete response. It is recommended that the labeling for NDA 206185, Xelpros (latanoprost ophthalmic emulsion) 0.005% be revised to match the draft labeling found in the Appendix at the end of this CDTL review. The proposed revisions are minor editorial changes identified by tracked changes.

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Proposed Labeling

SPARC has submitted revised package insert, carton and container labeling which includes the Agency's proposed changes to the label as presented in the Complete Response letter dated November 24, 2014. SPARC has made additional changes to the previously proposed labeling.

Following is the applicant's proposed draft labeling for the product.

The applicant's deletions are noted by and insertions by underline.
The reviewer's deletions are noted by and insertions by underline.

9 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

WILLIAM M BOYD
07/29/2015

WILEY A CHAMBERS
07/29/2015

RENATA ALBRECHT
07/30/2015

Medical Officer's Review of Complete Response
Safety Update and Proposed Labeling

NDA 206185	**Submission Date:**	April 9, 2015
SDN-018	**Receipt Date:**	April 9, 2015
	Review Date:	June 16, 2015

Applicant: Sun Pharm Advanced Research Company, Ltd.
Tandalja, Vadodara
Gujarat, India 390020

Applicant's Representative: Aron Shapiro, VP
Ora, Inc.
300 Brickstone Square
Andover, MA 01810

Drug: Xelpros™ (latanoprost ophthalmic emulsion), 0.005%

Pharmacologic Category: prostaglandin analog

Submitted:
The applicant has submitted a complete response to the Complete Response letter dated, November 24, 2014. The submitted Safety Update Report and proposed labeling will be reviewed here.

Safety Update Report

Since the submission of the NDA 206185 on January 31, 2014, there have been no ongoing or new clinical studies initiated with Xelpros (latanoprost ophthalmic emulsion), 0.005%. Sun Pharm Advanced Research Company, Ltd. (SPARC) is not marketing latanoprost ophthalmic emulsion, 0.005% in any foreign countries.

Since there have been no ongoing or new clinical trials, there is no new Xelpros-specific safety information on adverse events (AEs) with which to update the NDA. There has been no new information regarding Xelpros-specific deaths associated with NDA 206185.

SPARC, Ltd. conducted a clinical and nonclinical literature search utilizing the following methodology and databases:

- EMBASE® (1974 to present): Comprehensive index of the world's literature on human medicine and related disciplines. Includes citations from approximately 7,600 journals.
- MEDLINE® (1950 to present): Produced by the U.S. National Library of Medicine as a major source for biomedical literature. Includes citations from approximately 5,000 journals.
- BIOSIS Previews® (1926 to present): Coverage of research in life sciences including 1,500 biomedical meetings and patents and book contents not available in MEDLINE.

The specific clinical literature search strategy and results are detailed in the table below. No restrictions were placed on language. Duplicate citations were programmatically removed. The search was conducted on March 13, 2015 for the period from May 17, 2014 (the day after the last literature search was conducted for the submitted NDA application) through March 11, 2015. The search was conducted by a trained research associate using STN®.

The Clinical Search Strategy

Search date: 13 March 2015				
Connector	**Restriction Category**	**Specific Terms Used**	**Fields Searched**	**No. of Citations**
--	Drug name	latanoprost OR 130209-82-4 OR glaucostat OR klonaprost OR latanoflax OR louten OR ocuprost OR paraiop OR tanamof OR xalatan OR solusin OR unilat OR xaloptic OR gaax OR latof OR gaap(w) ofteno OR latsol OR laprost OR latanopress	All	303
AND	Clinical	clinical OR human OR man OR men OR wom!n OR patient# OR subjects OR volunteer# OR participant# OR pediatric? or geriatric? OR child OR children OR infant# OR adolescen? OR teen# OR teenager? OR youth# OR baby OR babies OR elderly OR adults	All	266
AND	Safety	(adverse OR side OR drug)(w)(event# OR effect? OR reaction# OR experience#) OR injurious OR poisoning OR toxic? OR chemically(w)induc? OR tolerab? OR safety OR drug(2a)(interact? OR synergism OR antagonism)	All	95
AND	After Duplicate citation removal		All	69
Footnotes: ? =truncation symbol; retrieves zero or more characters at the end of a term #= truncation symbol; retrieves zero or one character at the end of a term (w)= proximity connector; requires terms be adjacent to each other in the order specified (a)= proximity connector; requires terms be adjacent to each other but in any order				

Of the total of 69 clinical abstracts (and abstracts identified as clinical that were included in the nonclinical literature references), 3 were deemed as providing potentially new safety information and are described here.

Poliosis and hypertrichosis of malar vellus hairs. Increases in eyelash or vellus hair number, length, or thickness in the treated eye, as well as an increase in iris pigmentation, have previously been reported for latanoprost (Xalatan 2014). A recent case report also cites poliosis of the eyelashes and hypertrichosis of malar vellus hairs possibly associated with latanoprost in one 64- year old female patient who had been treated with latanoprost for at least 3.5 years (Ozyurt and Cetinkaya 2015). This patient had hypertension and diabetes mellitus for eight years and had been taking amlodipine tablets and oral acarbose. The authors cite a few other similar reports in the literature.

Increase in mean area of epithelial microcysts. The mean area of epithelial microcysts increased significantly in 40 glaucomatous patients who had not previously been receiving glaucoma treatment and subsequently received latanoprost for 3 months. The microcysts were present at baseline prior to treatment in all subjects and increased over the 3 months (Mastropasqua et al. 2014).

Long-term decrease in central corneal thickness. Sun Pharma previously provided information reported in the literature on shorter-term (e.g., 24 months) decreases in central corneal thickness (CCT) in patients receiving latanoprost (You and Cho 2013, Bafa et al. 2011). A recent retrospective study investigated CCT in 52 eyes of 52 glaucoma patients in Japan receiving latanoprost treatment for over 4 years. Mean CCT significantly decreased from pretreatment to final follow-up (i.e., 48 to 72 months). No significant difference was found between the mean CCT at midpoint and at final follow-up. Most of the significant CCT decrease occurred in the first 2 years (Maruyama et al. 2014).

Reviewer's Comment:
The Safety Update does not raise any new safety signals. No revisions to the current proposed labeling are recommended at this time.

Proposed Labeling

SPARC has submitted revised package insert, carton and container labeling which includes the Agency's proposed changes to the label as presented in the Complete Response letter dated November 24, 2014. SPARC has made additional changes to the previously proposed labeling.

Following is the applicant's proposed draft labeling for the product.

The applicant's deletions are noted by and insertions by underline.
The reviewer's deletions are noted by and insertions by underline.

11 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Recommendations:

The submitted carton and container labeling is consistent with the Agency recommendations and is acceptable.

The submitted package insert with the minor editorial changes contained within this review are acceptable.

From a clinical perspective, NDA 206185 for Xelpros (latanoprost ophthalmic emulsion) 0.005% is recommended for approval with the labeling revisions contained within this review.

Rhea A. Lloyd, MD
Medical Officer

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/s/

RHEA A LLOYD
07/20/2015

WILLIAM M BOYD
07/20/2015

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Renata Albrecht, MD
Subject	Division Director Summary Review
NDA/BLA # **Supplement #**	NDA 206185 N/A
Related IND	IND 102842
Applicant Name	Sun Pharma Advanced Research Company Limited
Agent for Applicant	Ora, Inc.
Application Type	505(b)(2)
Date of Submission	1/31/2014 (standard review)
PDUFA Goal Date	11/30/2014
Proprietary Name / **Established (USAN) Name**	XELPROS latanoprost ophthalmic emulsion
Dosage Forms / Strength	emulsion / 0.005%
Preservative	Potassium sorbate 0.47%
Route of Administration	Topical ophthalmic
Therapeutic Class	Prostaglandin
Proposed Indication(s)	Reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension
Dosage Regimen	One drop (1.5 µg latanorprost) in the affected eye(s) once daily in the evening
How Supplied	latanoprost 0.005% emulsion (50 µg/mL) will be supplied as a 2.5 mL emulsion in a 5 mL clear low density polyethylene (LDPE) bottle with a clear LDPE dropper tip and high-density polyethylene (HDPE) (b) (4) screw cap.
Action/Recommended	*Complete Response – CMC and labeling*

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Rhea Lloyd, William Boyd 11/3/2014, 11/18/2014
CDTL Review	William Boyd, Wiley Chambers 11/20/2014 (2)
Deputy Director Review	Wiley Chambers 11/20/2014
Statistical Review	Solomon Chefo, Yan Wang 10/14/2014
Pharmacology Toxicology Review	Maria Rivera, Lori Kotch 10/17/2014, 10/24/2014
Product Quality Review Drug Substance	Milton Sloane, Mariappan Chelliah, Balajee Shanmugam, Rapti Madurawe 10/24/2014
Quality Microbiology Review	Robert Mello, Neal Sweeney 9/26/2014
Biopharmaceutics Review	Banu Zolnik, Okponanabofa Eradiri 10/17/2014
Office of Compliance	Withhold 11/19/2014
Clinical Pharmacology Review	Yongheng Zhang, Philip Colangelo 9/30/2014
OPDP/DPDP	Christine Corser 11/14/2014
OSI/DGCPC	Roy Blay, Janice Pohlman, Kassa Ayalew 9/17/2014
OSE/DMEPA Proprietary Name Letter	Rachna Kappor, Yelena Maslov 5/14/2014 Kellie Taylor 5/19/2014
OSE/DMEPA	Rachna Kapoor, Yelena Maslov 9/15/2014
Project Manager	Diana Willard

OND=Office of New Drugs
CDTL=Cross-Discipline Team Leader
OSI/DGCPC=Office of Scientific Investigations/Division of Good Clinical Practice Compliance
OPDP/DPDP=Office of Prescription Drug Promotion/Division of Prescription Drug Promotion
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DDRE= Division of Drug Risk Evaluation
DRISK=Division of Risk Management

Table of Contents

Signatory Authority Review Template

1. Introduction

Sun Pharma Advanced Research Company Limited (Sun Pharma or SPARC) has submitted NDA 206185 for Xelpros (latanoprost ophthalmic emulsion) 0.005%, as a 505(b)(2) application. Xelpros represents a new dosage form of latanoprost, which is currently marketed as Xalatan® (latanoprost ophthalmic solution) 0.005%, NDA 20597, approved June 5, 1996, for the reduction of elevated IOP in patients with open-angle glaucoma or ocular hypertension. Xelpros was studied for the same dosage regimen (1 drop or 1.5 µg latanoprost once daily in the evening) as the approved Xalatan® product. There are currently multiple generic formulations of latanoprost ophthalmic solution marketed.

NDA 206185 for Xelpros was submitted on January 31, 2014, and given a standard review. The applicant proposed their product was a (b) (4); however, it was determined that this represented a new dosage form, an ophthalmic emulsion (microemulsion).

Support for the efficacy and safety of Xelpros was based on four studies:

- Phase 3 efficacy and safety study (Study CLR_09_12) 12 weeks QD, conducted in the US
- Phase 3 safety study (Study CLR_09_13, an extension of CLR_09_12) also conducted in the U.S.
- Phase 3 efficacy and safety study (Study CLR_08_01) 4 weeks QD, conducted in India
- Pilot safety study (Study CLR_10_01) 8 weeks QD, also conducted in India.

Only Phase 3 Study CLR_09_12 is considered an adequate and well-controlled study in support of the application because the design and analysis provides adequate information on the efficacy and safety results of the Xelpros product. The other studies are of shorter duration and small sample size (CLR_08_01) or not controlled and not designed to evaluate efficacy (CLR-09-13, CLR_10_01) and therefore provide only supportive information.

Study CLR_09_12 comparing Xelpros (latanoprost ophthalmic emulsion) 0.005% and Xalatan did not establish equivalence with the preplanned clinical endpoint of change from baseline in intraocular pressure. The decrease in mean intraocular pressure in Xelpros-treated patients was 5 – 6 mmHg approximately 0.5 mmHg less than Xalatan treated patients (See Section 7).

Unlike Xalatan®, Xelpros does not contain the preservative benzalkonium chloride (BAC), but uses potassium sorbate 0.47% as a preservative. The applicant indicated that BAC is a commonly used preservative in eye drops and has been shown to exhibit inflammatory and toxic ocular effects. As a result, the applicant suggests BAC-free Xelpros may provide a safer alternative to existing marketed BAC-containing latanoprost products. However, the results of the safety analysis did not support a benefit in terms of adverse reactions, and the rate of eye pain was higher in the Xelpros (64%) compared to the Xalatan (47%) arm in the Phase 3 Study CLR_09_12.

Xelpros also contains an excipient, (b) (4) that has not been previously approved in an ophthalmic product in the United States, but is qualified (See Section 4).

The review team recommends that adequate information has been submitted to support that the product is effective and safe. Labeling has been submitted in PLR format but needed extensive revisions, mainly intended to align the text with class labeling and the Xalatan package insert, currently undergoing PLR conversion review. The Office of Compliance has issued a recommendation of Withhold regarding approval of the application. The CDTL and Deputy Director Reviews provide an overall summary of the application, and further details are provided in the primary reviews for this NDA.

Reviewer Comment:
Although Xelpros was shown to be effective in terms of reducing the IOP by 5-6 mmHg in the clinical development program, there was a notable difference in the rate of eye pain reported: 64% in Xelpros and 47% in Xalatan treated patients in Phase 3 randomized, controlled, masked CLR_09_12. Based on further consideration of the benefit (clinically significant reduction of IOP by 5-6 mmHg) and the specific nature of the adverse reaction (transient stinging in the eye as recorded in patient diaries), the application can be approved from a clinical perspective and results of the Phase 3 clinical trial reflected in labeling for this 505(b)(2) product.

2. Background

Glaucoma is a life-long progressive disease that is characterized by irreversible damage to the optic nerve and corresponding loss of visual field. One of the primary risk factors is elevated intraocular pressure (IOP). The reduction and control of elevated IOP in open-angle glaucoma and ocular hypertension is usually managed by chronic, long-term topical ocular therapy.

There are currently multiple topical products in several classes available for the reduction of IOP, including beta-adrenergic antagonists (beta-blockers), alpha-adrenergic agonists, parasympathomimetic (miotic) agents, carbonic anhydrase inhibitors, prostaglandin analogs, and some combination products. A complete list is included in the Medical Officer's Review and CDTL Review.

The listed drug, Xalatan® (latanoprost ophthalmic solution) 0.005%, NDA 20597 was approved June 5, 1996 and indicated "for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma and ocular hypertension who are intolerant of other intraocular pressure lowering medications or insufficiently responsive (failed to achieve target IOP determined after multiple measurements over time) to another intraocular pressure lowering medication. The limitation was based on the reported adverse reactions of iris pigmentation changes, given the uncertainly of the long-term consequences of these findings (skin/eyelid pigmentation and eyelash changes were also noted). On December 20, 2002, the indication was revised to remove these limitations based on NDA 20597/S010, which contained follow up data of latanoprost-treated patients for multiple years showing the eyelash changes could be reversible while iris pigmentation was not. The follow-up and post-marketing information did not identify reports of pigmentary glaucoma or melanoma, which had been a potential concern.

Latanoprost is a prostaglandin analog, F2-α receptor agonist. Latanoprost is absorbed through the cornea where the isopropyl ester prodrug is hydrolyzed to latanoprost acid a derivative of prostaglandin F2-α which is biologically active. It is believed that latanoprost reduces intraocular pressure by increasing uveoscleral aqueous outflow from the eye.

Sun Pharma submitted their pre-IND 102842 on June 26, 2008, and a meeting was held on September 16, 2008, to discuss the development plan for their latanoprost product, including discussion of CMC recommendations and guidance documents, discussion of non-clinical studies including the need for 6-month systemic and ocular studies, and discussion of clinical pharmacology and clinical issues.

Sun Pharma submitted IND 102842 on August 19, 2009, and included protocols for Study CLR_09_12, a Phase 3 study designed to demonstrate equivalence[1] between the SPARC product and Xalatan and Study CLR_09_13, an open label extension study of Study CLR-09-12 to collect safety data for 6 months, and measure endothelial cell counts.

Sun Pharma met with the Division on February 20, 2013 for a pre-NDA meeting. The results of Study CLR_09_12 showed that while all IOP measurements were within the <1.5 mmHg margin, the majority were outside the <1 mm Hg margin; the applicant was told this was problematic and would be review issue. The recommendation that safety data be available for at least 100 patients treated for at least 6 months was not met; only 73 patients had adequate follow up. The applicant was advised this could become a potential filing issue. There was discussion that SPARC's proposed claim that their product is a safer alternative to Xalatan would need to be supported by data from adequate and well controlled studies. The Division provided advice on submitting the proprietary name and on the importance of clearly labeling the proposed different storage conditions for their product.

3. CMC

For details, see the CMC, Quality Microbiology and Biopharmaceutic reviews. The following summary is excerpted from the CMC review.

This application is not recommended for approval from Chemistry, Manufacturing, and Controls (CMC). The Office of Compliance has issued a recommendation of Withhold for this NDA. The applicant has been requested to update NDA with the correct dosage form of emulsion and the revised acceptance criteria. The final Biopharmaceutics review dated October 17, 2014 and Quality Microbiology review dated September 26, 2014 recommend approval.

[1]From the January 26, 2009 meeting minutes:
Latanoprost ophthalmic (b) (4) *administered once a day in the evening is an acceptable positive control agent for IOP lowering studies. To establish equivalence, the two sided, 95% confidence interval should be within 1.5 mmHg for all IOP measurement time points and within 1.0 mmHg for the majority of IOP measurement time points. IOP measurements should be evaluated at 8am, 10am and 4pm at baseline, Week 1, Week 6 and Week 12. Each time point should be evaluated separately. It is expected that a comparison of the mean IOP at each time point will be evaluated.*

Xelpros® is an emulsion composed of [redacted] ([redacted] Water for Injection (WFI), boric acid, sodium borate, edentate disodium, and potassium sorbate) and [redacted] ([redacted] castor oil, latanoprost, and [redacted]). The formulation has a different composition than the reference drug Xalatan®. Xelpros® is described as an off-white, translucent, isotonic, sterile emulsion. It is buffered to [redacted] and is preserved using potassium sorbate, NF. As such, SPARC's formulation of latanoprost ophthalmic emulsion is not preserved with benzalkonium chloride, in contrast to the RLD. The applicant has described the proposed drug product as a "microemulsion." "Microemulsion" is not a recognized dosage form. The ONDQA CMC review has determined that the proposed drug product is an emulsion.

Latanoprost ophthalmic emulsion, 0.005% w/v, 2.5 ml will be manufactured, processed, packaged, labeled and held by Sun Pharmaceutical Industries Ltd.–Halol. Testing to assure the identity, quality, purity and stability of the finish dosage form will be performed by Sun Pharmaceutical Industries Ltd.–Halol.

The drug product is sterilized by [redacted] manufacturing aspects were found adequate. SPARC has also conducted a microbial challenge test to evaluate the integrity of the selected container closure system components. Samples of sterile media (soybean casein digest medium) were packaged in the proposed container closure system, and incubated for 14 days. At the end of the study, no growth was observed in the test container compared to the positive control.

The container closure was qualified and evaluated on results of the extractable study, drop count study, weight loss study, and photostability study. The container closure system was found suitable per USP <87>. The drop size and drug content of each drop of latanoprost ophthalmic emulsion drug product is approximately [redacted]µg and 1.51µg respectively.

The proposed 24-month tentative expiration-dating period to be assigned to latanoprost ophthalmic emulsion 0.005% w/v when stored [redacted] is acceptable based on the stability data provided. The stability results show that the opening of the proposed container and use of the dropper does not affect the quality of the proposed drug product up to 45 days.

[redacted] also known as, polyoxyl 15 hydroxystearate, and [redacted] is supplied by [redacted] and used in the proposed formulation as [redacted] Ph.Eur. is not listed by FDA as an inactive ingredient in approved drugs; as such, it is considered a "novel" excipient. However, this excipient is contained in approved drug products in Canada [redacted] and Argentina [redacted]. Data exist regarding its safety in animals including repeated dose intravenous toxicity studies in rats and dogs of 3-month and 1-month duration, respectively. The animal safety data generated with the proposed ophthalmic emulsion are presented and discussed in the NDA and IND 102842 Pharmacology/Toxicology Reviews. [redacted] does not cause direct ocular toxicity but does have the potential to cause sensitization reactions.

The sponsor submitted a request for BA/BE waiver and was found acceptable based on the Biopharmaceutics Review.

The following CMC comments will be included in the Complete Response Letter:

1. Please update the NDA submission in all appropriate sections to indicate the correct dosage form of ophthalmic emulsion. This can be accomplished by submission of an "Erratum" page with a statement that throughout the NDA the product name was corrected from "latanoprost ophthalmic (b) (4) to "latanoprost ophthalmic emulsion."

2. The release and stability data indicate that the proposed acceptance limits for (b) (4) (specified identified impurity) and highest unspecified impurity can be tightened. Please revise the limits to the above referenced impurities to NMT (b) (4) % for release and stability.

Comment:
This application is not recommended for approval from Chemistry, Manufacturing, and Controls (CMC). The final inspection recommendation is OAI and the Office of Compliance has issued a Withhold recommendation for this NDA. Comments requesting the NDA be updated with the correct name of the product (latanoprost ophthalmic emulsion) and revised acceptance criteria will be sent to the applicant.

4. Nonclinical Pharmacology/Toxicology

For details, see the Pharmacology/Toxicology Review. A brief summary it provided below.

SPARC is relying on FDA's prior findings of efficacy and safety of latanoprost, as summarized in the most current labeling (revised August 2012) for the active pharmaceutical product. In addition, SPARC performed repeated-dose ocular toxicity studies of up to 180-day duration in dogs and rabbits to evaluate the systemic and local ocular toxicities of the new formulation. To provide information on the safety of (b) (4) SPARC provided full study reports of (b) (4) conducted studies.

In dogs, findings included an increased incidence of mild to moderate scleral congestion compared to controls (saline, placebo, and (b) (4) and miosis at all latanoprost doses (QD, BID, and QID). The miosis was an expected pharmacological effect. These findings reversed during the recovery period. There was no ocular NOAEL. No adverse systemic findings were observed in any of the latanoprost dose groups or (b) (4) alone arm (0.25% QID).

In rabbits, mild lacrimation and redness in the conjunctiva were observed at the latanoprost high dose (QID). These findings reversed during the recovery period. There were no adverse systemic findings. The NOAEL was the mid dose (BID). No ocular or adverse systemic findings were observed in the (b) (4) alone arm (0.25% QID). The ocular findings observed in the nonclinical studies are consistent with those observed in the clinical trials. Ocular findings in the clinic included ocular hyperemia, conjunctival hyperemia, and eye discharge. The sensitivity for the occurrence of miosis appears to be species dependent. Its occurrence in human following treatment with latanoprost is not common.

To evaluate the ocular safety of (b) (4) the above studies included an additional arm using this excipient. Systemic safety of (b) (4) was evaluated in repeated-dose oral toxicity studies in rats of up to 180- day duration. Intravenous administration of (b) (4) 0.25% to rats resulted in lipid accumulation in the sinus endothelial cells in the liver and spleen and an increase in the number and size of small granulomas (containing lipid droplets with brown pigment granules) in the liver. The lipid deposits were presumed to represent denaturation products of stearic acid.

Intravenous administration of (b) (4) to beagle dogs resulted in signs of an allergic reaction (pruritus, erythema, wheals) at doses ≥50 mg/kg which resolved within 15-60 min postdose.

In an embryofetal development toxicity study in rabbits, there was a significant increase (2.4-fold) in the number of resorptions and post-implantation loss and a decrease in live fetuses at the high (b) (4) dose of 464 mg/kg/day IV administered during organogenesis. In addition, fetal incidences of misaligned sternebrae and total skeletal variations were increased at this dose.

The exposure margins (based on mg/m^2) for systemic toxicities observed after IV dosing with (b) (4) are over 1,600X; those for the observed embryotoxicity are over 27,000X. The magnitude of the exposure margins indicate that similar findings are unlikely to be observed in the clinic at the intended clinical dosing regimen.

SPARC conducted a comparative plasma and ocular tissue distribution study of Xelpros and Xalatan®. The main differences in ocular tissue distribution include higher levels of latanoprost in the vitreous, optic nerve, and retina and lower levels in the conjunctiva, iris/ciliary body, and lens observed in Xelpros 0.005% compared to Xalatan®. Latanoprost free acid plasma levels were low for both formulations. The observed differences did not translate into differences observed in the general toxicity studies.

The nonclinical studies presented provide adequate safety information to support the intended dosing regimen of Latanoprost Ophthalmic (b) (4) 0.005% in humans. Approval is recommended.

Comment:
I concur with the conclusions reached by the pharmacology/toxicology reviewers to recommend approval. Labeling revisions have been incorporated in labeling.

5. Clinical Pharmacology/Biopharmaceutics

The following excerpts are from the Clinical Pharmacology Review:

Latanoprost is a prodrug analog of prostaglandin F2α; upon absorption into the cornea, it is converted to the active moiety, latanoprost acid, which has high affinity and selectivity for the FP subtype of prostanoid receptors. Latanoprost is believed to reduce intraocular pressure

(IOP) by increasing uveoscleral aqueous humor outflow, thereby reducing the pressure within the eye and reducing the risk of nerve damage and blindness.

The sponsor submitted a request for BA/BE waiver, which is acceptable based on the consideration that the differences in formulation between Xalatan and the proposed SPARC latanoprost ophthalmic (b) (4) 0.005% are not expected to influence the limited systemic exposure to latanoprost/latanoprost acid following topical ocular administration.

In conclusion, no labeling revisions (with respect to Section 12.3 Pharmacokinetics) are needed for this NDA from a clinical pharmacology perspective. NDA 206185 for latanoprost ophthalmic (b) (4) 0.005% is recommended for approval from a clinical pharmacology perspective.

Comment:
I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewers to recommend approval. There are no outstanding clinical pharmacology issues.

6. Clinical Microbiology

Not applicable

7. Clinical/Statistical-Efficacy

For details, see the Clinical and Statistical reviews. A brief summary is provided below. Four clinical studies were submitted, two controlled Phase 3 studies were reviewed for efficacy while an extension study CLR_09 _13 and pilot study CLR_10_01 were only evaluated for safety.

Table 1: Summary of Studies Reviewed

Study Number / Study Phase	**Study Objective**	**Study Design**	**Treatment groups (Number of Subjects)**	**Duration of Treatment/ Primary Efficacy endpoint**	**Study Population**
CLR_09_12 (U.S.) / Phase 3	Test the non-inferiority of Xelpros relative to Xalatan® for the reduction of IOP	Multicenter, assessor-masked, randomized, active-controlled, parallel group, non-inferiority study. Visits on Days -35, -7, 0, 7, 28, 56, and 84.	Xelpros (N = 289) Xalatan® (N = 289)	Once daily for 12 weeks / Change from baseline in intraocular pressure (IOP)	Patients diagnosed with open angle glaucoma or ocular hypertension and had un-medicated IOP ≥ 22 mmHg at the eligibility visit

CLR_08_01 (India)/ Phase 3	Compare the efficacy and safety of Xelpros with Xalatan® in subjects with OAG or OH	Multicenter, open label, randomized, active-controlled, parallel group. Visits on Days -7, 0, 8, 15, and 29.	Xelpros (N = 53) Xalatan® (N = 51)	Once daily for 4 Weeks / Reduction of IOP compared to baseline	Patients diagnosed with open angle glaucoma or ocular hypertension and screening IOP≥22.

Source: Table 2.7.3-1 of Applicant's Summary of Clinical Efficacy
Note: Study CLR_09_13 was an extension of Study CLR_09_12 designed for safety follow-up and Study CLR_10_01 was a Pilot study.

Source Statistical review, page 7

Study CLR_09_12 was a multicenter, assessor-masked, Phase 3, active-controlled, parallel group, randomized study of 12 week duration designed to evaluate the safety and IOP lowering efficacy of Xelpros relative to Xalatan® in adult patients with open angle glaucoma and ocular hypertension. In the study, a total of 578 subjects were randomized in a 1:1 ratio to receive either Xelpros (n=289) or Xalatan® (n=289) once daily at 8 PM.

At each investigational center, subjects were stratified by the eligibility visit IOP group (Low: 22-28 mmHg versus High: 29-35 mmHg group) in the study eye. According to the study protocol, the study eye was defined as the eye with higher IOP at the eligibility visit or if equal, subjects with an even randomization number were assigned the left eye and with an odd number the right eye.

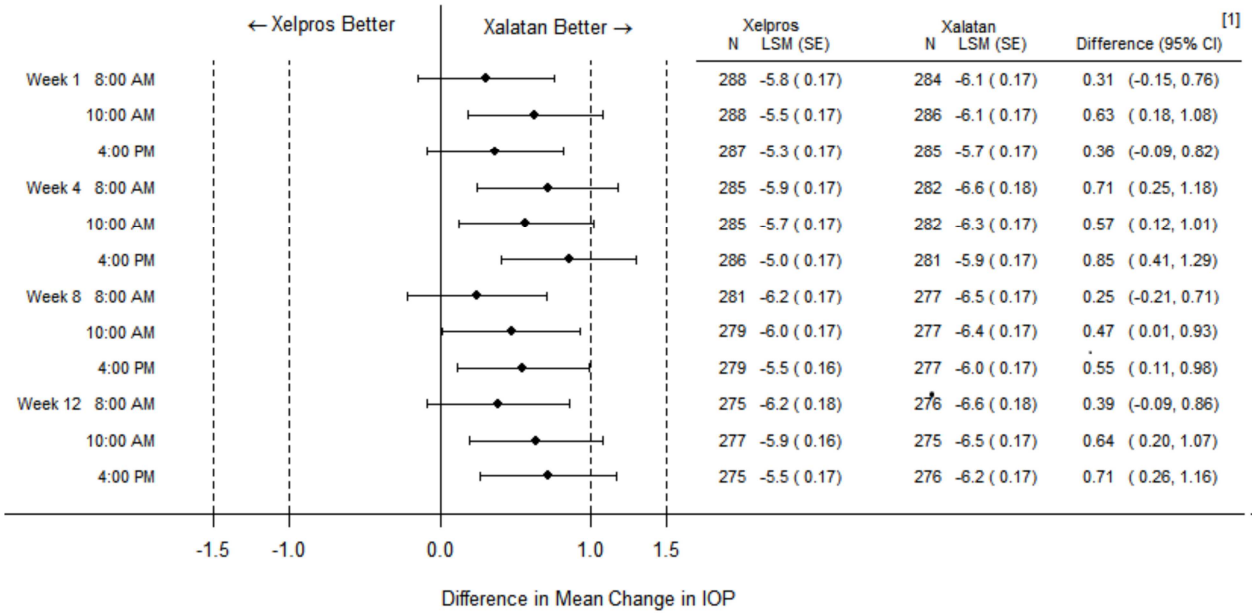
The primary efficacy endpoint of the study was the change in IOP from baseline evaluated at 8 AM, 10 AM, and 4 PM at the following visits: week 1, week 4, week 8, and week 12. The primary efficacy analysis of the study was based on the intent-to-treat (ITT) analysis population, and used the change from baseline in IOP as the primary efficacy variable. Analysis of covariance (ANCOVA) methodology with the change from baseline in IOP as the response variable and treatment, site, and baseline IOP as covariates was used in the statistical reviewer's primary efficacy analysis. The difference in the mean change in IOP between the treatment groups (Xelpros minus Xalatan®) was determined based the least square means using the ANCOVA model. Based on the model, non-inferiority of Xelpros to Xalatan® was established if the upper limit of the 95% CI for the difference in the mean change in IOP was <1.5 mmHg throughout the study (Statistical Criterion) and was < 1 mmHg at the majority of time points (Clinical Criterion).

Within the ITT analysis population, the majority of subjects in the study were white (68%) and female (63%). The average age of patients in the study was 65 years (range 27 to 88 years), about 53% of patients in the Xelpros group and 44% of patients in the Xalatan® group were ≥ 65 years of age. No marked difference between the treatment groups was observed in terms of the demographic characteristics.

The Medical Officer reports that for the Difference in Mean Change in IOP from Baseline for the ITT population without LOCF, the 95% confidence interval is within 1.5 mmHg for all time points, and the within 1.0 mmHg for 4 of 12 time points. Thus, SPARC latanoprost 0.005% has not demonstrated equivalence with Xalatan (latanoprost ophthalmic solution) 0.005%. For the Difference in Mean Change in IOP from Baseline – ANCOVA, for the ITT

population Observed Cases, the 95% confidence interval is within 1.5 mmHg for all time points and the within 1.0 mmHg for 6 of 12 time points. Thus, SPARC latanoprost 0.005% has demonstrated equivalence with Xalatan (latanoprost ophthalmic solution) 0.005% using the division's definition for this population.

Figure 1: Difference in Mean Change in IOP (mmHg) – ANCOVA Using Baseline IOP (CLR_09_12) (ITT Analysis Population, Observed Cases)



Source: Statistical review page 5.

Sensitivity Analyses were performed to assess the effect of missing data on the primary efficacy endpoint. Non-inferiority was not established for the ITT population analyzed with last observation carried forward, the ITT population with baseline observation carried forward or the ITT population with multiple imputations. The conclusions for these analyses were consistent with the primary analysis without imputations. (Source: MOR page 37)

The treatment and covariate adjusted mean IOP reductions from baseline throughout the study ranged from 5.0 to 6.2 mmHg in the Xelpros group and from 5.7 to 6.6 mmHg in the Xalatan® group. The test drug, Xelpros, demonstrated significant IOP reductions from baseline throughout the study; however, it was less effective compared to the active-control, Xalatan®, by about 0.3 to 0.9 mmHg units. (Source: Statistical Review, page 15)

The adjusted mean IOP ranged from 17.7 to 18.4 mmHg in the Xelpros group and from 17.0 to 18.1 mmHg in the Xalatan group. The mean IOP at each time point of each visit was lower in the Xalatan group. Xelpros was less effective in lowering IOP compared to Xalatan by about 0.5 mmHg. (Source: MO Review page 38)

The percentage of subjects who achieved IOP level of < 18 mmHg and the percent reduction in IOP of ≥ 30%, respectively, ranged from 47% to 56% and 26% to 38% in the Xelpros group and from 48% to 61% and 30% to 44% in the Xalatan® group. In both efficacy measures,

subjects in the Xalatan® group performed slightly better at all visits and time points compared to subjects in the Xelpros group. (Source: Statistical Review, page 18)

Miscoding of Data

Regarding the miscoding of patients and study visits, please see the MO Review page 9-10 and Statistical Review, page 8. This issue was identified and communicated to the applicant on June 5, 2014; the Statistical Reviewer was not able to reproduce the applicant's primary efficacy results as presented in the study report. The applicant responded that the ADaM dataset was correct but the study report was generated using an intermediate dataset. A second issue communicated on July 15, 2014, was that the link between visits 1, 2, 3 and 4 and week 1, 4, 8, and 12, respectively, resulted in the end-of-study visit linked to the week 12 visit even for early terminated subject. However, the amended Clinical Study Report and updated dateset submitted on September 3, 3014, still did not resolve the discrepancies. The Statistical Reviewer was initially unable to reproduce the primary efficacy results due to the difference in ADaM dataset which rounded the IOP data up (0.5 or greater) or down (0.49 or lower) to the nearest integers versus the updated dataset which used the actual IOP value used. The results were finally reproduced when the unrounded IOP data were used. Although there was no issue with the applicant using either the rounded or unrounded IOP data to produce the primary efficacy results, the applicant should have clearly communicated all the changes made when the updated dataset was submitted to the Agency.

Study CLR_08_01 was a multicenter, open label, Phase 3, active-controlled, parallel group, randomized study designed to evaluate the safety and IOP lowering efficacy of Xelpros relative to Xalatan® in adult patients with open angle glaucoma or ocular hypertension, conducted at eleven centers in India.

A total of 104 subjects 18 years or older with IOP ≥ 22 mmHg in one or both eyes, with no more than 5 mmHg inter-eye difference at the screen visit were enrolled in the study and randomized to Xelpros n=53 or Xalatan n=51. The study duration was four weeks and included five visits: screen (day -7 to -1), randomization (Day 0), and three follow-up visits: Days 8 to 10 (Visit 3), Days 15 to 17 (Visit 4), and Days 29 to 31 (Visit 5). Eye drops were given once daily in the evening for four weeks in one or both eyes as affected. The study eye was the eye with higher IOP at enrollment or if equal, subjects with an even randomization number were assigned the left eye and an odd number the right eye. IOP was measured twice at each study visit, − before administration of drug in the evening (trough effect) and 12-18 hours after administration of drug product in the following morning (peak effect).

The primary objective of study CL_08_01 was to demonstrate equivalence in IOP lowering efficacy of Xelpros to Xalatan® at the through and peak effect of the treatment. The primary endpoint of the study was the change in IOP from baseline during the morning and evening time points of each study visits at Day 8, Day 15, and Day 29. The applicant used the two samples independent T-test for the primary efficacy analysis, and the difference in the mean change in IOP between the treatment groups was determined based on the t-test. In the applicant's primary analysis, missing observations were imputed by LOCF method.

This study demonstrated a statistically significant change in mean IOP from baseline to both

time points at each study visit for both the Xelpros and Xalatan ($p<0.0001$) treatment groups. Although Xelpros demonstrated significant IOP reductions throughout the study, it was less effective compared to Xalatan® at the majority of time points during the study. However, the study did not meet both the statistical and clinical criteria for equivalence since at the majority of time points the two-sided 95% CIs were not within ± 1.5 mmHg. The reason for this may be due to the small sample size.

Comment:
In summary, study 12 met the pre-defined criteria for efficacy based on one analysis, but efficacy for Xelpros was less than for Xalatan; the latter lowered IOP by approximately 0.3 to 0.9 mmHg compared to Xelpros. The results of study 08 support the finding of efficacy but did not meet the statistical and clinical criteria for equivalence, possibly due to the small sample size.

8. Safety

For further details, the Clinical and Statistical Reviews should be consulted. A brief summary is provided below. Four studies were reviewed for safety information, and are tabulated below:

Study Number / Study Phase	Study Design	Treatment Groups (Numbers of Subjects Treated)	Duration of Treatment / Age
Study CLR_08_01 (India) Phase 3	Multicenter, open-label, randomized, active-controlled, parallel group. Visits on Days -7, 0, 8, 15, and 29.	SPARC latanoprost (N=53) Xalatan (N=51)	Once daily for 4 weeks Age ≥ 18 years
Study CLR_10_01 (India) Pilot	Multicenter, open-label, Single arm, pilot Visits on Days 0, 28, and 56.	Subjects previously treated with Xalatan® were switched over to BAK-free SPARC latanoprost (N=25 subjects, 46 eyes)	Once daily for 8 weeks Age ≥ 18 years
Study CLR_09_12 (US, IND 102,842) Phase 3	Multicenter, assessor-masked, randomized, active-controlled, parallel group, non-inferiority study. Visits on Days -35, -7, 0, 7, 28, 56, and 84	SPARC latanoprost (N=289) Xalatan® (N=289)	Once daily for 12 weeks Age ≥ 18 years
Study CLR_09_13 (US, IND 102,842) Phase 3	Multicenter, open-label, non-randomized, uncontrolled, single group assignment. Visits at Weeks 1, 4, 8, 12, 16, 20, 24, 28, 32, and 36.	Single group, all subjects received SPARC latanoprost (open label extension of prior Study CLR_09_12) (N=161)	Once daily for 36 weeks Age ≥ 18 years

Note: SPARC latanoprost 0.005% is the name used by the applicant during product development. SPARC latanoprost 0.005%
and Xelpros (latanoprost ophthalmic emulsion) are interchangeable terms.
Adapted from applicant Table 2.5.1-1 and MO Review, page 44.

Based on the pooled analysis of the four studies, there were 448 patients treated with Xelpros and 340 treated with Xalatan/reference drug. The vast majority of patients received at least 12 weeks of treatment. There were no deaths reported in these studies. Serious adverse events were reported in 2% Xelpros and 1% Xalatan patients. Discontinuation from the study was reported in 25% of Zelpros and 5% Xalatan patients.

Subject Disposition	**Treatment Group [1]**		
	Xelpros 0.005%	**Xalatan 0.005%**	**Total**
Subjects screened	---	---	867
Screening failures	---	---	160
Subjects randomized	---	---	707
Subjects not treated	---	---	0
Subjects Included in ISS Analysis Set	448	340	707
Subjects with ≥ 1 dose study drug [2]	448	340	707
Subjects completed study	334 (74.6%)	324 (95.3%)	577 (81.6%)
Subjects discontinued from the study	114 (25.4%)	16 (4.7%)	130 (18.4%)
Reasons for Discontinuation			
Withdrawal of Consent	76 (17.0%)	7 (2.1%)	83 (11.7%)
Protocol Violation	7 (1.6%)	1 (0.3%)	8 (1.1%)
Adverse Event	5 (1.1%)	2 (0.6%)	7 (1.0%)
Withdrawal of Subject by Investigator	10 (2.2%)	1 (0.3%)	11 (1.6%)
Lost to follow up	6 (1.3%)	2 (0.6%)	8 (1.1%)
Study Terminated by Sponsor	7 (1.6%)	2 (0.6%)	9 (1.3%)
Study Medication Failure	3 (0.7%)	1 (0.3%)	4 (0.6%)

1 81 subjects switched therapy from the Reference drug in Study CLR_09_12 to the Test drug in Study CLR_09_13. They both contributed data to both treatment groups. All subjects were counted once in the Total column.
2 Percentage was calculated based on the number of subjects treated with ≥ 1 dose of study drug in each group.
Source: ISS Table 14.1.1.1

Source: MO Review, page 50

Eye pain was reported in 55% or Xelpros subjects and 40% of Xalatan patients in the pooled analysis of the four studies. Other ocular adverse reactions appeared to be reported at fairly comparable rates. (Source: Application Module 5.3.5.3.2-Integrated Summary of Safety, Table 3 Summary of disposition-all screened subjects; and Table 10, TEAE's by preferred term occurring in >1% of subjects).

Because of the imbalances in discontinuation in the pooled analysis of the efficacy and safety studies, controlled and uncontrolled studies, the results of Study CLR_09_12 were examined separately since this represents an adequate and well controlled study of design and duration recommended by the Division.

In Study CLR_09_12, 95% of patients received greater than 70 days of treatment. The safety profiles between Xelpros and Xalatan® in Study CLR_09_12 showed that approximately 80% of subjects experienced at least one AE, and at least 1.4% of subjects in the study experienced

at least one serious AE. The most frequently reported AEs in each treatment group was eye pain, it was reported by 64% of Xelpros patients and 47% Xalatan patients. Other adverse events were reported in fairly comparable rates.

Table 10: Treatment-Emergent AEs occurring in ≥1% of subjects in any treatment group (CLR_09_12) (Safety Analysis Population)

System Organ Class/ Preferred Term	Xelpros (N = 289)	Xalatan (N = 289)
Eye disorders	**238 (82.4%)**	**231 (79.9%)**
Eye pain	185 (64.0%)	136 (47.1%)
Ocular hyperaemia	135 (46.7%)	143 (49.5%)
Conjunctival hyperaemia	58 (20.1%)	55 (19.0%)
Eye discharge	39 (13.5%)	41 (14.2%)
Growth of eyelashes	27 (9.3%)	36 (12.5%)
Eyelash thickening	15 (5.2%)	17 (5.9%)
Eye pruritus	16 (5.5%)	14 (4.8%)
Visual acuity reduced	11 (3.8%)	12 (4.2%)
Erythema of eyelid	9 (3.1%)	13 (4.5%)
Dry eye	12 (4.2%)	5 (1.7%)
Foreign body sensation in eyes	6 (2.1%)	5 (1.7%)
Punctate keratitis	1 (0.3%)	9 (3.1%)
Vision blurred	3 (1.0%)	7 (2.4%)
Chalazion	2 (0.7%)	7 (2.4%)
Blepharitis	3 (1.0%)	4 (1.4%)
Eyelash discolouration	5 (1.7%)	2 (0.7%)
Lacrimation increased	2 (0.7%)	4 (1.4%)
Meibomianitis	3 (1.0%)	3 (1.0%)
Eyelid margin crusting	4 (1.4%)	1 (0.3%)
Eyelid oedema	5 (1.7%)	0 (0.0%)
Conjunctival oedema	3 (1.0%)	1 (0.3%)
Conjunctival haemorrhage	0 (0.0%)	3 (1.0%)
Infections and infestations	**20 (6.9%)**	**12 (4.2%)**
Upper respiratory tract infection	8 (2.8%)	0 (0.0%)
Sinusitis	4 (1.4%)	0 (0.0%)
Nasopharyngitis	0 (0.0%)	3 (1.0%)
Investigations	**4 (1.4%)**	**5 (1.7%)**
Corneal staining	1 (0.3%)	3 (1.0%)
Musculoskeletal and connective tissue	**7 (2.4%)**	**2 (0.7%)**
Rotator cuff syndrome	3 (1.0%)	0 (0.0%)
Nervous system disorders	**4 (1.4%)**	**7 (2.4%)**
Headache	3 (1.0%)	5 (1.7%)
Psychiatric disorders	**2 (0.7%)**	**4 (1.4%)**
Anxiety	2 (0.7%)	3 (1.0%)
Skin and subcutaneous tissue disorders	**10 (3.5%)**	**5 (1.7%)**
Rash	3 (1.0%)	0 (0.0%)
Vascular disorders	**1 (0.3%)**	**6 (2.1%)**
Hypertension	1 (0.3%)	6 (2.1%)

Source: Adapted from Section 2.7.4, Table 2.7.4-10 of submission and statistical Review, page 25

Reviewer Comment:

Based on further review of the application, the Medical Officer located information on the mapping of preferred terms and literal terms used in the diary reported by patients (Source: NDA 206185, Table 14.3.1.2.1.2, pages 309 of 510, CLR_09_12) The literal terms that were mapped to "Eye Pain" included transient stinging, stinging, ocular stinging, transient ocular

stinging and mild ocular stinging. The information on stinging associated with the instillation of the medication will be included in labeling.

In CLR_08_01, there was an imbalance in the subjects who discontinued (page 40/72 MOR): Xelpros 8/53 (15%) vs. Xalatan 3/51 (6%). Adverse reactions reporting was overall much lower than in the US study, with approximately 14% of subjects reporting ocular adverse reactions. Eye pain was reported by one Xalatan patient, eye irritation was reported by four Xelpros patients. (Source: Module 5.3.5.1, CLR_08_01 study report)

Study Disposition of Randomized Subjects

	Total N (%)	Number (%) of Subjects	
		Test	Reference
Randomized	104	53	51
Received study medication	104(100)	53(100)	51(100)
Completed study	93(89.42)	45(84.91)	48(94.12)
Discontinued	11(10.58)	8(15.09)	3(5.88)
Major Protocol Violation	2(1.92)	1(1.89)	1(1.96)
Consent Withdrawn	2(1.92)	2(3.77)	0(0)
Subject Lost to Follow-up	6(5.77)	4(7.55)	2(3.92)
Failure of study medication	1(0.96)	1(1.89)	0(0)
Analyzed for efficacy	104(100)	53(100)	51(100)
Analyzed for safety	104(100)	53(100)	51(100)

Source: Table D1, D4

MedDRA System Organ Class / Preferred Term	Test n=53 n (%)	Reference n=51 n (%)
OCULAR		
Eye Disorders	8(15.09)	6(11.76)
Conjunctivitis	2(3.77)	0(0)
Dry eye	0(0)	1(1.96)
Eye discharge	0(0)	1(1.96)
Eye irritation	4(7.55)	0(0)
Eye pain	0(0)	1(1.96)
Eye pruritus	1(1.89)	3(5.88)
Eyelid disorder	1(1.89)	0(0)
Eyelid oedema	0(0)	1(1.96)
Foreign body sensation in eyes	0(0)	1(1.96)
Keratitis	0(0)	1(1.96)
Lacrimation increased	0(0)	2(3.92)
Meibomianitis	1(1.89)	0(0)
Ocular hyperaemia	1(1.89)	2(3.92)
Retinal vein occlusion	1(1.89)	0(0)
Vision blurred	0(0)	1(1.96)
Vitreous floaters	1(1.89)	0(0)
NON OCULAR		
Body as a Whole	4(7.55)	2(3.92)
Ear and labyrinth disorders	1(1.89)	0(0)
Vertigo	1(1.89)	0(0)
Gastrointestinal disorders	0(0)	1(1.96)
Epigastric discomfort	0(0)	1(1.96)
Infections and infestations	1(1.89)	0(0)
Urinary tract infection	1(1.89)	0(0)
Musculoskeletal and connective tissue disorders	1(1.89)	0(0)
Pain in extremity	1(1.89)	0(0)
Nervous system disorders	2(3.77)	1(1.96)
Headache	2(3.77)	0(0)
Migraine	0(0)	1(1.96)

Source: Table S2.3.1

In Study CLR_09_13, the extension study, 153 subjects were followed for 36 weeks.

Comment:
SPARC stated their development of this new emulsion formulation containing a new stabilizer and using potassium sorbate instead of benzalkonium chloride as preservative was intended to create a formulation that had less toxicity. However, while the adverse reaction profile of Xelpros is fairly comparable to Xalatan for most ocular adverse reactions, there is a notably higher percentage of patients reporting eye pain with Xelprox than Xalatan. Overall, in this Phase 3 trial this adverse reaction was not associated with more discontinuation on the Xelpros arm than Xalatan arm.

9. Advisory Committee Meeting

This is a new dosage form (emulsion) of a marketed product. The application did not identify scientific issues for presentation and discussion at the Advisory Committee meeting.

10. Pediatrics

The Pediatric Review Committee agreed on August 13, 2014, with the applicant's proposal that pediatric studies be waived because the necessary studies would be impossible or highly impracticable because there are too few children with glaucoma to study.

11. Other Relevant Regulatory Issues

11.1 Office of Compliance Facility Inspections

Manufacturing facilities are not acceptable, the recommendation from compliance is Withhold approval.

11.2 Office of Scientific Investigation (OSI) Audits

Inspections of three investigators were completed; two were no issued Form FDA 483s, and the final classification of these inspections was No Action Indicated (NAI). One clinical site was issued a Form FDA 483, and the final classification of this inspection was Voluntary Action Indicated (VAI). OSI recommended that the data generated by these clinical sites appear adequate.

11.3 Debarment certification

Pursuant to section 306(k)(I) of the Federal Food. Drug and Cosmetic Act, as amended by the Generic Drug Enforcement Act of 1992, Sun Pharma Advanced Research Company Ltd. hereby certifies that it did not and will not use, in any capacity, the services of any person debarred under subsection (a) or (b) of the Generic Drug Enforcement Act of 1992 in connection with this NDA.

11.4 Financial Disclosure

(b) (4) has adequately disclosed financial arrangements with the clinical investigators who participated in the clinical development program for latanoprost 0.005%. None of the investigators had financial arrangements or interests to disclose.

11.5 Other Regulatory Issues

This is a 505(b)(2) application relying on the non-clinical information from Xalatan. The application was evaluated in this cycle, but is not cleared at this time because of the pending Complete Response action.

12. Labeling

- The proprietary name Xelpros for latanoprost ophthalmic emulsion 0.005% was found acceptable and the applicant notified via letter on 5/19/2014. It will need to be reviewed again before an approval action.
- Physician labeling (PLR) has been finalized and input from the reviewers and consultants was discussed and incorporated as applicable. The labeling has been updated to make it consistent with Xalatan.
- Carton and immediate container labels have been finalized; input from reviewers and consultants was discussed and changes incorporated as applicable
- Patient labeling/Medication guide – these are not proposed for the current product

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action

NDA 206185 will receive a *Complete Response* letter due to manufacturing facility deficiencies, outstanding CMC requests. Labeling was not discussed with the applicant during this cycle, given the facility inspection deficiencies. The labeling submitted is in PLR format but not consistent with the planned Xalatan PLR labeling revisions. The Division will include revised labeling (package insert, carton and container labels) with the CR letter.

- Risk Benefit Assessment

Glaucoma is a life-long progressive disease that is characterized by irreversible damage to the optic nerve and corresponding loss of visual field. One of the primary risk factors is elevated intraocular pressure (IOP). The reduction and control of elevated IOP in open angle glaucoma and ocular hypertension is usually managed by chronic, long-term topical ocular therapy.

There are currently multiple topical products in several classes available for the reduction of IOP, including beta-adrenergic antagonists (beta-blockers), alpha-adrenergic agonists, parasympathomimetic (miotic) agents, carbonic anhydrase inhibitors, prostaglandin analogs, and some combination products. A complete list is included in the Medical Officer's Review and CDTL Review.

One controlled, randomized, single-masked clinical trial of 12 week duration was submitted that compared Xelpros to Xalatan (latanoprost ophthalmic solution) 0.005% . The results showed that Xelpros was within a 1.5 mmHg margin, but was not clinically equivalent at the 1 mmHg level. Xelpros reduced IOP about 0.5 mmHg less than Xalatan and was not as effective as Xalatan. Study CR_01_08 providing supportive evidence of efficacy, but failed to

meet either the 1.5 mmHg or 1 mmHg margin, possibly due to sample size. Xelpros reduced IOP by 5-6 mmHg, about 0.5 mmHg less effective than Xalatan.

In study CLR_09_12, the rates of discontinuation and adverse events for most ocular adverse reactions were comparable; with the exception of eye pain. The rate of eye pain was 64% on Xelpros and 47% on Xalatan.

Although Xelpros is approximately 10% less effective than Xalatan the reduction of IOP by 5-6 mmHg is clinically significant and clearly effective in lowering intraocular pressure. The incidence of eye pain was reported in 64% on Xelpros and 47% on Xalatan treated patients. The literal terms were mapped to the preferred term "Eye Pain" included transient stinging, stinging, ocular stinging, transient ocular stinging and mild ocular stinging. The stinging associated with the instillation of the medication will be included in labeling. Of note, there was no difference to the rate of discontinuation due to stinging on installation.

There are differences in the two formulations; Xelpros is an emulsion that contains potassium sorbate while Xalatan has benzalkonium chloride as the preservative. The formulation differences may in part account for the difference in irritation. Xelpros can provide another option in the treatment of patients with open angle glaucoma and ocular hypertension; patient and physician decisions to use this product may be based on various factors, including the anticipated benefit and risk of adverse reactions.

Manufacturing facility deficiencies need to be resolved. Two pending chemistry information requests regarding correction of the name (ophthalmic emulsion, not (b) (4)) and revision of acceptance criteria need to be submitted.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

None at this time

- Recommendation for other Postmarketing Requirements and Commitments

None at this time

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RENATA ALBRECHT
11/24/2014

Cross-Discipline Team Leader Review #2

Date	November 20, 2014
From	William M. Boyd, M.D.
Subject	Cross-Discipline Team Leader Review
NDA #	206185
Applicant	Sun Pharm Advanced Research Company Ltd. U.S Representative: Ora., Inc.
Date of Submission	January 31, 2014
PDUFA Goal Date	November 30, 2014
Type of Application	505(b)(2)
Name	Xelpros (latanoprost ophthalmic emulsion) 0.005%
Dosage forms / Strength	Topical ophthalmic emulsion
Proposed Indication(s)	Reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension
Recommended:	Not Recommended for Approval

NDA 206185, Xelpros (latanoprost ophthalmic emulsion) 0.005% is not currently recommended for approval for the reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension. Once the facilities to be used to manufacture the product are found to be in compliance with current good manufacturing procedures (cGMPs), approval is recommended with the draft labeling found in this CDTL review #2.

This product does not contain benzalkonium chloride. Section 4 of the draft package insert has been updated.

Container label - 2.5 mL (b) (4) in a 5 mL bottle

Comments:

"(b) (4)," should be revised to read, "For Topical Use in the Eye."

Carton label – single bottle presentation

Comments:

"(b) (4)," should be revised to read, "For Topical Use in the Eye."

Carton label – three (3) bottle presentation

Comments:

"(b) (4)," should be revised to read, "For Topical Use in the Eye."

9 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

WILLIAM M BOYD
11/20/2014

WILEY A CHAMBERS
11/20/2014

Cross-Discipline Team Leader Review

Date	November 19, 2014
From	William M. Boyd, M.D.
Subject	Cross-Discipline Team Leader Review
NDA #	206185
Applicant	Sun Pharm Advanced Research Company Ltd. U.S Representative: Ora., Inc.
Date of Submission	January 31, 2014
PDUFA Goal Date	November 30, 2014
Type of Application	505(b)(2)
Name	Xelpros (latanoprost ophthalmic emulsion) 0.005%
Dosage forms / Strength	Topical ophthalmic emulsion
Proposed Indication(s)	Reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension
Recommended:	Not Recommended for Approval

1. Introduction

Latanoprost is a prostaglandin analog, F2-α receptor agonist. Latanoprost is absorbed through the cornea where the isopropyl ester prodrug is hydrolyzed to latanoprost acid a derivative of prostaglandin F2-α which is biologically active. It is believed that latanoprost reduces intraocular pressure by increasing uveoscleral aqueous outflow from the eye.

The concentration of latanoprost selected for this application is 0.005% the same as the approved reference listed drug (RLD) Xalatan. However, Xalatan (NDA 20-597) which was approved in 1996 with once daily dosing for the reduction of elevated IOP in subjects with open-angle glaucoma or ocular hypertension is an ophthalmic solution, and the submitted latanoprost product is an emulsion.

For the proposed indication, a demonstration of efficacy is recommended to include equivalence or superiority to an acceptable active control, in this instance, Xalatan (latanoprost ophthalmic solution) 0.005% administered once a day in the evening. Equivalence is attained if the difference in mean IOP between treatment groups is within ±1.5 mm Hg at all post-baseline time points; and within ±1.0 mm Hg at the majority of post-baseline time points. The time points should include both the peak and trough efficacy times. Although equivalence is not required for approval it serves as a useful evaluation tool for IOP lowering products.

Latanoprost is currently available as Xalatan (latanoprost ophthalmic solution) 0.005%. There are also multiple generic formulations of latanoprost ophthalmic solution, 0.005% currently marketed.

Note: The ONDQA CMC review has determined that the proposed drug product is an emulsion. This determination was made at the time of NDA submission; some submitted application material may still incorrectly refer to the drug product as a "(b) (4)."

2. Background

A Pre-IND meeting was held on September 16, 2008, to discuss the development plans for IND 102,842 for latanoprost ophthalmic emulsion. Advice was given regarding CMC, nonclinical and clinical development including recommended study design, criteria for determining IOP equivalence and expectations for reformulations of an approved drug product in the preliminary comments and face-to-face meeting.

SPARC, Ltd. submitted an IND application for SPARC latanoprost ophthalmic emulsion 0.005% to the Agency in 2009. SPARC completed two clinical studies (CLR_09_12 and CLR_09_13) under this IND in 2012. Recommendations for a minimum of 100 patients followed for 6 months in one of the studies as well as an evaluation of the endothelial cell counts were included in comments to the sponsor.

A Pre-NDA meeting was held on February 20, 2013, to discuss the results from the Phase 3 efficacy and safety studies performed by SPARC, Ltd. At this meeting, the Division reiterated the criteria for establishing IOP equivalence and expected safety information in light of the study results submitted.

There are many ophthalmic drug products approved for lowering intraocular pressure in patients with open-angle glaucoma and ocular hypertension. These treatments include beta-adrenergic antagonists (beta-blockers), alpha-adrenergic agonists, parasympathomimetic (miotic) agents, carbonic anhydrase inhibitors, and prostaglandin analogs.

Drug Products with Approved NDAs

Pharmacologic Class/ Applicant	**Trade Name**	**Established Name**
Alpha-2 agonists		
Allergan, Inc.	Alphagan/ Alphagan P	brimonidine tartrate
Beta-adrenergic antagonists		
Alcon	Betoptic/ Betoptic S	betaxolol hydrochloride
Novartis	Ocupress	carteolol hydrochloride
Allergan	Betagan	levobutanol hydrochloride
Bausch & Lomb	Optipranolol	metipranolol
Vistakon	Betimol	timolol hemihydrate
Aton Pharma	Timoptic	timolol maleate
Ista	Istalol	timolol maleate
Aton Pharma	Timoptic XE	timolol maleate gel forming solution
Carbonic Anhydrase Inhibitors		
Duramed Pharamaceuticals	Diamox	acetazolamide

Pharmacologic Class/ Applicant	Trade Name	Established Name
Sandoz, Inc.	N/A	methazolamide
Topical Carbonic Anhydrase Inhibitors		
Alcon	Azopt	brinzolamide
Merck	Trusopt	dorzolamide hydrochloride
Cholinergic agonist		
Alcon	Pilopine HS	pilocarpine hydrochloride gel
Alcon	Isopto Carpine	pilocarpine hydrochloride
Prostaglandin Analogues		
Allergan	Lumigan	bimatoprost
Pharmacia	Xalatan	latanoprost
Alcon	Travatan	travoprost
Alcon	Travatan Z	travoprost
Merck	Zioptan	tafluprost
Alcon	Izba	travoprost
Sympathomimetics		
Allergan	Propine	dipivefrin hydrochloride
Combination Products		
Merck	Cosopt	dorzolamide hydrochloride/timolol maleate
Merck	Cosopt PF	dorzolamide hydrochloride/timolol maleate
Allergan	Combigan	brimonidine tartrate/timolol maleate
Alcon	BetopticPilo	betaxolol hydrochloride/pilocarpine hydrochloride
Alcon	Simbrinza	Carbonic anhydrase inhibitor/alpha-agonist
Other		
Sucampo Pharma Americas, Inc.	Rescula	unoprostone isopropyl

3. CMC

From the Product Quality Review finalized 10/24/14:

Sun Pharma Advanced Research Company (SPARC) has developed a new formulation of latanoprost that is prepared as an emulsion in aqueous phase. The formulation has a different composition than the reference drug Xalatan®. The proposed drug product, Xelpros is an emulsion composed of an (b) (4) Water for Injection (WFI), boric acid, sodium borate, edentate disodium, and

potassium sorbate) and [redacted] castor oil, latanoprost, and [redacted]). Xelpros® is described as an off-white, translucent, isotonic, sterile emulsion. It is buffered to [redacted] and is preserved using potassium sorbate, NF. As such, SPARC's formulation of latanoprost ophthalmic emulsion is not preserved with benzalkonium chloride, in contrast to the RLD, and storage is recommended [redacted].

Latanoprost ophthalmic emulsion, 0.005% w/v, 2.5 ml will be manufactured, processed, packaged, labeled and held by Sun Pharmaceutical Industries Ltd.–Halol. Testing to assure the identity, quality, purity and stability of the finish dosage form will be performed by Sun Pharmaceutical Industries Ltd.–Halol. The intended commercial batch size and exhibit batch size for Latanoprost ophthalmic emulsion, 0.005%, w/v, 2.5 ml, is [redacted] vials and [redacted] bottles respectively. The drop size and drug content of each drop of the drug product, packaged in the selected primary packaging materials, is approximately [redacted] µL and 1.51 µg, respectively.

DESCRIPTION AND COMPOSITION OF THE DRUG PRODUCT:

3.2.P.1 Description and Composition of the Drug Product [Latanoprost ophthalmic [redacted] 0.005%, Sun Pharmaceutical Industries Limited]

The components, their function, and quality are provided in *Table 3.2.P.1-1*.

Table 3.2.P.1-1. Components of Latanoprost ophthalmic emulsion, 0.005%

Component	Amount (per mL)	% w/v	Function	Reference to Quality Standards
Latanoprost	0.05	0.005	Active	In house
Potassium sorbate	4.70	0.47	Preservative	NF
Boric acid	[redacted]	[redacted]	[redacted]	NF
Edetate disodium				USP
Castor oil				USP
[redacted]				Ph.Eur.
Propylene glycol				USP
Sodium borate				NF
Hydrochloric acid				NF
Sodium hydroxide				NF
Water for injection				USP
[redacted]				

The proposed drug product will be supplied as a 2.5-mL [redacted] in a [redacted] 5-mL low-density polyethylene bottle with a low-density polyethylene (LDPE) dropper tip, equipped with a high- density polyethylene [redacted] screw cap.

PROPOSED REGULATORY SPECIFICATIONS:

Description	Off white to pale yellow translucent (b) (4)
Identification by HPLC	The retention time of the latanoprost peak in the chromatogram of the assay preparation corresponds to that of the standard preparation as obtained in the assay.
Identification by HPLC	The PDA spectrum, in the range of (b) (4) nm, of latanoprost peak in the sample preparation corresponds to that of latanoprost peak in standard preparation as obtained in the related substances method II.
pH	Between (b) (4)
Absorbance at 420 nm	Not more than (b) (4) AU
Osmolality	(b) (4) mOsm
Volume in container	Between (b) (4) mL
Volume variation	Between (b) (4)
Viscosity	(b) (4) cp – (b) (4) cp
Particle size distribution	D10: (b) (4) D50: D90:
Particulate Matter	NMT (b) (4) particles ≥ (b) (4) µm in diameter NMT (b) (4) particles ≥ (b) (4) µm in diameter NMT particle ≥ (b) (4) µm in diameter
Sterility	(b) (4)
Bacterial Endotoxins	Not more than (b) (4) EU/mL
Highest unspecified impurity – Method I	Not more than (b) (4) %
Total impurities – Method I	Not more than %
(b) (4) – Method II	Not more than %
Highest unspecified impurity – Method II	Not more than %
Total impurities – Method II	Not more than %
Assay – content of potassium sorbate (by HPLC)	Not less than (b) (4) %
Assay- of EDTA	(b) (4) mg/mL
Assay of Latanoprost by HPLC	(b) (4) % of label claim
(b) (4)	(b) (4)

The Product Quality Reviewer has identified the following two issues for inclusion in the action letter for this drug product:

1. The release and stability data indicate that the proposed acceptance limits for (b) (4) (specified identified impurity) and highest unspecified impurity can be tightened. Please revise the limits to the above referenced impurities to NMT (b) (4) % for release and stability.

2. Please update the NDA submission in all appropriate sections to indicate the correct dosage form of emulsion and the revised acceptance criteria or submit a cover page (i.e., an "Erratum" page) with a statement that the product name was revised to emulsion.

From a clinical prospective, there are no expected clinical consequences if the applicant does not change the specifications (b) (4) and the highest unspecified impurity from NMT (b) (4)% to NMT (b) (4)% (b) (4) (b) (4) in this product.

FACILITIES INSPECTIONS:
The Office of Compliance has not issued an acceptable recommendation on this NDA. Approval for this NDA is recommended only when all supporting sites have an acceptable recommendation.

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application:	NDA 206185/000	**Action Goal:**	
Stamp Date:	31-JAN-2014	**District Goal:**	01-OCT-2014
Regulatory:	30-NOV-2014		
Applicant:	SUN PHARMA ADV	**Brand Name:**	LATANOPROST 0.005% OPHTHALMIC (b) (4)
	300 BRICKSTONE SQ	**Estab. Name:**	
	ANDOVER, MA 01810	**Generic Name:**	LATANOPROST 0.005% OPHTHALMIC (b) (4)
Priority:	3	**Product Number; Dosage Form; Ingredient; Strengths**	
Org. Code:	590	001; (b) (4) DROPS; LATANOPROST; 0.005%	

Application Comment:

FDA Contacts:			
M. SLOAN	Prod Qual Reviewer		3017961464
R. MELLO	Micro Reviewer	(HFD-805)	3017961574
N. BHANDARI	Product Quality PM		2404023815
R. BLAY	Regulatory Project Mgr	(HFD-45)	3017963332

Overall Recommendation: PENDING on 21-FEB-2014 by EES_PROD

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** **FEI:** 3006560887
(b) (4)
DMF No: **AADA:**
Responsibilities: (b) (4)
Establishment Comment: (b) (4)
Profile: (b) (4) **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
Reason					
SUBMITTED TO OC	21-FEB-2014				BHANDARIN
OC RECOMMENDATION	30-JUL-2014			ACCEPTABLE	SAFAALIAZIR

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** 9611130 **FEI:** 3002809586
SUN PHARMACEUTICAL INDUSTRIES LTD.
HALOL-BARODA HWY HALOL-389350
HALOL, GUJARAT, INDIA
DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE OTHER TESTER
FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER

Establishment Comment: DRUG PRODUCT MANUFACTURER, PACKAGING, RELEASE TESTING AND STABILITY TESTING.
DRUG SUBSTANCE ACCEPTANCE TESTING (on 03-FEB-2014 by N. BHANDARI () 2404023815)

Profile: STERILE LIQUID (EXCLUDE SUSPENSIONS & EMULSIONS) **OAI Status:** POTENTIAL OAI

Milestone Name / Comment / OAI Submit To OC / Request to Extend Re-eval Date To / Extension Request Comment / Reason	Milestone Date	Request Type	Planned Completion	Decision	Creator
SUBMITTED TO OC	21-FEB-2014				BHANDARIN
SUBMITTED TO DO STERILE NO SLQ.	21-FEB-2014	10-Day Letter			WITTORFR
DO RECOMMENDATION	06-MAR-2014			ACCEPTABLE	PHILPYE
SUBMITTED TO DO	26-MAR-2014	Product Specific and GMP Inspection			SAFAAIJAZIR
NEW DOSAGE FOR ESTABLISHMENT - DO AC REC. PROVIDED BUT NO COMMENTS AS TO SLQ NOT BEING PROFILED. ALSO IT WILL BE MORE THAN 2 YRS SINCE LAST INSPECTION BY PDUFA GOAL DATE.					
ASSIGNED INSPECTION TO IB	11-APR-2014	Product Specific and GMP Inspection			PHILPYE

Overall Manufacturing Inspection Recommendation | Next task »

NDA 206185-Orig1-New/NDA(1)

Facility Inspection - Overall Application Recommendation

Facility Inspection - Overall Application Recommendation
Withhold

Facility Inspection - Overall Application Re-evaluation Date
3/1/15

The methods used in and the facilities and controls used for, the manufacture, processing, packing, or holding of the drug product do not comply with the current good manufacturing practice (cGMP) regulations in parts 210 and 211. Satisfactory resolution of this deficiency is required before this application may be approved. All facilities and controls will need to comply with the cGMP regulations.

4. Nonclinical Pharmacology/Toxicology

From the original Pharmacology/Toxicology Review finalized 10/17/14:

SPARC seeks approval of Latanoprost Ophthalmic Emulsion, 0.005%, which is intended for the same dosage (1 drop QD or 1.5 μg/day) and administration (once daily in the evening) as that of the approved Listed Drug (LD) Xalatan (NDA 20-597), for the reduction of elevated IOP in patients with open-angle glaucoma or ocular hypertension. The new formulation contains an excipient, (b) (4) which has not been previously approved in an ophthalmic product in the United States. SPARC is relying on FDA's prior findings of the efficacy and safety of latanoprost, as summarized in the most current Xalatan labeling (revised August 2012). In addition, SPARC performed repeated-dose ocular toxicity studies of up to 180-day duration in dogs and rabbits to evaluate the systemic and local ocular toxicities of the new formulation. To evaluate the ocular safety of (b) (4) these studies included an additional arm(s) using this excipient. Systemic safety of (b) (4) was evaluated in repeated-dose oral toxicity studies of (b) (4) in rats of up to 180-day duration. In addition, SPARC used the extensive battery of systemic toxicity studies conducted by (b) (4)

5. Clinical Pharmacology/Biopharmaceutics

From the original Clinical Pharmacology Review finalized 9/30/14:

The applicant (Sun Pharmaceutical Industries, Ltd; SPARC) has submitted this current NDA for a different formulation of latanoprost ophthalmic emulsion 0.005%. The proposed SPARC latanoprost formulation differs from Xalatan in several ways: SPARC latanoprost includes (b) (4) as a (b) (4) and potassium sorbate as a preservative. Xalatan contains 0.02% w/v benzalkonium chloride (BKC) as a preservative. The submitted latanoprost product is an emulsion, not a (b) (4) The applicant submitted a request for an *in vivo* bioavailability (BA) or bioequivalence (BE) waiver, which is acceptable based on the consideration that the differences in formulation between Xalatan and the proposed SPARC latanoprost ophthalmic emulsion 0.005% are not expected to influence the limited systemic exposure to latanoprost/latanoprost acid following topical ocular administration.

From the Biopharmaceutics Review dated 10/17/14:

Based on 21 CFR § 320.22 (e), Biopharmaceutics is of the opinion that for good cause, the requirement for the submission of evidence of in vivo bioavailability or bioequivalence can be waived, because the proposed drug product is an ophthalmic product intended only for local therapeutic effect. Therefore,

the biowaiver request is granted.

The ONDQA-Biopharmaceutics team has reviewed NDA 206185 and its amendments (Seq. 0008 and Seq.0014) submitted on May 23, and July 19, 2014. From the Biopharmaceutics perspective, NDA 206185 Xelpros (latanoprost) ophthalmic emulsion, 0.005% w/v is recommended for **APPROVAL.**

6. Sterility Assurance

From the original Product Quality Microbiology Review finalized 9/26/14:

There are no microbiology deficiencies identified. Endotoxin specification of the drug product is (b) (4) EU/mL. The Applicant has demonstrated adequate controls over the manufacturing process to mitigate the sterility and pyrogenicity risks to the final drug product. (b) (4) There was also adequate primary container closure integrity study data supporting the sterility maintenance of the final packaged product. The drug product is preserved and adequate preservative effectiveness testing was conducted during development. This testing is also a part of the long term stability program.

7. Clinical/Statistical - Efficacy

From the original Medical Officer Review dated 11/3/14:

Study CLR_09_12 was an adequate, well-controlled study designed with endpoints to evaluate the safety and efficacy of the intended indication, reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension. Studies CLR_09_13, CLR_08_01 and CLR_10_01 were open-label studies.

Analyses of Endpoints

Primary Efficacy Variable for Study CLR_09_12

The primary efficacy endpoint in this study was the change from baseline in IOP at each of 12 time points as follows: 3 time points per visit (8 AM, 10 AM, and 4 PM) recorded during four post-baseline visits (Weeks 1, 4, 8, and 12).

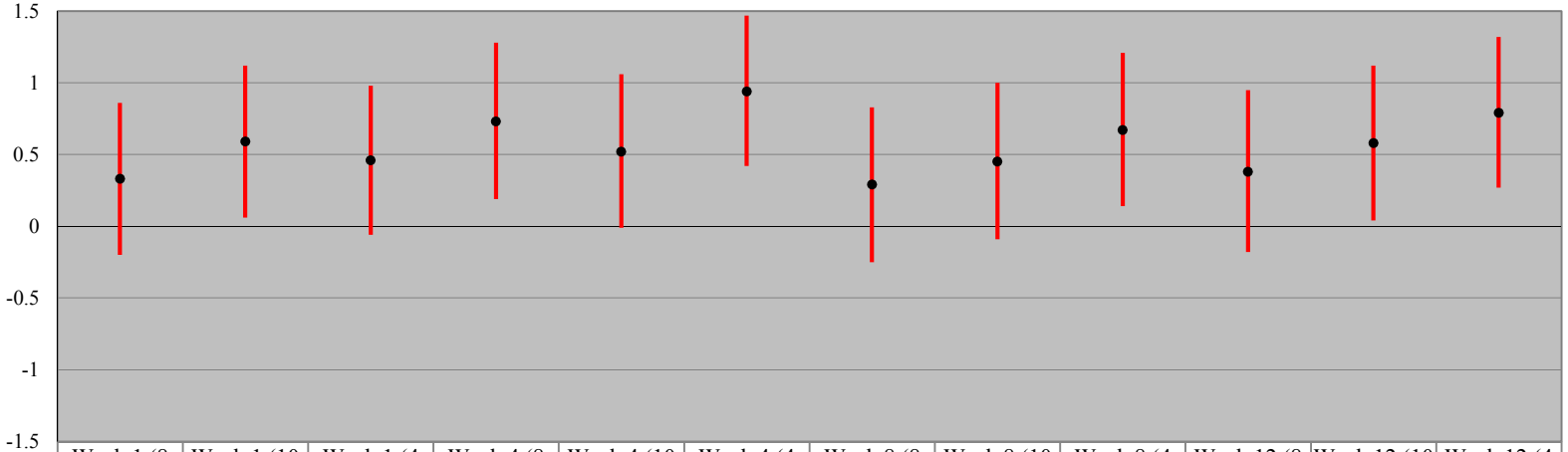
The primary efficacy analysis was conducted on the ITT population without LOCF.

Non-inferiority was considered established if the following 3 steps were established simultaneously:

Step 1: 95% CI included 0 for all (12) time points.
Step 2: The upper limit of the 95% CI was <1.5 at all (12) time points.
Step 3: The upper limit of 95% CI was <1 at most (at least 7 of 12) time points.

Chart 6.1.4-1

**Difference in Mean Change in IOP from Baseline
(SPARC Latanoprost 0.005% - Xalatan) with 95% Confidence Intervals
Study CLR_09_12 - ITT without LOCF**

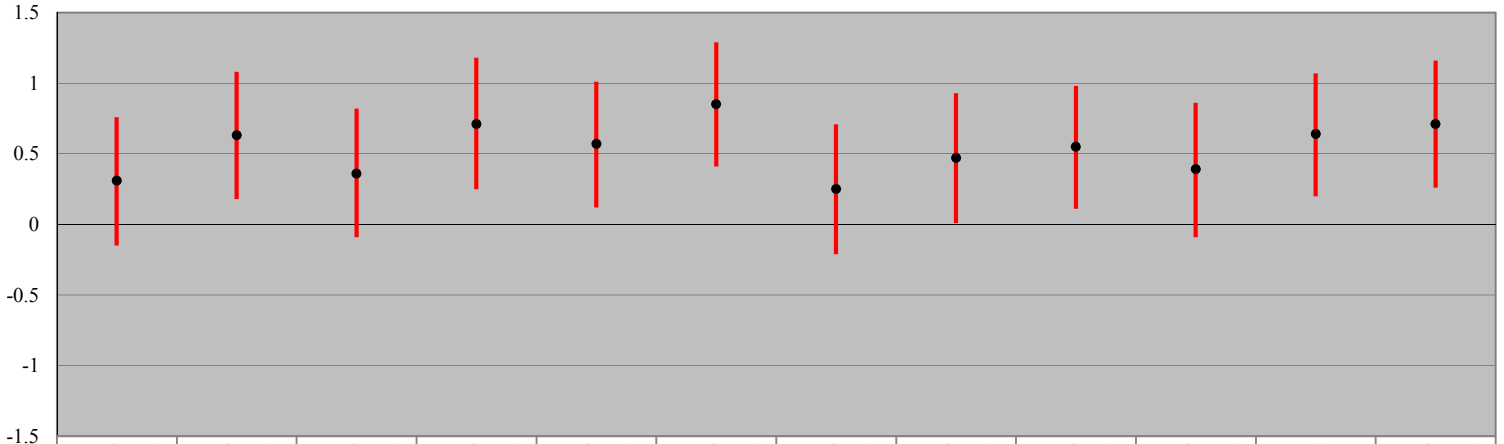


	Week 1 (8 AM)	Week 1 (10 AM)	Week 1 (4 PM)	Week 4 (8 AM)	Week 4 (10 AM)	Week 4 (4 PM)	Week 8 (8 AM)	Week 8 (10 AM)	Week 8 (4 PM)	Week 12 (8 AM)	Week 12 (10 AM)	Week 12 (4 PM)
Lower CI	-0.2	0.06	-0.06	0.19	-0.01	0.42	-0.25	-0.09	0.14	-0.18	0.04	0.27
Upper CI	0.86	1.12	0.98	1.28	1.06	1.47	0.83	1	1.21	0.95	1.12	1.32
Mean Difference	0.33	0.59	0.46	0.73	0.52	0.94	0.29	0.45	0.67	0.38	0.58	0.79

For the ITT population without LOCF, the 95% confidence interval is within 1.5 mmHg for all time points, and the within 1.0 mmHg for 4 of 12 time points. Thus, SPARC latanoprost 0.005% has not demonstrated equivalence with Xalatan (latanoprost ophthalmic solution) 0.005%.

Chart 6.1.4-2

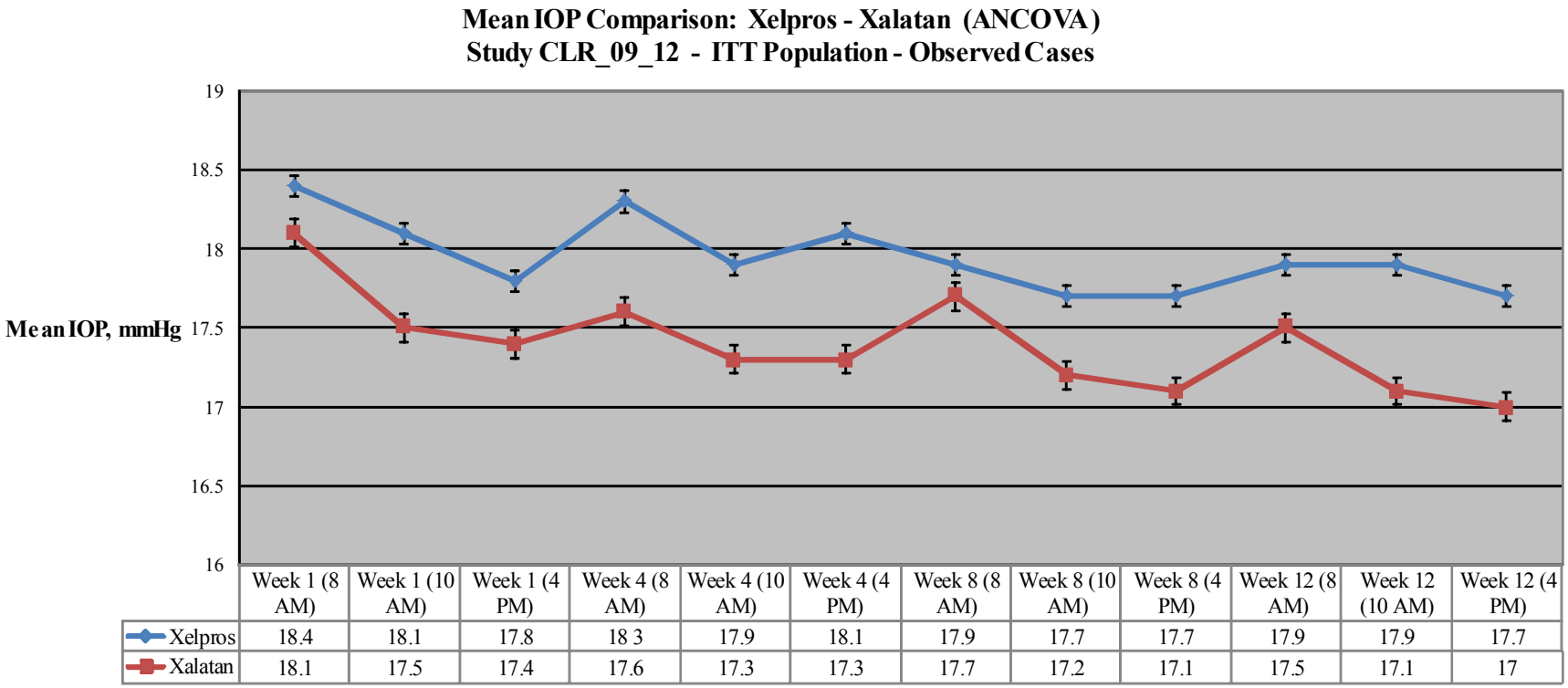
Difference in Mean Change in IOP from Baseline - ANCOVA
(SPARC Latanoprost 0.005% - Xalatan) with 95% Confidence Intervals
Study CLR_09_12 - ITT Population - Observed Cases



	Week 1 (8 AM)	Week 1 (10 AM)	Week 1 (4 PM)	Week 4 (8 AM)	Week 4 (10 AM)	Week 4 (4 PM)	Week 8 (8 AM)	Week 8 (10 AM)	Week 8 (4 PM)	Week 12 (8 AM)	Week 12 (10 AM)	Week 12 (4 PM)
Lower CI	-0.15	0.18	-0.09	0.25	0.12	0.41	-0.21	0.01	0.11	-0.09	0.2	0.26
Upper CI	0.76	1.08	0.82	1.18	1.01	1.29	0.71	0.93	0.98	0.86	1.07	1.16
Mean Difference	0.31	0.63	0.36	0.71	0.57	0.85	0.25	0.47	0.55	0.39	0.64	0.71

For the ITT population Observed Cases, the 95% confidence interval is within 1.5 mmHg for all time points and the within 1.0 mmHg for 6 of 12 time points. Thus, SPARC latanoprost 0.005% has demonstrated equivalence with Xalatan (latanoprost ophthalmic solution) 0.005% using the Division's definition for this population.

Chart 6.1.4-3



	Week 1 (8 AM)	Week 1 (10 AM)	Week 1 (4 PM)	Week 4 (8 AM)	Week 4 (10 AM)	Week 4 (4 PM)	Week 8 (8 AM)	Week 8 (10 AM)	Week 8 (4 PM)	Week 12 (8 AM)	Week 12 (10 AM)	Week 12 (4 PM)
Xelpros	18.4	18.1	17.8	18 3	17.9	18.1	17.9	17.7	17.7	17.9	17.9	17.7
Xalatan	18.1	17.5	17.4	17.6	17.3	17.3	17.7	17.2	17.1	17.5	17.1	17

The adjusted mean IOP ranged from 17.7 to 18.4 mmHg in the Xelpros group and from 17.0 to 18.1 mmHg in the Xalatan group. The mean IOP at each time point of each visit was lower in the Xalatan group. Xelpros was less effective in lowering IOP compared to Xalatan by about 0.5 mmHg.

Sensitivity Analyses were performed to assess the effect of missing data on the primary efficacy endpoint. Non-inferiority was not established for the ITT population analyzed with last observation carried forward, the ITT population with baseline observation carried forward or the ITT population with multiple imputations. The conclusions for these analyses were consistent with the primary analysis without imputations.

Efficacy Summary Statement

Study CLR_09_12 comparing Xelpros (latanoprost ophthalmic emulsion) 0.005% and Xalatan did not establish equivalence with the preplanned clinical endpoint of change from baseline in intraocular pressure. The decrease in mean intraocular pressure in Xelpros-treated patients was 5 – 6 mmHg approximately 0.5 mmHg less than Xalatan treated patients. The data obtained from other submitted open-label studies provides supportive information regarding the decrease from baseline in mean intraocular pressure.

Although inferior to Xalatan, the IOP reduction is a clinically significant reduction in IOP and represents a benefit over the potential risks of using the product.

8. Safety

From the original Medical Officer Reviews dated 11/3/14 and 11/18/14:

The following studies were included in the Integrated Summary of Safety (ISS) for Xelpros (latanoprost ophthalmic emulsion) 0.005%. The safety analysis dataset for the Integrated Safety Summary included all subjects that were included in the safety analyses in each study.

Table 7.1.1 Studies Used to Evaluate Safety

Study Number / Study Phase	Study Design	Treatment Groups (Numbers of Subjects Treated)	Duration of Treatment / Age
Study CLR_08_01 (India) Phase 3	Multicenter, open-label, randomized, active-controlled, parallel group. Visits on Days -7, 0, 8, 15, and 29.	SPARC latanoprost (N=53) Xalatan (N=51)	Once daily for 4 weeks Age ≥ 18 years
Study CLR_10_01 (India) Pilot	Multicenter, open-label, randomized, active-controlled, parallel group Visits on Days 0, 28, and 56.	Subjects previously treated with Xalatan were switched over to SPARC latanoprost (N=25 subjects, 46 eyes)	Once daily for 8 weeks Age ≥ 18 years
Study CLR_09_12 (US, IND 102,842) Phase 3	Multicenter, assessor-masked, randomized, active-controlled, parallel group, non-inferiority study.	SPARC latanoprost (N=289) Xalatan (N=289)	Once daily for 12 weeks Age ≥ 18 years

Study Number / Study Phase	Study Design	Treatment Groups (Numbers of Subjects Treated)	Duration of Treatment / Age
	Visits on Days -35, -7, 0, 7, 28, 56, and 84		
Study CLR_09_13 (US, IND 102,842) Phase 3	Multicenter, open-label, non-randomized, uncontrolled, single group assignment. Visits at Weeks 1, 4, 8, 12, 16, 20, 24, 28, 32, and 36.	Single group, all subjects received SPARC latanoprost (open label extension of prior Study CLR_09_12) (N=161)	Once daily for 36 weeks Age ≥ 18 years

Note: SPARC latanoprost 0.005% is the name used by the applicant during product development. SPARC latanoprost 0.005% and Xelpros (latanoprost ophthalmic emulsion) are interchangeable terms.

Four-hundred and forty-eight subjects were exposed to SPARC latanoprost 0.005% ophthalmic emulsion for a mean of 131.2 days.

Table 7.2.1-1
Summary of Duration of Exposure to SPARC latanoprost by Study
Safety Populations

Study	Duration of Exposure to Xelpros [1]	N
Study CLR_08_01	> 1 day	53
	> 1 day and < 7 days	2
	> 7 days and < 29 days	5
	Completed 29 days	46
Study CLR_10_01	> 1 day	46
	> 1 day and < 28 days	6
	> 28 days and < 56 days	6
	Completed 56 days	34
Study CLR_09_12	> 1 day	289
	> 1 day and < 12 weeks	15
	Completed 12 weeks	274
Study CLR_09_13 [2]	24 weeks	153
	36 weeks	153
	48 weeks	37

- All dosing was once per day in the study eye. All numbers refer to study eyes treated.
- Total exposure from studies CLR_09_12 and the open label extension study CLR_09_13.

Source: ISS, Table 5

There were no deaths in any study.

Table 7.3.3-1
Subject Disposition
All Screened Subjects

Subject Disposition	Treatment Group [1]		
	Xelpros 0.005%	**Xalatan 0.005%**	**Total**
Subjects screened	---	---	867
Screening failures	---	---	160
Subjects randomized	---	---	707
Subjects not treated	---	---	0
Subjects Included in ISS Analysis Set	448	340	707
Subjects with ≥ 1 dose study drug [2]	448	340	707
Subjects completed study	334 (74.6%)	324 (95.3%)	577 (81.6%)
Subjects discontinued from the study	114 (25.4%)	16 (4.7%)	130 (18.4%)
Reasons for Discontinuation			
Withdrawal of Consent	76 (17.0%)	7 (2.1%)	83 (11.7%)
Protocol Violation	7 (1.6%)	1 (0.3%)	8 (1.1%)
Adverse Event	5 (1.1%)	2 (0.6%)	7 (1.0%)
Withdrawal of Subject by Investigator	10 (2.2%)	1 (0.3%)	11 (1.6%)
Lost to follow up	6 (1.3%)	2 (0.6%)	8 (1.1%)
Study Terminated by Sponsor	7 (1.6%)	2 (0.6%)	9 (1.3%)
Study Medication Failure	3 (0.7%)	1 (0.3%)	4 (0.6%)

- 81 subjects switched therapy from the Reference drug in Study CLR_09_12 to the Test drug in Study CLR_09_13. They both contributed data to both treatment groups. All subjects were counted once in the Total column.
- Percentage was calculated based on the number of subjects treated with ≥ 1 dose of study drug in each group.

Source: ISS Table 14.1.1.1

The percentage of subjects who withdrew from the study was 18% overall but the dropout rate was higher in the Xelpros group (25%) compared to the Xalatan group (5%). The number of subjects who discontinued was higher in the Xelpros group in every category.

Table 7.4.1-1
Treatment-Emergent Adverse Events[a]
Occurring in ≥ 1% of Subjects in Any Treatment Group
ISS Analysis Population

Preferred Term	Xelpros 0.005% (N = 448)	Xalatan® (N = 340)
Eye Disorders		
Eye pain	248 (55.4%)	137 (40.3%)
Ocular hyperemia	189 (42.2%)	145 (42.6%)
Conjunctival hyperemia	67 (15.0%)	55 (16.2%)
Eye discharge	56 (12.5%)	41 (12.1%)
Growth of eyelashes	54 (12.1%)	36 (10.6%)
Eyelash thickening	40 (8.9%)	17 (5.0%)
Eye pruritus	20 (4.5%)	16 (4.7%)
Visual acuity reduced	16 (3.6%)	12 (3.5%)
Erythema of eyelid	15 (3.3%)	13 (3.8%)
Dry eye	13 (2.9%)	6 (1.8%)
Foreign body sensation in eyes	9 (2.0%)	6 (1.8%)
Punctate keratitis	6 (1.3%)	9 (2.6%)
Vision blurred	4 (0.9%)	8 (2.4%)
Chalazion	3 (0.7%)	7 (2.1%)
Eyelid edema	7 (1.6%)	1 (0.3%)
Blepharitis	3 (0.7%)	4 (1.2%)
Eyelash discoloration	6 (1.3%)	2 (0.6%)
Lacrimation increased	4 (0.9%)	5 (1.5%)
Meibomianitis	4 (0.9%)	3 (0.9%)
Infections and infestations		
Upper respiratory tract infection	8 (1.8%)	0 (0.0%)
Nervous system disorders		
Headache	8 (1.8%)	5 (1.5%)
Vascular disorders		
Hypertension	3 (0.7%)	6 (1.8%)

Source: Module 5: ISS Table 14.3.3.2
a Adverse events that existed before study drug administration and increased in severity or adverse events that only occurred after study drug administration were considered TEAEs.

Treatment-emergent adverse events which occurred in ≥ 5 % of subjects and more frequently in the Xelpros group compared to the Xalatan group (highlighted above) were: eye pain (55%), eye discharge (13%), growth of eyelashes (12%) and eyelash thickening (9%).

Treatment-emergent adverse events which occurred in between 1 % and 5 % of subjects and more frequently in the Xelpros group compared to the Xalatan group (highlighted above) were: visual acuity reduced (4%), dry eye (3%), foreign body sensation in the eyes (2%), headache (2%), upper respiratory

tract infection (2%), eyelid edema (2%), and eyelash discoloration (1%).

Safety Summary Statement

There is substantial evidence of safety consisting of an adequate and well controlled study and supportive evidence from three additional open-label studies which demonstrate that Xelpros dosed once daily in the evening, is safe for the reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

Treatment-emergent adverse events which occurred in ≥ 5 % of subjects and more frequently in the Xelpros group compared to the Xalatan group were: eye pain (55%), eye discharge (13%), growth of eyelashes (12%) and eyelash thickening (9%)

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9. Advisory Committee Meeting

No Advisory Committee Meeting was held. There were no new issues raised in the review of the application which were thought to benefit from an Advisory Committee Meeting.

10. Pediatrics

Safety and effectiveness in pediatric patients have not been established.

This application was presented at the Pediatric Regulatory Committee (PeRC) on August 13, 2014. It received a full waiver from studies for all pediatric age groups for this indication. Necessary studies would be impossible or highly impracticable because there are too few children with disease/condition to study.

The prevalence and incidence of pediatric glaucoma is very low. The number of pediatric patients is very small and geographically dispersed.

11. Other Relevant Regulatory Issues

DSI
A Division of Scientific Investigations (DSI) audit was requested.

Per the DSI review finalized 9/17/14:

The Applicant submitted this NDA to support the use of Xelpros ((b) (4) ophthalmic emulsion) for the treatment of open-angle glaucoma or ocular hypertension.

The studies, CLR_09_12 entitled "Comparison of the Efficacy and Safety of Sparc's Latanoprost 0.005% Ophthalmic (b) (4) (Test) and Xalatan (Latanoprost 0.005% Ophthalmic Solution - Reference) when Administered Once Daily in Subjects with Open Angle Glaucoma or Ocular

Hypertension: a Clinical Non-inferiority Study" and CLR_09_13, entitled "A Clinical Evaluation of Safety of Sparc's Latanoprost 0.005% Ophthalmic (b) (4) when Administered Once Daily in Subjects with Open Angle Glaucoma or Ocular Hypertension: an Open Label Extension Study" were inspected in support of the indication.

The clinical sites of Drs. Tepedino, Gira, and Perez were selected for inspection because they were among the highest enrolling sites.

II. RESULTS (by Site):

Name of CI, Location	Protocol #/ Site #/ # of Subjects (enrolled)	Inspection Dates	Final Classification
Michael Tepedino, M.D. Cornerstone Eye Care 1400 E. Hartley Drive High Point, NC 27262-4317	CLR_09_012/ 03/ 43 and CLR_09_013/ 03/ 18	27-30 May 2014	NAI
Joseph Gira, M.D. Ophthalmology Consultants, Ltd. 12990 Manchester Road, Suite 201 St. Louis, MO 63131	CLR_09_013/ 08/ 16	2-4 Jun 2014	NAI
Bernard R. Perez, M.D. International Research Center 4506 Wishart Place Tampa, FL 33603	CLR_09_013/ 13/ 16	2-4 Jun 2014	VAI

Key to Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.
Pending = Preliminary classification based on information in Form FDA 483 or preliminary communication with the field; EIR has not been received from the field or complete review of EIR is pending.

The clinical investigator sites of Drs. Tepedino and Gira were not issued Form FDA 483s, and the final classification of these inspections was No Action Indicated (NAI). Dr. Perez's clinical site was issued a Form FDA 483, and the final classification of this inspection was Voluntary Action Indicated (VAI). The data generated by these clinical sites appear adequate in support of the respective indication.

FINANCIAL DISCLOSURE

The applicant has examined its financial data regarding significant payments of other sorts made to all investigators in the studies and equity information as provided by the investigators, as defined in 21 CFR 54.2.

There is no evidence to suggest that the results of the study were impacted by any financial payments.

DMEPA

The Division of Medication Error Prevention and Analysis (DMEPA) finalized a letter to the applicant

dated 5/19/14 finding the proprietary name, Xelpros, to be conditionally acceptable.

DMEPA also provided recommendations on the packaging configuration and the package insert labeling.

OPDP
The Office of Prescription Drug Promotion (OPDP) reviewed the substantially complete draft product labeling for Xelpros ((b) (4) ophthalmic emulsion) 0.005% and offered the following comments in their review finalized 11/14/14:

Comment [CGC1]: OPDP Comment: To clearly communicate that this potential serious risk [changes to pigmented tissues] has occurred in Xelpros, we recommend revising to "XELPROS." Alternatively, we recommend deleting, " (b) (4) ."

DTOP Response: *This is a 505(b)(2) application. The Warning is most accurate and informative as written. These are class effects seen with prostaglandins/prostaglandin analogs.*

Comment [CGC2]: OPDP Comment: We note that the ADVERSE REACTIONS section does not identify all of these adverse reactions as being common/ most frequently reported. We recommend revising here or in the ADVERSE REACTIONS section for consistency throughout this PI.

DTOP Response: *This has been revised in the final draft package insert.*

Comment [CGC3]: OPDP Comment: Should this be Sun Pharmaceutical Industries, Ltd.?

DTOP Response: *No.* (b) (4) *operates as a subsidiary unit of Sun Pharmaceutical Industries, Ltd.*

Comment [CGC4]: OPDP Comment: We note that some of the headers listed here are not in the full PI, and some of the headers in the full PI are omitted here. We recommend revising. that this PI refers to the drug in various ways, such as, "XELPROS Ophthalmic Emulsion," "XELPROS," "Xelpros," "latanoprost ophthalmic emulsion," and "XELPROS (latanoprost ophthalmic emulsion) 0.005%." For consistency throughout the label and clarity, should one term be used throughout? OPDP defers to DTOP.

DTOP Response: *In the final draft package insert, the headers in the table of contents match the full prescribing information.*

Comment [CGC6]: OPDP Comment: We note that the Xalatan PI has a contraindication related to "known hypersensitivity to latanoprost…or any other ingredients in this product." Should this Xelpros PI have a similar contraindication? OPDP defers to DTOP.

DTOP Response: *This has been revised in the final draft package insert.*

Comment [CGC7]: OPDP Comment: OPDP is concerned that this general statement minimizes this serious risk. We recommend adding, "including XELPROS" to make clear that this risk is also

associated with this specific drug.

DTOP Response: *This is a 505(b)(2) application. The Warning is most accurate and informative as written. These are class effects seen with prostaglandins/prostaglandin analogs.*

Comment [CGC8]: OPDP Comment: OPDP is concerned that the use of the established name here minimizes that this risk is associated with XELPROS. We recommend revising to "XELPROS."

DTOP Response: *This is a 505(b)(2) application. The Warning is most accurate and informative as written. These are class effects seen with prostaglandins/prostaglandin analogs.*

Comment [CGC9]: OPDP Comment: OPDP is concerned that the use of the established name here minimizes that this risk is associated with XELPROS. We recommend revising to "XELPROS."

DTOP Response: *This is a 505(b)(2) application. The Warning is most accurate and informative as written. These are class effects seen with prostaglandins/prostaglandin analogs.*

Comment [CGC10]: OPDP Comment: OPDP is concerned that the use of the established name here minimizes that this risk is associated with XELPROS. We recommend revising to "XELPROS."

DTOP Response: *This is a 505(b)(2) application. The Warning is most accurate and informative as written. These are class effects seen with prostaglandins/prostaglandin analogs.*

Comment [CGC11]: OPDP Comment: OPDP is concerned that the use of the established name here minimizes that this risk is associated with XELPROS. We recommend revising to "XELPROS."

DTOP Response: *This is a 505(b)(2) application. The Warning is most accurate and informative as written. These are class effects seen with prostaglandins/prostaglandin analogs.*

Comment [CGC12]: OPDP Comment: We recommend revising to, "XELPROS."

DTOP Response: *This is a 505(b)(2) application. The Warning is most accurate and informative as written. These are class effects seen with prostaglandins/prostaglandin analogs.*

Comment [CGC13]: OPDP Comment: We recommend revising to, "XELPROS."

DTOP Response: *This is a 505(b)(2) application. The Warning is most accurate and informative as written. These are class effects seen with prostaglandins/prostaglandin analogs.*

Comment [CGC14]: OPDP Comment: We recommend including additional details regarding this study. For example, we note the Xalatan PI communicates the doses received, number of patients studied, and patient demographics. If possible, we recommend including similar details here.

DTOP Response: *The Xalatan package insert is being converted to PLR; we do not agree that the*

requested information provides useful information for the prescribing physician. These are not placebo controlled, trials.

The XELPROS and Xalatan PLRS will utilize similar prostaglandin class labeling.

Comment [CGC15]: OPDP Comment: We recommend revising to, "XELPROS."

DTOP Response: *This is a 505(b)(2) application. The current wording, latanoprost ophthalmic emulsion, is most accurate and informative as written.*

Comment [CGC16]: OPDP Comment: We note that the Highlights section communicates several more common adverse reactions. We recommend revising here or in the Highlights for consistency throughout this PI.

DTOP Response: *This has been revised in the final draft package insert.*

Comment [CGC17]: OPDP Comment: OPDP note that no incidences or incidence ranges are communicated here for the most common adverse reactions. We recommend disclosing the incidence of each of these common ocular adverse reactions, similar to how the incidences are disclosed for the common systemic adverse events below. We note that the Xalatan PI discloses the incidence of each common adverse reaction.

DTOP Response: *This has been revised in the final draft package insert.*

Comment [CGC18]: OPDP Comment: We note that this discontinuation rate only relates to those patients that discontinued due to ocular hyperemia. Did any patients discontinue the drug due to other adverse reactions? If possible, we recommend communicating the discontinuation rate due to all adverse reactions. We also recommend communicating which adverse reaction(s) resulted in most of these discontinuations.

DTOP Response: *Hyperemia was the most common adverse reaction associated with discontinuation (less than 1%) due to an adverse event. The majority of other discontinuations related to a withdrawal of consent and it was not possible to identify a precipitating event(s) which lead to the discontinuation. The other adverse events leading to discontinuation occurred were isolated.*

Comment [CGC19]: OPDP Comment: OPDP notes that 2-20% is a fairly broad range of incidences. If possible, we recommend communicating the specific incidence for each of these adverse reactions, similar to how it is presented in the Xalatan PI.

DTOP Response: *This has been revised in the final draft package insert.*

Comment [CGC20]: OPDP Comment: We note that most PI's have a section 6.2 "Postmarketing Experience" header. Should this header be titled similarly? OPDP defers to DTOP.

DTOP Response: *This has been revised in the final draft package insert.*

Comment [CGC21]: OPDP Comment: We note that this adverse event is already listed in section 6.1. We recommend deleting here.

DTOP Response: *This has been revised in the final draft package insert.*

Comment [CGC22]: OPDP Comment: We recommend disclosing the specific age cutoff that the safety and effectiveness of Xelpros has not been established. For example, "The safety and effectiveness in pediatric patients ≤ X years of age have not been established," or similar.

DTOP Response: *This recommendation is not consistent with the CDER Labeling Tool format or with recommendations from PeRC.*

Comment [CGC23]: OPDP Comment: Is there substantial evidence to support that this drug decreases the risk of glaucomatous field loss, optic nerve damage, and/or visual field loss? We note that the clinical studies only observed IOP reductions. If there is no substantial evidence to support that Xelpros decreases the likelihood of glaucomatous field loss, optic nerve damage, and/or visual field loss, we recommend deleting this information. OPDP acknowledges that these statements are in the Xalatan PI; however, if there is no substantial evidence to support that Xelpros reduces the likelihood of these events, OPDP maintains our position and recommends deleting this information here.

DTOP Response: *This is standard language found in all IOP-lowering ophthalmic products, and it is factually correct as written. There are no approved products for the treatment of glaucoma.*

Comment [CGC24]: OPDP Comment: Should the established name and concentration be used here instead of the proprietary name of the competitor, Xalatan? We recommend communicating the established name and concentration of this comparison treatment arm. In addition, if the brand name is not necessary for this PI, we recommend deleting mentions of "Xalatan" in this Clinical Studies section.

DTOP Response: *This is a 505(b)(2) application. Xalatan is the reference listed drug product.*

Comment [CGC26]: OPDP Comment: We note that some of these confidence intervals depict a statistically significant difference between the treatment arms. We acknowledge the statement above that indicates that Xalatan was more effective than Xelpros; however, OPDP is concerned that the Xalatan sponsor could ultimately use the data in this PI to support superiority claims when compared to Xelpros. Is this single study considered substantial evidence to support that Xalatan is superior to Xelpros in the lowering of IOP at select timepoints? If not, we recommend including a disclaimer to explain that this single study was not designed to and/or does not support superiority claims.

DTOP Response: *Study CLR_09_12 comparing Xelpros (latanoprost ophthalmic emulsion) 0.005% and Xalatan did not establish equivalence with the preplanned clinical endpoint of change from baseline in intraocular pressure. This was not a superiority trial; the Xalatan applicant would not be*

able to utilize the trial as evidence of superiority without a second confirmatory trial.

Comment [CGC27]: OPDP Comment: We remind DTOP to unbold this mention of the proprietary name.

DTOP Response: *This has been revised in the final draft package insert*

Comment [CGC28]: OPDP Comment: We recommend revising to, "Advise patients that contact lenses…" or similar.

DTOP Response: *This has been revised in the final draft package insert*

Comment [CGC29]: OPDP Comment: We recommend revising to, "Advise patients that if more…" or similar.

DTOP Response: *This has been revised in the final draft package insert*

BIOSTATISTICS

Per the Biostatistics consultative review finalized 10/14/14:

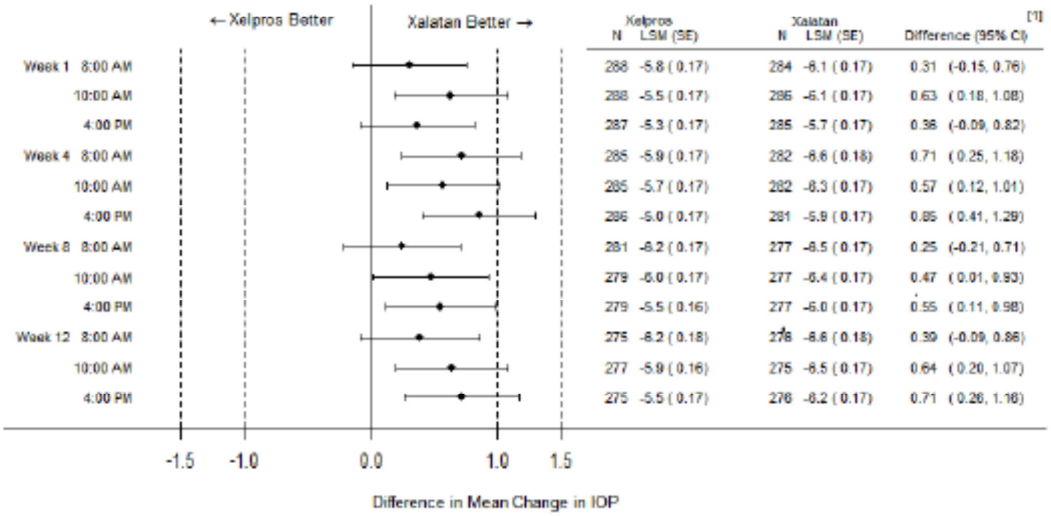
In this NDA submission, the applicant seeks approval of Xelpros (latanoprost ophthalmic emulsion), 0.005% for the reduction of elevated IOP in patients with open-angle glaucoma (OAG) or ocular hypertension (OH).

Support for the safety and efficacy of Xelpros for the treatment of patients with OAG or OH was based on clinical data from four clinical studies: a phase 3 efficacy and safety study conducted in the U.S. (Study CLR_09_12); a phase 3 safety study conducted in the U.S. (Study CLR_09_13); a phase 3 efficacy and safety study conducted in India (Study CLR_08_01); and a pilot safety study conducted in India (Study CLR_10_01). In this review, the primary evidence to evaluate the safety and the IOP lowering efficacy of Xelpros relative to Xalatan was based on Study CLR_09_12. The efficacy data from Study CLR_08_01 was used as supporting evidence.

Even though Xelpros was numerically less effective compared to Xalatan, the pre-defined statistical criterion for non-inferiority was met throughout the study, but the pre-defined clinical criterion for non-inferiority was not met in six of the 12 time points. The IOP lowering effect of Xelpros administered once daily in the evening was about 5.0 to 6.2 mmHg in study CLR_09_12, and about 25% to 40% of patients in the Xelpros group had at least 30% IOP reductions throughout the study. Although the test product, Xelpros, demonstrated significant IOP reductions throughout the study, it was less effective compared to the active control, Xalatan, by about 0.3 to 0.9 mmHg .

The least square means and the two-sided 95% CIs for the difference in the mean change in IOP between the treatment groups are shown in Figure 1 below:

Figure 1: Difference in Mean Change in IOP (mmHg) – ANCOVA Using Baseline IOP (CLR_09_12)
(ITT Analysis Population, Observed Cases)



SE= Standard Error; CI = Confidence Interval; LSM = Least Square Mean
[1] Estimates at each time point of each visit were based on ANCOVA model that included treatment, site, and actual baseline IOP as covariates. Dots and horizontal bars represent the point and 95% CI estimates for the difference in mean change in IOP.

Issues were identified during the review process of Study CLR_09_12 related to: (i) the applicant's primary efficacy results and (ii) the analysis dataset that contained the primary efficacy variable.

Regarding the primary efficacy results, the reviewer was initially unable to reproduce the applicant's primary efficacy results presented in the clinical study report (CSR). The issue was brought to the attention of the applicant through an information request dated on June 5, 2014. In an email response dated on June 11, 2014, the applicant acknowledged the issue and indicated that the primary efficacy results reported in the CSR were incorrect and were produced based on using an intermediate dataset instead of using the final ADaM dataset that was submitted to the Agency. With that the applicant confirmed that even though the results reported in the CSR were incorrect, the ADaM dataset that was submitted to the Agency as part of the NDA submission was correct and agreed to submit an updated CSR. Based on the applicant's confirmation regarding the dataset, the reviewer continued using the ADaM dataset in the review.

The issue concerning the analysis dataset was related to the way data collected in the case report form (CRF) were linked to the analysis visits in the clinical database. In the CRF, data were recorded under visit names visit 1, visit 2, visit 3, and visit 4 (end-of-study visit); and irrespective of the dates these visits had occurred, the CRF data collected at visit 1, visit 2, visit 3, and visit 4 were respectively linked to analysis visits week 1, 4, 8, and 12 in the clinical database. Due to this link, the end-of-study visit data for the majority of early terminated subjects were incorrectly linked to the week 12 visit. Note that the majority of early terminated subjects withdrew the study before the week 12 visit. In the reviewer's opinion, the analysis visits should have been defined programmatically by taking the visit dates into account. This issue was also brought to the attention of the applicant through an information request dated on July 15, 2014. The applicant acknowledged the issue and submitted an updated dataset on July 23, 2014. The reviewer confirmed the corrections made to the analysis visits.

On September 03, 2014 the applicant submitted an amended CSR based on the updated dataset. Assuming updates were made only in the analysis visits, the reviewer had performed all the efficacy analyses using the original ADaM dataset with the updated analysis visits; however, the results were still not matching. After a thorough investigation of the updated dataset, the reviewer noted changes in the precision used in the primary efficacy data (IOP data) between the updated and the original ADaM dataset. In the ADaM dataset, the IOP data were rounded up (0.5 or greater) or down (0.49 or lower) to the nearest integers while no rounding was made in the updated dataset.

Although the reviewer was initially unable to reproduce the primary efficacy results due to the difference in precision in the IOP data between the two datasets, the results were finally reproduced when the unrounded IOP data were used.

12. Labeling

NDA 206185, Xelpros (latanoprost ophthalmic emulsion) 0.005% is recommended for approval for the reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension with the draft labeling found in the Appendix at the end of this CDTL review once the facilities to be used to manufacture the product are found to be in compliance with current good manufacturing procedures (cGMPs).

13. Recommendations/Risk Benefit Assessment

RECOMMENDED REGULATORY ACTION:
NDA 206185, Xelpros (latanoprost ophthalmic emulsion) 0.005% is not recommended for approval for the reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

Although inferior to Xalatan, the IOP reduction is a clinically significant reduction in IOP and represents a benefit over the potential risks of using the product. The decrease in mean intraocular pressure in Xelpros-treated patients was 5 – 6 mmHg approximately 0.5 mmHg less than Xalatan treated patients. The data obtained from other submitted open-label studies provides supportive information regarding the decrease from baseline in mean intraocular pressure.

There is substantial evidence of safety consisting of an adequate and well controlled study and supportive evidence from three additional open-label studies which demonstrate that Xelpros dosed once daily in the evening, is safe for the reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

Treatment-emergent adverse events which occurred in ≥ 5 % of subjects and more frequently in the Xelpros group compared to the Xalatan group were: eye pain (55%), eye discharge (13%), growth of eyelashes (12%) and eyelash thickening (9%).

The following cGMP Product Quality issue should be included in the Complete Response letter:

"The methods used in and the facilities and controls used for, the manufacture, processing, packing, or holding of the drug product do not comply with the current good manufacturing practice (cGMP) regulations in parts 210 and 211. Satisfactory resolution of this deficiency is required before this application may be approved. All facilities and controls will need to comply with the cGMP regulations."

RISK BENEFIT ASSESSMENT:

The efficacy endpoints chosen for the phase 3 study have been widely used in clinical studies of ophthalmic topical IOP-lowering products and are recognized as reliable, accurate, and relevant for evaluation of the efficacy and safety of investigational products.

Although inferior to Xalatan, the IOP reduction is a clinically significant reduction in IOP and represents a benefit over the potential risks of using the product.

Prostaglandin associated safety issues are described in current class labeling. The safety issues identified in class labeling include increased eyelash, iris and periocular pigmentation, eyelash growth and intraocular inflammation. Information regarding these safety concerns is presented in the approved labeling of the reference listed drug, Xalatan, and in the Xelpros labeling found in the Appendix of this review.

Pharmacology/Toxicology, CMC, Biostatistics, Clinical, Clinical Pharmacology, and Microbiology have recommended approval for this application. Product Quality has not recommended approval until the overall recommendation from the Office of Compliance is "Acceptable."

RECOMMENDATION FOR POSTMARKETING RISK MANAGEMENT ACTIVITIES:

There are no risk management activities recommended beyond the routine monitoring and reporting of all adverse events.

There are no recommended Postmarketing Requirements or Phase 4 Commitments.

Appendix

NDA 206185, Xelpros (latanoprost ophthalmic emulsion) 0.005% is recommended for approval for the reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension with the draft labeling found in the Appendix at the end of this CDTL review once the facilities to be used to manufacture the product are found to be in compliance with current good manufacturing procedures (cGMPs).

Container label - 2.5 mL (b) (4) in a 5 mL bottle

Comments:

"(b) (4)," should be revised to read, "For Topical Use in the Eye."

Carton label – single bottle presentation

Comments:

(b) (4)," should be revised to read, "For Topical Use in the Eye."

Carton label – three (3) bottle presentation

Comments:

"(b) (4)," should be revised to read, "For Topical Use in the Eye."

9 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

WILLIAM M BOYD
11/19/2014

WILEY A CHAMBERS
11/20/2014

Deputy Division Director Review

Date	November 20, 2014
From	Wiley A. Chambers, M.D.
NDA #	206185
Applicant	Sun Pharm Advanced Research Company Ltd. U.S Representative: ORA., Inc.
Date of Submission	January 31, 2014
PDUFA Goal Date	November 30, 2014
Type of Application	505(b)(2)
Name	Xelpros (latanoprost ophthalmic emulsion) 0.005%
Dosage forms / Strength	Topical ophthalmic emulsion
Proposed Indication(s)	Reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension
Recommendation:	Not Recommended for Approval

1. Introduction

Latanoprost is a prostaglandin analog, F2-α receptor agonist. It is believed that latanoprost reduces intraocular pressure predominately by increasing uveoscleral outflow from the eye. This product is a reformulation of Xalatan (latanoprost ophthalmic solution) 0.005%, changing a number of the inactive ingredients and in doing so changing the dosage form to an emulsion. The concentration of latanoprost (0.005%), indication and the dosing regimen remain the same as Xalatan.

2. Background

Sun Pharma Advanced Research Company (SPARC) submitted an IND application for latanoprost ophthalmic emulsion, 0.005% to the Agency in 2009. SPARC completed two clinical studies (CLR_09_12 and CLR_09_13) under this IND in 2012. There are many ophthalmic drug products approved for lowering intraocular pressure in patients with open-angle glaucoma and ocular hypertension. These treatments include beta-adrenergic antagonists (beta-blockers), alpha-adrenergic agonists, parasympathomimetic (miotic) agents, carbonic anhydrase inhibitors, and prostaglandin analogs.

3. CMC

Latanoprost ophthalmic emulsion, 0.005% is an emulsion in aqueous phase and will be manufactured, processed, packaged, labeled, and tested by Sun Pharmaceutical Industries Ltd.–Halol. The intended commercial batch size and exhibit batch size for the 2.5 mL fill, is (b) (4) vials and (b) (4) bottles respectively. The drop size and drug content of each drop of the drug product, packaged in the selected primary packaging materials, is approximately (b) (4) µL and 1.5 µg, respectively. Adequate controls over the manufacturing process are in place to mitigate the sterility and pyrogenicity risks. (b) (4)

There was adequate primary container closure integrity study data supporting the sterility maintenance of the final packaged product. The drug product is preserved and adequate preservative effectiveness

testing was conducted during development. This testing is also a part of the long term stability program.

DESCRIPTION AND COMPOSITION OF THE DRUG PRODUCT:

Component	Amount per mL	Proposed Function	Reference
Latanoprost	0.05	Active	In house
Potassium sorbate	4.70	Preservative	NF
Boric acid	(b) (4)	(b) (4)	NF
Edetate disodium			USP
Castor oil			USP
(b) (4)			Ph.Eur.
Propylene glycol			USP
Sodium borate			NF
Hydrochloric acid			NF
Sodium hydroxide			NF
Water for injection			USP

PROPOSED REGULATORY SPECIFICATIONS:

Description	Off white to pale yellow translucent (b) (4)
Identification by HPLC	The retention time of the latanoprost peak in the chromatogram of the assay preparation corresponds to that of the standard preparation as obtained in the assay.
Identification by HPLC	The PDA spectrum, in the range of (b) (4) nm, of latanoprost peak in the sample preparation corresponds to that of latanoprost peak in standard preparation as obtained in the related substances method II.
pH	Between (b) (4)
Absorbance at 420 nm	Not more than (b) (4) AU
Osmolality	(b) (4) mOsm
Volume in container	Between (b) (4) mL
Volume variation	Between (b) (4)
Viscosity	(b) (4) cp – (b) (4) cp
Particle size distribution	D10: (b) (4) D50: D90:
Particulate Matter	NMT (b) (4) particles ≥ (b) (4) µm in diameter NMT (b) (4) particles ≥ (b) (4) µm in diameter NMT particle ≥ (b) (4) µm in diameter
Sterility	(b) (4)
Bacterial Endotoxins	Not more than (b) (4) EU/mL
Highest unspecified impurity – Method I	Not more than (b) (4) %
Total impurities – Method I	Not more than %
(b) (4) – Method II	Not more than %
Highest unspecified impurity – Method II	Not more than %
Total impurities – Method II	Not more than %
Assay – content of potassium sorbate (by HPLC)	Not less than (b) (4) %
Assay- of EDTA	(b) (4) mg/mL
Assay of Latanoprost by HPLC	(b) (4) % of label claim
Residual solvents	Comply with USP <467> (b) (4)

FACILITIES INSPECTIONS:
The September 2014 inspection of Sun Pharmaceutical Industries in Halol, Gujarat, India identified a number of good manufacturing practice (GMP) deficiencies. **Approval for this NDA is not recommended until all facilities are in compliance with current GMPs.**

4. Nonclinical Pharmacology/Toxicology

The new formulation contains an excipient, (b) (4) which has not been previously approved in an ophthalmic product in the United States. SPARC is relying on FDA's prior decision of the efficacy and safety of latanoprost ophthalmic solution, as summarized in the most current Xalatan labeling (revised August 2012). In addition, SPARC performed repeated-dose ocular toxicity studies of up to 180-days duration in dogs and rabbits to evaluate the systemic and local ocular toxicities of the new formulation. To evaluate the ocular safety of (b) (4) these studies included an additional arm(s) using this excipient. Systemic safety of (b) (4) was evaluated in repeated-dose oral toxicity studies of (b) (4) in rats of up to 180-day duration. In addition, SPARC used the extensive battery of systemic toxicity studies conducted by (b) (4)

5. Clinical Pharmacology/Biopharmaceutics

SPARC submitted a request for an *in vivo* bioavailability (BA) or bioequivalence (BE) waiver, which was acceptable based on the consideration that the differences in formulation between Xalatan and the proposed SPARC latanoprost ophthalmic emulsion 0.005% are not expected to influence the limited systemic exposure to latanoprost/latanoprost acid following topical ocular administration.

6. Clinical/Statistical - Efficacy

Study CLR_09_12 was an adequate, well-controlled study designed with endpoints to evaluate the safety and efficacy of the intended indication, reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

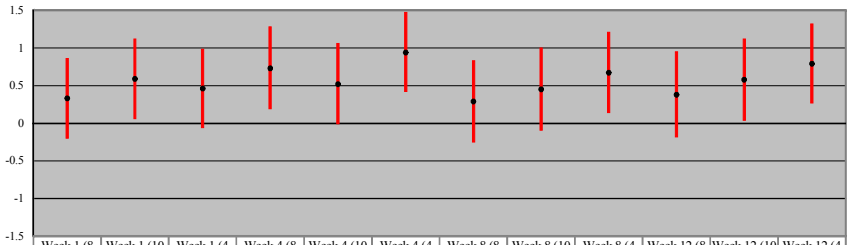
The primary efficacy endpoint in this study was the change from baseline in IOP at each of 12 time points as follows: 3 time points per visit (8 AM, 10 AM, and 4 PM) recorded during four post-baseline visits (Weeks 1, 4, 8, and 12) conducted on the ITT population without LOCF.

Issues were identified during the review of Study CLR_09_12 related to: (i) the applicant's primary efficacy results and (ii) the analysis dataset that contained the primary efficacy variable. The statistical reviewer was initially unable to reproduce the applicant's primary efficacy results presented in the clinical study report (CSR). The issue was brought to the attention of the applicant through an information request dated on June 5, 2014. In an email response dated on June 11, 2014, the applicant acknowledged the issue and indicated that the primary efficacy results reported in the CSR were incorrect and were produced based on using an intermediate dataset instead of using the final ADaM dataset that was submitted to the Agency. With that the applicant confirmed that even though the results reported in the CSR were incorrect, the ADaM dataset that was submitted to the Agency as part of the NDA submission was correct and agreed to submit an updated CSR. Based on the applicant's confirmation regarding the dataset, the reviewer continued using the ADaM dataset in the review.

The issue concerning the analysis dataset was related to the way data collected in the case report form (CRF) were linked to the analysis visits in the clinical database. In the CRF, data were recorded under

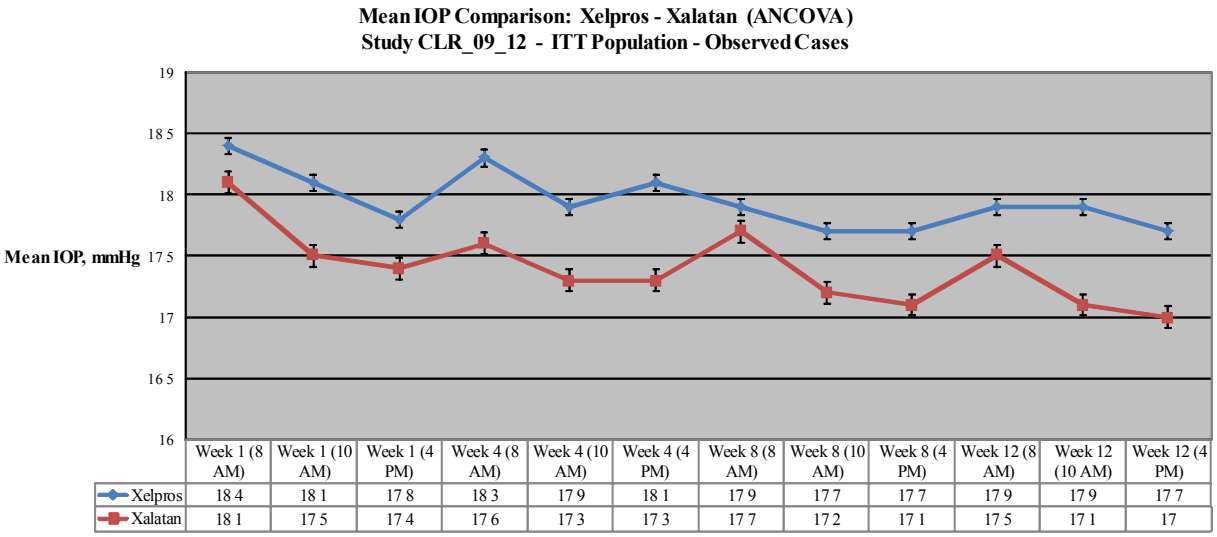
visit names visit 1, visit 2, visit 3, and visit 4 (end-of-study visit); and irrespective of the dates these visits had occurred, the CRF data collected at visit 1, visit 2, visit 3, and visit 4 were respectively linked to analysis visits week 1, 4, 8, and 12 in the clinical database. Due to this link, the end-of-study visit data for the majority of early terminated subjects were incorrectly linked to the week 12 visit. Note that the majority of early terminated subjects withdrew the study before the week 12 visit. In the statistical reviewer's opinion, the analysis visits should have been defined programmatically by taking the visit dates into account. This issue was also brought to the attention of the applicant through an information request dated on July 15, 2014. The applicant acknowledged the issue and submitted an updated dataset on July 23, 2014. The reviewer confirmed the corrections made to the analysis visits. On September 03, 2014, the applicant submitted an amended CSR based on the updated dataset. Assuming updates were made only in the analysis visits, the reviewer had performed all the efficacy analyses using the original ADaM dataset with the updated analysis visits; however, the results were still not matching. After a thorough investigation of the updated dataset, the reviewer noted changes in the precision used in the primary efficacy data (IOP data) between the updated and the original ADaM dataset. In the ADaM dataset, the IOP data were rounded up (0.5 or greater) or down (0.49 or lower) to the nearest integers while no rounding was made in the updated dataset. The results were finally reproduced when the unrounded IOP data were used.

Difference in Mean Change in IOP from Baseline
(SPARC Latanoprost 0.005% - Xalatan) with 95% Confidence Intervals
Study CLR_09_12 - ITT without LOCF



	Week 1 (8 AM)	Week 1 (10 AM)	Week 1 (4 PM)	Week 4 (8 AM)	Week 4 (10 AM)	Week 4 (4 PM)	Week 8 (8 AM)	Week 8 (10 AM)	Week 8 (4 PM)	Week 12 (8 AM)	Week 12 (10 AM)	Week 12 (4 PM)
Lower CI	-0.2	0.06	-0.06	0.19	-0.01	0.42	-0.25	-0.09	0.14	-0.18	0.04	0.27
Upper CI	0.86	1.12	0.98	1.28	1.06	1.47	0.83	1	1.21	0.95	1.12	1.32
Mean Difference	0.33	0.59	0.46	0.73	0.52	0.94	0.29	0.45	0.67	0.38	0.58	0.79

For the ITT population without LOCF, the 95% confidence interval is within 1.5 mmHg for all time points, and the within 1.0 mmHg for 4 of 12 time points. Thus, while the latanoprost ophthalmic emulsion, 0.005% demonstrated efficacy in lowering intraocular pressure, it did not demonstrate equivalence with Xalatan (latanoprost ophthalmic solution) 0.005%.



The adjusted mean IOP ranged from 17.7 to 18.4 mmHg in the Xelpros group and from 17.0 to 18.1 mmHg in the Xalatan group. The decrease in mean intraocular pressure in Xelpros-treated patients was 5–6 mmHg approximately 0.5 mmHg less than Xalatan treated patients.

Sensitivity Analyses were performed to assess the effect of missing data on the primary efficacy endpoint. While efficacy was demonstrated, equivalence was not established for the ITT population analyzed with last observation carried forward, the ITT population with baseline observation carried forward or the ITT population with multiple imputations. The conclusions for these analyses were consistent with the primary analysis without imputations.

The data obtained from other submitted open-label studies provided supportive information regarding the decrease from baseline in mean intraocular pressure. Although inferior to Xalatan, the IOP reduction was a clinically significant reduction in IOP and represents a benefit over the potential risks of using the product.

7. Safety

The following studies were included in the Integrated Summary of Safety (ISS) for Xelpros (latanoprost ophthalmic emulsion) 0.005%. The safety analysis dataset for the Integrated Safety Summary included all subjects that were included in the safety analyses in each study.

Table 7.1.1 Studies Used to Evaluate Safety

Study Number / Study Phase	Study Design	Treatment Groups (Numbers of Subjects Treated)	Duration of Treatment / Age
Study CLR_08_01 (India) Phase 3	Multicenter, open-label, randomized, active-controlled, parallel group. Visits on Days -7, 0, 8, 15, and 29.	SPARC latanoprost (N=53) Xalatan (N=51)	Once daily for 4 weeks Age ≥ 18 years
Study CLR_10_01 (India)	Multicenter, open-label, randomized, active-controlled, parallel group	Subjects previously treated with Xalatan were switched over to SPARC latanoprost	Once daily for 8 weeks

Study Number / Study Phase	Study Design	Treatment Groups (Numbers of Subjects Treated)	Duration of Treatment / Age
Pilot	Visits on Days 0, 28, and 56.	(N=25 subjects, 46 eyes)	Age ≥ 18 years
Study CLR_09_12 (US, IND 102,842) Phase 3	Multicenter, assessor-masked, randomized, active-controlled, parallel group, non-inferiority study. Visits on Days -35, -7, 0, 7, 28, 56, and 84	SPARC latanoprost (N=289) Xalatan (N=289)	Once daily for 12 weeks Age ≥ 18 years
Study CLR_09_13 (US, IND 102,842) Phase 3	Multicenter, open-label, non-randomized, uncontrolled, single group assignment. Visits at Weeks 1, 4, 8, 12, 16, 20, 24, 28, 32, and 36.	Single group, all subjects received SPARC latanoprost (open label extension of prior Study CLR_09_12) (N=161)	Once daily for 36 weeks Age ≥ 18 years

Note: SPARC latanoprost 0.005% is the name used by the applicant during product development. SPARC latanoprost 0.005% and Xelpros (latanoprost ophthalmic emulsion) are interchangeable terms.

Four-hundred and forty-eight subjects were exposed to SPARC latanoprost 0.005% ophthalmic emulsion for a mean of 131.2 days. There were no deaths in any study.

Table 7.3.3-1 Subject Disposition

Subject Disposition	Treatment Group [1]	
	Xelpros 0.005%	Xalatan 0.005%
Subjects Included in ISS Analysis Set	448	340
Subjects with ≥ 1 dose study drug [2]	448	340
Subjects completed study	334 (74.6%)	324 (95.3%)
Subjects discontinued from the study	114 (25.4%)	16 (4.7%)
Reasons for Discontinuation		
Withdrawal of Consent	76 (17.0%)	7 (2.1%)
Protocol Violation	7 (1.6%)	1 (0.3%)
Adverse Event	5 (1.1%)	2 (0.6%)
Withdrawal of Subject by Investigator	10 (2.2%)	1 (0.3%)
Lost to follow up	6 (1.3%)	2 (0.6%)
Study Terminated by Sponsor	7 (1.6%)	2 (0.6%)
Study Medication Failure	3 (0.7%)	1 (0.3%)

1 81 subjects switched therapy from the Reference drug in Study CLR_09_12 to the Test drug in Study CLR_09_13. They both contributed data to both treatment groups. All subjects were counted once in the Total column.
2 Percentage was calculated based on the number of subjects treated with ≥ 1 dose of study drug in each group.
Source: ISS Table 14.1.1.1

Treatment-Emergent Adverse Events[a] Occurring in ≥ 1% of Subjects -ISS Analysis Population

Preferred Term	Xelpros 0.005% (N = 448)	Xalatan® (N = 340)
Eye Disorders		
Eye pain	248 (55%)	137 (40%)
Ocular hyperemia	189 (42%)	145 (43%)
Conjunctival hyperemia	67 (15%)	55 (16%)
Eye discharge	56 (12%)	41 (12%)
Growth of eyelashes	54 (12%)	36 (11%)
Eyelash thickening	40 (9%)	17 (5%)
Eye pruritus	20 (4%)	16 (5%)
Visual acuity reduced	16 (4%)	12 (3%)
Erythema of eyelid	15 (3%)	13 (4%)
Dry eye	13 (3%)	6 (2%)
Foreign body sensation in eyes	9 (2%)	6 (2%)
Punctate keratitis	6 (1%)	9 (3%)
Vision blurred	4 (1%)	8 (2%)
Chalazion	3 (1%)	7 (2%)
Eyelid edema	7 (2%)	1 (<1%)
Blepharitis	3 (1%)	4 (1%)
Eyelash discoloration	6 (1%)	2 (1%)
Lacrimation increased	4 (1%)	5 (1%)
Meibomianitis	4 (1%)	3 (1%)
Infections and infestations		
Upper respiratory tract infection	8 (2%)	0
Nervous system disorders		
Headache	8 (2%)	5 (1%)
Vascular disorders		
Hypertension	3 (1%)	6 (2%)

Source: ISS Table 14.3.3.2

Treatment-emergent adverse events which occurred in ≥ 5 % of subjects and more frequently in the Xelpros group compared to the Xalatan group were: eye pain (55%), conjunctival hyperemia (42%), and eye pruritus (4%).

Treatment-emergent adverse events which occurred in between 1 % and 5% of subjects and more frequently in the Xelpros group compared to the Xalatan group (highlighted above) were: dry eye (3%), upper respiratory tract infection (2%), foreign body sensation in the eyes (2%), eyelash discoloration (1%), eyelid edema (2%), eyelid margin crusting (1%), and meibomianitis (1%).

8. Advisory Committee Meeting

No Advisory Committee Meeting was held. There were no new issues raised in the review of the application which were thought to benefit from an Advisory Committee Meeting.

9. Pediatrics

Safety and effectiveness in pediatric patients have not been established. This application was presented at the Pediatric Regulatory Committee (PeRC) on August 13, 2014. A full waiver from studies for all pediatric age groups for this indication was considered acceptable for the reason that necessary studies would be impossible or highly impracticable because there are too few children with disease/condition to study. The prevalence and incidence of pediatric glaucoma and ocular hypertension is very low. The number of pediatric patients is very small and geographically dispersed.

10. Other Relevant Regulatory Issues

DSI

A Division of Scientific Investigations (DSI) audit was requested. The clinical sites of Drs. Tepedino, Gira, and Perez were selected for inspection because they were among the highest enrolling sites.

II. RESULTS (by Site):

Name of CI, Location	Protocol #/ Site #/ # of Subjects (enrolled)	Inspection Dates	Final Classification
Michael Tepedino, M.D. Cornerstone Eye Care 1400 E. Hartley Drive High Point, NC 27262-4317	CLR_09_012/ 03/ 43 and CLR_09_013/ 03/ 18	27-30 May 2014	NAI
Joseph Gira, M.D. Ophthalmology Consultants, Ltd. 12990 Manchester Road, Suite 201 St. Louis, MO 63131	CLR_09_013/ 08/ 16	2-4 Jun 2014	NAI
Bernard R. Perez, M.D. International Research Center 4506 Wishart Place Tampa, FL 33603	CLR_09_013/ 13/ 16	2-4 Jun 2014	VAI

Key to Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.
Pending = Preliminary classification based on information in Form FDA 483 or preliminary communication with the field; EIR has not been received from the field or complete review of EIR is pending.

The clinical investigator sites of Drs. Tepedino and Gira were not issued Form FDA 483s, and the final classification of these inspections was No Action Indicated (NAI). Dr. Perez's clinical site was issued a Form FDA 483, and the final classification of this inspection was Voluntary Action Indicated (VAI). The data generated by these clinical sites appear adequate in support of the respective indication.

FINANCIAL DISCLOSURE

The applicant has examined its financial data regarding significant payments of other sorts made to all investigators in the studies and equity information as provided by the investigators, as defined in 21 CFR 54.2. There is no evidence to suggest that the results of the study were impacted by any financial payments.

DMEPA

The Division of Medication Error Prevention and Analysis (DMEPA) finalized a letter to the applicant dated May 19, 2014, finding the proprietary name, Xelpros, to be conditionally acceptable.

11. Labeling

The labeling of NDA 206185, Xelpros (latanoprost ophthalmic emulsion) 0.005% is recommended to be revised to be consist with the labeling found in the Appendix at the end of the Cross Discipline Team Leader (CDTL) review once the facilities to be used to manufacture the product are found to be in compliance with current good manufacturing procedures (cGMPs).

12. Recommendations/Risk Benefit Assessment

RECOMMENDED REGULATORY ACTION:

NDA 206185, Xelpros (latanoprost ophthalmic emulsion) 0.005% is **not** recommended for approval at this time due to the need for all facilities to be in compliance with current Good Manufacturing Procedures and for the labeling to be revised as described in the CDTL review. There is substantial evidence of safety and efficacy consisting of an adequate and well controlled study and supportive evidence from three additional open-label studies which demonstrate that Xelpros dosed once daily in the evening, is safe for the reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

Wiley A. Chambers, MD
Deputy Division Director
Division of Transplant and Ophthalmology Products

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/s/

WILEY A CHAMBERS
11/20/2014

Medical Officer's Review of NDA 206-185
Review #2

NDA 206-185	**Submission Date:**	January 31, 2014
	Receipt Date:	January 31, 2014
	Review Date:	November 18, 2014
Applicant:	Sun Pharma Advanced Research Company, Ltd. Tandalja, Vadodara Gujarat, India 309920	
Applicant's Representative:	Aron Shapiro, VP. Ora Inc. 300 Brickstone Square Andover, MA 01810	
Drug:	Xelpros (latanoprost ophthalmic emulsion) 0.005%	
Pharmacologic Category:	prostaglandin analog	

Provided is an updated Table 7.4.1-1 and updated Reviewer Comments for Section 7.4.1 (page 52) of the Medical Officer's Review dated November 3, 2014.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Table 7.4.1-1
Treatment-Emergent Adverse Events
Occurring in ≥ 1% of Subjects in Any Treatment Group[1, 2]
ISS Analysis Population

Preferred Term	Xelpros 0.005% (N = 448)	Xalatan® (N = 340)
Eye Disorders		
Eye pain	248 (55.4%)	137 (40.3%)
Ocular hyperemia	189 (42.2%)	145 (42.6%)
Conjunctival hyperemia	67 (15.0%)	55 (16.2%)
Eye discharge	56 (12.5%)	41 (12.1%)
Growth of eyelashes	54 (12.1%)	36 (10.6%)
Eyelash thickening	40 (8.9%)	17 (5.0%)
Eye pruritus	20 (4.5%)	16 (4.7%)
Visual acuity reduced	16 (3.6%)	12 (3.5%)
Erythema of eyelid	15 (3.3%)	13 (3.8%)
Dry eye	13 (2.9%)	6 (1.8%)
Foreign body sensation in eyes	9 (2.0%)	6 (1.8%)
Punctate keratitis	6 (1.3%)	9 (2.6%)
Vision blurred	4 (0.9%)	8 (2.4%)
Chalazion	3 (0.7%)	7 (2.1%)
Eyelid edema	7 (1.6%)	1 (0.3%)
Blepharitis	3 (0.7%)	4 (1.2%)
Eyelash discoloration	6 (1.3%)	2 (0.6%)
Lacrimation increased	4 (0.9%)	5 (1.5%)
Meibomianitis	4 (0.9%)	3 (0.9%)
Infections and infestations		
Upper respiratory tract infection	8 (1.8%)	0 (0.0%)
Nervous system disorders		
Headache	8 (1.8%)	5 (1.5%)
Vascular disorders		
Hypertension	3 (0.7%)	6 (1.8%)

Source: Module 5.3.5.3 ISS Table 14.3.2.2

1 81 subjects switched therapy from the RLD in study CLR_09_12 TO THE Test drug in study CLR_09_13. They contributed data to both treatment groups. **2** n= number of subjects with at least one event. Each subject was counted once per event if the subject had more than one occurrence of the same event.

Reviewer's Comment:
Treatment-emergent adverse events which occurred in ≥ 5 % of subjects and more frequently in the Xelpros group compared to the Xalatan group (highlighted above) were: eye pain (55%), eye discharge (13%), growth of eyelashes (12%) and eyelash thickening (9%).

Treatment-emergent adverse events which occurred in between 1 % and 5 % of subjects and more frequently in the Xelpros group compared to the Xalatan group (highlighted above) were: visual acuity reduced (4%), dry eye (3%), foreign body sensation in the eyes (2%), headache (2%), upper respiratory tract infection (2%), eyelid edema (2%), and eyelash discoloration (1%).

Rhea Lloyd, M.D.
Medical Officer
Division of Transplant and Ophthalmology Products

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/s/

RHEA A LLOYD
11/18/2014

WILLIAM M BOYD
11/18/2014

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	206185
Priority or Standard	Standard
Submit Date(s)	January 31, 2014
Received Date(s)	January 31, 2014
PDUFA Goal Date	November 30, 2014
Division / Office	DTOP/OAP
Reviewer Name(s)	Rhea A. Lloyd, MD
Review Completion Date	October 31, 2014
Established Name	Latanoprost ophthalmic emulsion, 0.005%
(Proposed) Trade Name	Xelpros
Therapeutic Class	Prostaglandin analog
Applicant	Sun Pharm Advanced Research Company Ltd. Tandalja, Vadodara Gujarat, India 390020 91-265-663-5500
US Representative	Aron Shapiro, VP Ora., Inc. 300 Brickstone Square Andover, MA 01810 978-685-8900
Formulation(s)	Ophthalmic emulsion
Dosing Regimen	Once daily in the evening
Indication(s)	Reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension.
Intended Population(s)	Patients with open-angle glaucoma or ocular hypertension

Template Version: March 6, 2009

Table of Contents

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

From a clinical perspective, it is recommended that NDA 206185, Xelpros (latanoprost ophthalmic emulsion) 0.005% be approved for the reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension with labeling revisions listed in this review.

The dosing recommendation is for one drop daily in the evening.

This application relies upon the Agency's findings of safety and efficacy for NDA 20-597, Xalatan (latanoprost ophthalmic solution) approved in 1996. Xalatan (latanoprost ophthalmic solution) is the same in strength and route of administration as Xelpros (latanoprost ophthalmic emulsion). Xalatan and Xelpros are different dosage forms, i.e., solution versus emulsion.

Study CLR_09_12 comparing Xelpros (latanoprost ophthalmic emulsion) 0.005% and Xalatan did not establish equivalence with the preplanned clinical endpoint of change from baseline in intraocular pressure. The decrease in mean intraocular pressure in Xelpros-treated patients was 5 – 6 mmHg approximately 0.5 mmHg less than Xalatan treated patients. The data obtained from other submitted open-label studies provided supportive information regarding the decrease from baseline in mean intraocular pressure.

1.2 Risk Benefit Assessment

Study CLR_09_12, the bioequivalence study, submitted in this application revealed that Xelpros was less effective than Xalatan by up to 1.06 to 1.47 mmHg (95% confidence interval upper bound) at 7 of 12 timepoints. Although inferior to Xalatan, the IOP reduction is a clinically significant reduction in IOP and represents a benefit over the potential risks of using the product.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

There are no risk management activities recommended beyond the routine monitoring and reporting of all adverse events.

1.4 Recommendations for Postmarket Requirements and Commitments

There are no recommended Postmarketing Requirements or Phase 4 Commitments.

2 Introduction and Regulatory Background

2.1 Product Information

Latanoprost is a prostaglandin analog, F2-α receptor agonist. Latanoprost is absorbed through the cornea where the isopropyl ester prodrug is hydrolyzed to latanoprost acid a derivative of prostaglandin F2-α which is biologically active. It is believed that latanoprost reduces intraocular pressure by increasing uveoscleral aqueous outflow from the eye.

The concentration of latanoprost selected for this application is 0.005% the same as the approved reference listed drug (RLD) Xalatan. However, Xalatan (NDA 20-597) which was approved in 1996 for the once daily dosing for the reduction of elevated IOP in subjects with open-angle glaucoma or ocular hypertension is an ophthalmic solution, and the submitted latanoprost product is an emulsion.

Table 2.1-1 Composition of SPARC's Latanoprost Ophthalmic Formulation (W/V %)

	Xelpros 0.005%			
Component	**Amount (per mL)**	**% w/v**	**Function**	**Reference to Quality Standards**
Latanoprost	0.05	0.005	Active ingredient	In house
Potassium sorbate	4.70	0.47	Preservative	NF
Boric acid	(b) (4)			NF
Disodium EDTA				USP
Castor Oil				USP
(b) (4)				Ph. Eur.
Propylene Glycol				USP
Sodium Borate				NF
Hydrochloric acid				NF
Sodium Hydroxide				NF
Water for injection				USP

The proposed drug product formulation differs from the RLD Xalatan. Xalatan contains the following excipients: monobasic sodium phosphate, dibasic sodium phosphate, sodium hydroxide, benzalkonium chloride (preservative), water for injection.

Reviewer's Comment:
The applicant has described the proposed drug product as a "microemulsion." "Microemulsion" is not a recognized dosage form. The ONDQA CMC review has determined that the proposed drug product is an emulsion.

2.2 Tables of Currently Available Treatments for Proposed Indications

There are many ophthalmic drug products approved for lowering intraocular pressure in patients with open-angle glaucoma and ocular hypertension. These treatments include beta-adrenergic antagonists (beta-blockers), alpha-adrenergic agonists, parasympathomimetic (miotic) agents, carbonic anhydrase inhibitors, and prostaglandin analogs.

Drug Products with Approved NDAs

Pharmacologic Class/ Applicant	**Trade Name**	**Established Name**
Alpha-2 agonists		
Allergan, Inc.	Alphagan/ Alphagan P	brimonidine tartrate
Beta-adrenergic antagonists		
Alcon	Betoptic/ Betoptic S	betaxolol hydrochloride
Novartis	Ocupress	carteolol hydrochloride
Allergan	Betagan	levobutanol hydrochloride
Bausch & Lomb	Optipranolol	metipranolol
Vistakon	Betimol	timolol hemihydrate
Aton Pharma	Timoptic	timolol maleate
Ista	Istalol	timolol maleate
Aton Pharma	Timoptic XE	timolol maleate gel forming solution
Carbonic Anhydrase Inhibitors		
Duramed Pharamaceuticals	Diamox	acetazolamide
Sandoz, Inc.	N/A	methazolamide
Topical Carbonic Anhydrase Inhibitors		
Alcon	Azopt	brinzolamide
Merck	Trusopt	dorzolamide hydrochloride
Cholinergic agonist		
Alcon	Pilopine HS	pilocarpine hydrochloride gel
Alcon	Isopto Carpine	pilocarpine hydrochloride
Prostaglandin Analogues		
Allergan	Lumigan	bimatoprost
Pharmacia	Xalatan	latanoprost
Alcon	Travatan	travoprost
Alcon	Travatan Z	travoprost
Merck	Zioptan	tafluprost
Alcon	Izba	travoprost
Sympathomimetics		
Allergan	Propine	dipivefrin hydrochloride

Pharmacologic Class/ Applicant	Trade Name	Established Name
Combination Products		
Merck	Cosopt	dorzolamide hydrochloride/timolol maleate
Merck	Cosopt PF	dorzolamide hydrochloride/timolol maleate
Allergan	Combigan	brimonidine tartrate/timolol maleate
Alcon	BetopticPilo	betaxolol hydrochloride/pilocarpine hydrochloride
Alcon	Simbrinza	Carbonic anhydrase inhibitor/alpha-agonist
Other		
Sucampo Pharma Americas, Inc.	Rescula	unoprostone isopropyl

2.3 Availability of Proposed Active Ingredient in the United States

Latanoprost is currently available as Xalatan (latanoprost ophthalmic solution) 0.005%. There are also multiple generic formulations of latanoprost ophthalmic solution, 0.005% currently marketed.

2.4 Important Safety Issues With Consideration to Related Drugs

Prostaglandin associated safety issues are described in current class labeling. The safety issues identified in class labeling include increased eyelash, iris and periocular pigmentation, eyelash growth and intraocular inflammation. Information regarding these safety concerns is presented in the approved labeling of the reference listed drug, Xalatan.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

SPARC, Ltd., submitted an IND application for SPARC latanoprost ophthalmic emulsion 0.005% to the Agency in 2009. SPARC completed two clinical studies (CLR_09_12 and CLR_09_13) under this IND in 2012.

A Pre-IND meeting was held on September 16, 2008, to discuss the development plans for IND 102,842 for latanoprost ophthalmic emulsion. Advice was given regarding CMC, nonclinical and clinical development including recommended study design, criteria for determining IOP equivalence and expectations for reformulations of an approved drug product in the preliminary comments and face-to-face meeting.

The original IND was submitted in January 2009 and included protocols for Studies CLR_09_12 and CLR_09_13. The need for safety information on a minimum of 100 patients followed for 6

months in one of the studies as well as endothelial cell counts were included in the comments to the sponsor.

A Pre-NDA meeting was held on February 20, 2013, to discuss the results from the Phase 3 non-inferiority and safety studies performed by SPARC, Ltd. At this meeting, the Division reiterated the criteria for establishing IOP equivalence and expected safety information in light of the study results submitted.

2.6 Other Relevant Background Information

Intraocular pressure (IOP) is currently the accepted standard for establishing the efficacy of ocular hypotensive medications.

For the proposed indication, a demonstration of efficacy is recommended to include equivalence or superiority to an acceptable active control, in this instance, Xalatan® (latanoprost ophthalmic solution) 0.005% administered once a day in the evening. Efficacy is attained if the difference in mean IOP between treatment groups is within ±1.5 mm Hg at all post-baseline time points; and within ±1.0 mm Hg at the majority of post-baseline time points. The time points should include both the peak and trough efficacy times. This requirement for equivalence has been used for the approval of several IOP lowering products.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The NDA was submitted in the eCTD format including, among other documents, the clinical study report, the finalized protocol and statistical analysis plan.

The statistical reviewer identified several issues during the review process of Study CLR_09_12. These issues were related to the applicant's primary efficacy results and the analysis dataset that contained the primary efficacy variable.

From the Statistical Review:

> Regarding the primary efficacy results, the reviewer was initially unable to reproduce the applicant's primary efficacy results presented in the clinical study report (CSR). The issue was brought to the attention of the applicant through an information request dated on June 5, 2014. In an email response dated on June 11, 2014, the applicant acknowledged the issue and indicated that the primary efficacy results reported in the CSR were incorrect and were produced based on using an intermediate dataset instead of using the final ADaM dataset that was submitted to the Agency. With that the applicant confirmed that even though the results reported in the CSR were incorrect, the ADaM dataset that was submitted to the Agency as part of the NDA submission was correct and agreed to submit an updated CSR. Based on the applicant's confirmation regarding the dataset, the reviewer continued using the ADaM dataset in the review.

The issue concerning the analysis dataset was related to the way data collected in the case report form (CRF) were linked to the analysis visits in the clinical database. In the CRF, data were recorded under visit names visit 1, visit 2, visit 3, and visit 4 (end-of-study visit); and irrespective of the dates these visits had occurred, the CRF data collected at visit 1, visit 2, visit 3, and visit 4 were respectively linked to analysis visits week 1, 4, 8, and 12 in the clinical database. Due to this link, the end-of-study visit data for the majority of early terminated subjects were incorrectly linked to the week 12 visit. Note that the majority of early terminated subjects withdrew the study before the week 12 visit. In the reviewer's opinion, the analysis visits should have been defined programmatically by taking the visit dates into account. This issue was also brought to the attention of the applicant through an information request dated on July 15, 2014. The applicant acknowledged the issue and submitted an updated dataset on July 23, 2014. The reviewer confirmed the corrections made to the analysis visits.

On September 03, 2014 the applicant submitted an amended CSR based on the updated dataset. Assuming updates were made only in the analysis visits, the reviewer had performed all the efficacy analyses using the original ADaM dataset with the updated analysis visits; however, the results were still not matching. After a thorough investigation of the updated dataset, the reviewer noted changes in the precision used in the primary efficacy data (IOP data) between the updated and the original ADaM dataset. In the ADaM dataset, the IOP data were rounded up (0.5 or greater) or down (0.49 or lower) to the nearest integers while no rounding was made in the updated dataset.

Although the reviewer was initially unable to reproduce the primary efficacy results due to the difference in precision in the IOP data between the two datasets, the results were finally reproduced when the unrounded IOP data were used.

In summary, the reviewer has no issue with the applicant using either the rounded or unrounded IOP data to produce the primary efficacy results; however, they should have communicated all the changes made when the updated dataset was submitted to the Agency.

3.2 Compliance with Good Clinical Practices

The studies performed under IND 102,842 (CLR_09_12 and CLR_09_13) were conducted in accordance with the International Conference of Harmonization E6 Guidelines for Good Clinical Practices (GCPs), the Declaration of Helsinki. The studies performed in India were performed in compliance with relevant local and national regulations for informed consent and protection of subject's rights in the country of conduct.

Before initiation of the studies, the original protocol, all protocol amendments, the informed consent documents and all supportive information were reviewed and approved by the appropriate ethics committees (EC) or institutional review boards (IRB) for each of the centers involved in the study. The study began after receiving written approval from each EC/IRB.

Between June 2 and 4, 2014, the Office of Scientific Investigations (OSI) performed a clinical inspection which included a data audit of the clinical site for Protocol CLR_09_13 for

Investigator Bernard R. Perez, MD. Dr. Perez's site randomized 16 subjects and 6 subjects completed the study. At the conclusion of the inspection, the site was classified VAI and a Form FDA 483 was issued noting the following deficiencies: failure to obtain subject consent and failure to adhere to the protocol. Dr. Perez responded in writing to the Form 483 committing to corrective actions including increased oversight of studies, formal training for all study coordinators emphasizing SAE reporting and consent procedures, and the inclusion of clarifying language in the study visit source documents as reminders of when re-consenting procedures or SAE reporting would be applicable. Dr. Perez's response appeared adequate. OSI determined that the data generated by this site appeared acceptable in support of the indication.

Between May 27 and 30, 2014, OSI performed a clinical inspection at the site of investigator Michael E. Tepedino, MD for Protocol CLR_09_12. Dr. Tepedino's site screened 47 subjects, enrolled 43 subjects and completed 41 subjects in the study. For Protocol CLR_09_13, 18 subjects were screened and 5 subjects completed the study. The site was classified NAI. No Form FDA 483 was issued. The studies appeared to have been conducted adequately and the data generated by the site appeared acceptable in support of the indication.

3.3 Financial Disclosures

(b) (4) has adequately disclosed financial arrangements with the clinical investigators who participated in the clinical development program for latanoprost 0.005%. None of the investigators had financial arrangements or interests to disclose.

Refer to Appendix 9.3 Clinical Investigator Financial Disclosure for further details.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The proposed drug product is latanoprost ophthalmic emulsion, 0.005%. It is an off white, translucent, isotonic, sterile emulsion preserved using potassium sorbate, NF. It will be supplied as a 2.5 mL (b) (4) in a (b) (4) 5 mL low density polyethylene bottle.

Composition of SPARC's Latanoprost Ophthalmic Formulation (W/V %)

Component	Amount (per mL)	% w/v	Function	Reference to Quality Standards
Latanoprost	0.05	0.005	Active ingredient	In house
Potassium sorbate	4.70	0.47	Preservative	NF
Boric acid	(b) (4)		(b) (4)	NF
Disodium EDTA				USP
Castor Oil				USP
(b) (4)				Ph. Eur.
Propylene Glycol				USP
Sodium Borate				NF
Hydrochloric acid				NF
Sodium Hydroxide				NF
Water for injection				USP

4.2 Clinical Microbiology

There is no clinical microbiology review for this product. It is not an anti-infective.

4.3 Nonclinical Pharmacology/Toxicology

The application relies upon the Agency's findings for NDA 20-597 Pfizer's Xalatan (latanoprost ophthalmic solution) 0.005% for demonstration of safety and efficacy for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension. The appropriateness of this reliance will be on the basis of demonstrating nonclinical comparability and clinical equivalence to Xalatan, the reference listed drug (RLD).

All of the inactive excipients included in the final formulation are in concentrations that have been previously approved by the FDA for ophthalmic products except [redacted] (b) (4) ([redacted] (b) (4)). [redacted] (b) (4) is a non-ionic solubilizer for parenteral applications (injections) and for other liquid and solid dosage formulations requiring a solubilizing agent. SPARC and [redacted] (b) (4), the manufacturer of [redacted] (b) (4), have performed ocular and systemic toxological studies which showed that it is nontoxic. [redacted] (b) (4) did produce histamine release after IV administration in dogs.

Refer to the non-clinical review for further details.

4.4 Nonclinical Pharmacology

4.4.1 Mechanism of Action

Latanoprost is a prostaglandin analog, F2-α receptor agonist. Latanoprost is absorbed through the cornea where the isopropyl ester prodrug is hydrolyzed to latanoprost acid a derivative of prostaglandin F2-α which is biologically active. It is believed that latanoprost reduces intraocular pressure by increasing uveoscleral aqueous outflow from the eye.

4.4.2 Pharmacodynamics

The pharmacologic profiles of latanoprost have been well characterized in the past. Reference is made to the Agency's finding of safety and efficacy for NDA 20-597 Xalatan approved in 1996.

4.4.3 Pharmacokinetics

SPARC performed a comparative PK/ tissue distribution study of subocular exposure to Xelpros (latanoprost ophthalmic emulsion) 0.005% and Xalatan in NZW rabbits. In this study, both Xelpros (latanoprost ophthalmic emulsion) 0.005% and Xalatan were rapidly absorbed into the eye with the highest concentration found in anterior tissues and aqueous humor and low concentrations found in posterior tissues and vitreous humor. Latanoprost was rapidly eliminated from ocular tissues and fluids, with the exception of the eyelid. No latanoprost was detected in the lens. Latanoprost did not preferentially accumulate in melanin-rich tissues such as the iris and ciliary body and retina. Overall the ocular tissue distribution appears to be comparable between SPARC's product and Xalatan in NZW rabbits.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Summary of All Clinical Studies

Study Identifier / Study Type	Study Objective	Study Design	Treatment Group	Duration of Treatment	Endpoints	
					Efficacy	Safety
US Safety and Efficacy Studies						
Study CLR_09_12 (IND 102,842) Phase 3	Test the non-inferiority of SPARC latanoprost vs. Xalatan for the reduction of IOP	Multicenter, assessor-masked, randomized, active-controlled, parallel group, non-inferiority study. Visits on Days -35, -7, 0, 7, 28, 56, and 84.	• SPARC latanoprost (N=289) • Xalatan (N=289)	Once daily for 12 weeks Age ≥ 18 years	*1º Efficacy Endpoint:* Change from baseline in IOP	Adverse events and serious adverse events Ophthalmic exams: VA, SLE, conjunctival hyperemia, DFE, VF, iris-eyelash photos, Endothelial cell count Vital signs: HR, BP
Study CLR_09_13 (IND 102,842) Phase 3	Investigate the long-term safety of SPARC latanoprost 0.005% ophthalmic (b) (4) when administered once daily in subjects aged 18 years and above	Multicenter, *open-label*, non-randomized, uncontrolled, single group assignment study. Visits at Weeks 1, 4, 8, 12, 16, 20, 24, 28, 32, and 36.	Single group, all subjects received SPARC latanoprost (open label extension of prior Study CLR_09_12) N=161	Once daily for 36 weeks Age ≥ 18 years	Not applicable	IOP, VA, SLE, conjunctival hyperemia, DFE, endothelial cell count, VF, iris-eyelash photos, Vital signs: HR, BP, AEs.

Study CLR_08_01 (India) Phase 3	Compare the efficacy and safety of latanoprost 0.005% (SPARC Ltd.) with latanoprost 0.005% ophthalmic (b) (4) (Xalatan) in subjects with POAG or OH.	Multicenter, *open-label*, randomized, active-controlled, parallel group study. Visits on Days -7, 0, 8, 15, and 29.	• SPARC latanoprost (N=53) • Xalatan (N=51)	Once daily for 4 weeks Age ≥ 18 years	*1º Efficacy Endpoint:* Reduction of IOP compared to baseline *2º Efficacy Endpoints:* Mean defect score on VF, C/D ratio, Investigator's clinical glaobal impression of change, Subject's global impression of change	Adverse events Vital signs, ophthalmic exams, dilated slit lamp exams, DFE, VA, clinical laboratory tests
Study CLR_10_01 (India) Pilot	Evaluate tear break-up time, inferior corneal staining, ocular surface disease, and IOP	Multicenter, *open-label,* randomized, single arm pilot study. Visits on Days -0, 28, and 56.	Subjects previously treated with Xalatan were switched over to BKC-free SPARC latanoprost (N=25 subjects, 46 eyes)	Once daily for 8 weeks Age ≥ 18 years	*1º Efficacy Endpoint:* Tear break-up time *2º Efficacy Endpoints:* OSDI, inferior corneal staining, conjunctival hyperemia, change in IOP	Adverse events

Note: SPARC latanoprost 0.005% is the name used by the applicant during product development. SPARC latanoprost 0.005% and Xelpros (latanoprost ophthalmic emulsion) are interchangeable terms.

Reviewer's Comments: *Of the studies submitted for review, only Study CLR_09_12 was adequate, well-controlled and aligned with the Division's recommendations for study design and endpoints for the demonstration of safety and efficacy for the intended indication, reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension. Studies CLR_09_13, CLR_08_01 and CLR_10_01 were open-label studies.*

5.2 Review Strategy

The submitted clinical study reports, clinical protocols and literature reports related to were reviewed. Modules 1 and 5 of the submission were reviewed in depth.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 Protocol – CLR_09_12

Comparison of the Efficacy and Safety of SPARC's Latanoprost 0.005% Ophthalmic (b) (4) *(Test) and Xalatan (Latanoprost 0.005% Ophthalmic Solution – Reference) When Administered Once Daily in Subjects with Open Angle Glaucoma or Ocular Hypertension: A Clinical Non-Inferiority Study*

Study Centers
This study was conducted at 21 investigational centers within the US.

Site No.	No. of Randomized Subjects	Principal Investigator Name, Address	Subinvestigators
	Module 5.3.5.1.1\ CLR_09_12\ Section 16.2.1.2	Module 5.3.5.1.1\CLR_09_12\Section 16.1.4.1	
01	16	David Shulman, M.D. David Shulman, M.D., P.A. 999 E. Basse Rd., Suite 127 San Antonio, TX 78209	F Trujillo MD
02	39	Eugene Protzko, M.D. Seidenberg Protzko Eye Associates 2023 Pulaski Hwy. Havre De Grace, MD 21078	J. Seidenberg MD, M. Trottini MD, W. Batista OD, N. Frank OD, S. Spearman OD, M. Steg OD
03	43	Michael Tepedino, M.D. Cornerstone Eye Care 307 N. Lindsay St. High Point, NC 27262	R. DaVanzo MD, Y. Radionchenko MD, C. Tara MD
04	24	Stephen Smith, M.D. Eye Associates of Fort Myers 4225 Evans Ave. Ft. Myers, FL 33901	None

Site No.	No. of Randomized Subjects	Principal Investigator Name, Address	Subinvestigators
05	30	Douglas Day, M.D. Coastal Research Associates, LLC 11205 Alpharetta Hwy., Suite J-3 Roswell, GA 30076	None
06	11	Katherine Ochsner, M.D. Eye Associates of Wilmington 1729 New Hanover Medical Park Dr. Wilmington, NC 28403	None
07	21	Ranjan Malhotra, M.D. Ophthalmology Associates 12990 Manchester Rd., Suite 200 St. Louis, MO 63131	A. Fedyk MD, G.Berdy MD, R. Malhotra MD, R. Brusatti OD
08	30	Joseph Gira, M.D. Ophthalmology Consultants, Ltd. 12990 Manchester Rd., Suite 201 St. Louis, MO 63131	J. Amato MD, S. Lee MD, E. Sullivan OD
09	24	Sherif EI-Harazi, M.D. Lugene Eye Institute 801 S. Chevy Chase Dr., Suite 103 Glendale, CA 91205	T. Dinh MD
10	24	Fiaz Zaman, M.D. Houston Eye Associates 2855 Gramercy St. Houston, TX 77025	W. Stewart MD, J. Arnault MD
11	0	Bruce Koffler, M.D. Koffler Vision Group 120 N. Eagle Creek Dr., Suite 431 Lexington, KY 40509	None
12	25	Asra Firozvi, M.D. North Carolina Eye, Ear, Nose and Throat 4102 N. Roxboro Rd. Durham, NC 27704	M. James MD
13	26	Bernard Perez, M.D. International Research Center 4506 Wishart Place Tampa, FL 33603	D. Perez Ortiz MD
14	16	Steve Simmons, M.D. Glaucoma Consultants of the Capital Region 1240 New Scotland Rd., Suite 201 Slingerlands, NY 12159	M. Kaback MD, R. Sanchez MD

Site No.	No. of Randomized Subjects	Principal Investigator Name, Address	Subinvestigators
15	5	Johann Ohly, M.D. St. Johns Clinic- Eye Specialists 1229 E. Seminole, Suite 430 Springfield, MO 65804	S. Tauber MD
16	31	Gregory Sulkowski, M.D. Taustine Eye Center 1169 Eastern Parkway, Suite 3427 Louisville, KY 40217	J. Hurt OD
17	4	Sanjiv Kumar, M.D. DCT - Kumar Research 927 E. Main St. Uvalde, TX 78801	None
18	70	Kenneth Sall, M.D. Sall Research Medical Center 11423 187th St., Suite 200 Artesia, CA 90701	None
19	76	David Wirta, M.D. Eye Research Foundation 520 Superior Ave., Suite 235 Newport Beach, CA 92663	K. Kurteeva MD
22	53	James Peace, M.D. United Medical Research Institute 431 N Prairie Ave. Inglewood, CA 90301	None
23	22	Matthew McMenemy, M.D. Lone Star Eye Care, P.A. 3515 Town Center Blvd. South Sugar Land, TX 77479	J. Cruz MD

Study Objectives

To demonstrate that SPARC's latanoprost 0.005% ophthalmic (b) (4) is non-inferior to the reference drug Xalatan (latanoprost ophthalmic solution) 0.005% in mean IOP reduction from baseline at each visit and at each time point throughout the study.

Methodology

This study was a multicenter, assessor-masked, randomized, parallel group study to evaluate the efficacy and safety of SPARC latanoprost 0.005% ophthalmic (b) (4) Subjects were randomized in a 1:1 ratio to receive either SPARC latanoprost or Xalatan once daily at 8 PM. There were seven study visits scheduled: Screening Visit (Day -35), Eligibility Visit (Day -7), Baseline Visit (Day 0), Visit 1 (Day 7), Visit 2 (Day 28), Visit 3 (Day 56), and End-of-Study Visit (Day 84). Within each study center, subjects were stratified by baseline IOP in the study eye. The stratification levels were Low IOP (22-28 mmHg group [Stratum 1]) and High IOP (29-35 mmHg group [Stratum 2]). A double-masked design was not feasible due to differences in treatment packaging. However, the assessor (responsible for all ophthalmic examinations)

was masked to treatment assignment. All study procedures other than ophthalmic examinations were performed by a study coordinator.

If needed, appropriate washout of previous medication was performed by the discontinuation of existing treatments on the following schedule.

Minimum Washout Periods of Previous Medications	
Glaucoma Medication Class	**Minimum Washout Period from Screening to Eligibility Visit**
Beta-antagonists	4 weeks
Topical corticosteroids	1 week
All other IOP altering medications	72 hours

Study Schedule

Activity	Screening Day-35	Eligibility Day -7	Day 0 Baseline			Day 7 (Week 1± 1 day) Visit 1			Day 28 (Week 4 ± 1 day) Visit 2			Day 56 (Week 8 ± 1 day) Visit 3			Day 84 (Week 12 ± 1 day) End-of-Study		
			8 AM	10 AM	4 PM	8 AM	10 AM	4 PM	8 AM	10 AM	4 PM	8 AM	10 AM	4 PM	8 AM	10 AM	4 PM
Screen subject	×																
Informed consent	×																
Medical & Surgical History	×																
Demographics	×																
Discontinue Glaucoma Rx	×																
Vital Signs (Resting pulse, Blood pressure [sitting])	×	×	×			×			×			×			×		
Gonioscopy[1]	×																
Central corneal thickness (ultrasound pachymeter)		×															
Corneal endothelial cell count (Non-contact specular microscope)[3]		×													×		
IOP[2] with Goldmann applanation tonometer	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×
Visual Acuity (best corrected) on ETDRS	×	×	×			×			×			×			×		
Slit lamp biomicroscopy	×	×	×			×			×			×			×		
Conjunctival hyperemia assessment with ORA scale #6.0b		×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×
Dilated ophthalmoscopy	×														×		
Humphrey 24-2 / 30-2 visual field (SITA standard)[3]	×														×		
Iris- eyelash photography (standardized digital camera)		×													×		
Concomitant medication			×			×			×			×			×		
Treatment emergent adverse events						×	×	×	×	×	×	×	×	×	×	×	×
Dispense study diary			×			×			×			×					
Collect study diary						×			×			×			×		
Dispense study medication					×						×			×			
Collect study medication									×			×			×		
Urine Pregnancy Test		×													×		
Complete exit exam															×		

[1] Gonioscopy was conducted only if this procedure had not been performed and documented within the last 6 (six) months
[2] At eligibility visit, IOP was measured once, at 10 AM or at 4 PM. All IOP measurements were ± 30 minutes of the required time
[3] Exit corneal endothelial cell count and visual field examination were performed after the 8 AM exam and before the 4 PM exam (only once)

Number of Subjects

Planned:

Screened: 650 Randomized: 576

Analyzed:

Screened: 723 Randomized: 578

Diagnosis and Main Criteria for Inclusion

Each subject entered into this trial was diagnosed with ocular hypertension (OHT) or primary open-angle glaucoma (POAG). Pseudoexfoliation or pigment dispersion component was acceptable. Each subject had to have had an unmedicated IOP ≥ 22 mmHg in one or both eyes with no more than 5 mmHg inter-eye IOP difference at the Eligibility Visit.

Efficacy

Primary Efficacy Variable

Change from baseline in intraocular pressure (IOP) of the study eye at each of the 12 time points (8 AM, 10AM, and 4 PM on Days 7, 28, 56, and 84).

Safety

Safety Variables

- Adverse events
- Visual acuity – Best corrected logMAR acuity was assessed using an ETDRS chart
- Slit lamp biomicroscopy
- Conjunctival hyperemia
- Dilated ophthalmoscopy
- Corneal endothelial cell count
- Visual field
- Iris and eyelash changes
- Vital signs (HR and sitting BP)

Analysis Populations

Intent-to-Treat (ITT) population: All randomized subjects. The primary efficacy analysis was performed on the ITT population without last observation carried forward (LOCF).
Per-Protocol (PP) population: All subjects who had completed the End-of-Study visit (Week 12/ Day 84) and did not have any major protocol violations.
Safety population: All subjects who were randomized and received at least one dose of study medication.

Efficacy Analysis

The change from baseline in IOP was analyzed using an analysis of covariance (ANCOVA) methodology that included treatment, site, and baseline IOP group (Low IOP: 22-28 mmHg and High IOP group: 29-35 mmHg) as a covariate in the model. To test the null hypothesis, a two-sided 95% CI for mean difference between Xalatan and SPARC latanoprost in terms of mean IOP change from baseline at each time point (or 12 time points) was computed. Robustness of the treatment effect was explored by removing the baseline IOP group covariate from the ANCOVA model.

Non-inferiority of SPARC latanoprost relative to Xalatan was established if the following 3 steps were established simultaneously:

- *Step 1: 95% CI included 0 for all 12 time points*
- *Step 2: The upper limit of the 95% CI was < 1.5 at all 12 time points*

- *Step 3: The upper limit of 95% CI was < 1 at most (at least 7 of 12) time points*

The efficacy analysis was also conducted using the PP population without LOCF.

Efficacy sensitivity analyses were conducted on the ITT population to assess the impact of missing data, and secondary analyses were conducted to analyze the impact of potential interactions between treatment, site, and baseline IOP on the efficacy conclusions drawn from the primary analysis. Three different missing data imputation methods were examined: LOCF, baseline observation carried forward (BOCF), and multiple imputation (MI).

Subgroup analysis was performed on the ITT population; the subgroup was defined based on baseline IOP: Low IOP group (22-28 mmHg) and High IOP group (29-35 mmHg). Change from baseline was analyzed for each subgroup in a similar way to the primary efficacy analysis.

Two exploratory analyses were conducted, one by site, and the second by using a modified ITT population, both without LOCF. The modified ITT population exploratory analysis excluded ITT subjects whose IOP had dropped below 22 mmHg at baseline visit.

Safety Analysis

Safety analyses were performed using all subjects in the safety population. Safety parameters included AEs, vital signs (resting pulse and sitting blood pressure), urine pregnancy tests, IOP, BCVA, SLE, conjunctival hyperemia, dilated ophthalmoscopy, VF evaluation, iris/eyelash changes, and corneal endothelial cell count. Change from baseline was provided for all safety parameters. For each safety parameter, the last assessment made prior to the first dose of study medication was used as the baseline for all analyses. Safety analysis included both eyes (study and non-study). Descriptive statistics were provided for vital signs, IOP, visual acuity, slit lamp biomicroscopy, dilated ophthalmoscopy, visual field, and corneal endothelial cell count. Additionally, paired t-tests were used to detect significant mean changes from baseline within each eye for IOP, slit-lamp biomicroscopy, dilated ophthalmoscopy, and visual field.

Summary tables were provided for all treatment emergent adverse events (TEAEs). A TEAE was defined as any event that existed before study medication administration and increased in intensity or frequency, or any event that occurred after the start of study medication administration. The incidence of TEAE was presented by system organ class (SOC) and preferred term (PT) according to the Medical Dictionary for Regulatory Activities (MedDRA, Version 12.0), by relationship to the study treatment, and by severity. Incidence of TEAEs and SAEs were summarized by treatment group. Ocular AEs as recorded in the daily symptom diary were transcribed in the eCRF, summarized, and listed. If more than one TEAE occurred with the same PT for the same subject, the subject was counted only once for that PT and at the highest severity and strongest relationship to the study drug. Subject listings for all TEAEs were provided. SAEs were presented in the data listings and discussed individually.

Reviewer's Comment:

As the only masked and controlled study submitted in support of the proposed indication, Study CLR_09_12 provided the primary evidence to evaluate safety and efficacy of Xelpros compared

to Xalatan for the NDA. Study CLR_08_01, an open-label study of safety and efficacy, provided supportive evidence for efficacy

5.3.2 Protocol - CLR_09_13

A Clinical Evaluation of Safety of SPARC's Latanoprost 0.005% Ophthalmic (b) (4) *When Administered Once Daily in Subjects With Open Angle Glaucoma or Ocular Hypertension: An Open Label Extension Study*

Site No.	No. of Randomized Subjects	Principal Investigator Name and Address	Subinvestigators
	Module 5.3.5.1.1\ CLR_09_13\ Section 16.2.1	Module 5.3.5.1.1\CLR_09_13\Section 16.1.4.1	
01	12	David Shulman, M.D., P.A. 999 E. Basse Rd., Suite 127 San Antonio, TX 78209	F Trujillo MD
02	21	Eugene Protzko, M.D. Seidenberg Protzko Eye Associates 2023 Pulaski Hwy. Havre De Grace, MD 21078	J. Seidenberg MD, M. Trottini MD, W. Batista OD, N. Frank OD, S. Spearman OD, M. Steg OD
03	18	Michael Tepedino, M.D. Cornerstone Eye Care 307 N. Lindsay St. High Point, NC 27262	R. DaVanzo MD, Y. Radionchenko MD, C. Tara MD
04	13	Stephen Smith, M.D. Eye Associates of Fort Myers 4225 Evans Ave. Ft. Myers, FL 33901	None
05	3	Douglas Day, M.D. Coastal Research Associates, LLC 11205 Alpharetta Hwy., Suite J-3 Roswell, GA 30076	None
06	6	Katherine Ochsner, M.D. Eye Associates of Wilmington 1729 New Hanover Medical Park Dr. Wilmington, NC 28403	None
07	13	Ranjan Malhotra, M.D. Ophthalmology Associates 12990 Manchester Rd., Suite 200	A. Fedyk MD, G.Berdy MD, R. Malhotra MD,

Site No.	No. of Randomized Subjects	Principal Investigator Name and Address	Subinvestigators
		St. Louis, MO 63131	R. Brusatti OD
08	16	Joseph Gira, M.D. Ophthalmology Consultants, Ltd. 12990 Manchester Rd., Suite 201 St. Louis, MO 63131	J. Gira MD, J. Amato MD, S. Lee MD, E. Sullivan OD
09	15	Sherif EI-Harazi, M.D. Lugene Eye Institute 801 S. Chevy Chase Dr., Suite 103 Glendale, CA 91205	T. Dinh MD
10	5	Fiaz Zaman, M.D. Houston Eye Associates MD 2855 Gramercy St. Houston, TX 77025	W. Stewart MD, J. Arnault
12	14	Asra Firozvi, M.D. North Carolina Eye, Ear, Nose and Throat 4102 N. Roxboro Rd. Durham, NC 27704	M. James MD
13	16	Bernard Perez, M.D. International Research Center 4506 Wishart Place Tampa, FL 33603	D. Perez Ortiz MD
14	8	Steve Simmons, M.D. Glaucoma Consultants of the Capital Region 1240 New Scotland Rd., Suite 201 Slingerlands, NY 12159	M. Kaback MD, R. Sanchez MD
15	1	Johann Ohly, M.D. St. Johns Clinic- Eye Specialists 1229 E. Seminole, Suite 430 Springfield, MO 65804	S. Tauber MD

Study Objectives:
To investigate the long term safety of SPARC's Latanoprost 0.005% ophthalmic (b) (4) when administered once daily in subjects aged 18 years older.

Methodology:
This study was a multicenter, open label, non-randomized, single group assignment, extension safety study to evaluate the long-term safety of SPARC Ltd.'s latanoprost 0.005% ophthalmic (b) (4) In this extension study, 161 subjects who completed the prior evaluator-masked clinical non-inferiority Study CLR_09_12 participated in the current study. All subjects instilled SPARC latanoprost 0.005% ophthalmic (b) (4) once daily at approximately 8 PM. There were 10 study visits. Visit 1 (Day 1) was the Baseline Visit and included all safety evaluations. IOP, BCVA, SLE, and conjunctival hyperemia evaluations were also conducted at: Visit 2 (Day 28), Visit 3 (Day 56), Visit 4 (Day 84), Visit 5 (Day 112), and Visit 6 (Day 140). These parameters, as well as dilated ophthalmoscopy, endothelial cell count, visual field, and iris/eyelash evaluations, were also conducted at Visit 7 (End of Evaluations Visit [Day 168]). Vital signs were assessed at Visits 1-7. Adverse events were assessed at all study visits, including Visit 8 (Day 196), Visit 9 (Day 224) and End-of-Study Visit (Day 252, Week 36).

Study Schedule

Activities	Day 1 Week 1 (Baseline)	Day 28 Week 4 Visit 2**	Day 56 Week 8 Visit 3**	Day 84 Week 12 Visit 4**	Day 112 Week 16 Visit 5**	Day 140 Week 20 Visit 6**	Day 168 Week 24 Visit 7** End of Evaluations	Day 196* Week 28 Visit 8**	Day 224* Week 32 Visit 9**	Day 252* Week 36 Visit 10** End of Study
Informed consent	X	-	-	-	-	-	-	-	-	-
Medical History and demographics	X	-	-	-	-	-	-	-	-	-
Resting pulse rate and seated blood pressure	X[2]	X	X	X	X	X	X	-	-	-
IOP measurement with Goldmann applanation tonometer[1]	X[2]	X	X	X	X	X	X	-	-	-
Visual Acuity (best corrected) on ETDRS	X[2]	X	X	X	X	X	X	-	-	-
Slit lamp biomicroscopy	X[2]	X	X	X	X	X	X	-	-	-
Conjunctival hyperemia assessment with ORA scale #6.0b	X[2]	X	X	X	X	X	X	-	-	-
Dilated ophthalmoscopy	X[2]	-	-	-	-	-	X	-	-	-
Humphrey 24-2 / 30-2 visual field (SITA standard)[4]	X[2]	-	-	-	-	-	X	-	-	-
Iris – eyelash photography with standardized digital camera	X[2]	-	-	-	-	-	X	-	-	-
Endothelial cell count with non-contact specular microscope	X[2]	-	-	-	-	-	X	-	-	-
Concomitant medication record	X	X	X	X	X	X	X	-	-	-
AE / SAE evaluation	X	X	X	X	X	X	X	X	X	X
Dispense study drug	X	X	X	X	X	X	X	X	X	-
Collect study drug	-	X	X	X	X	X	X	X	X	X
Urine Pregnancy Test	X[3]	-	-	-	-	-	X	-	-	-
Schedule next visit	X	X	X	X	X	X	X	X	X	-

*Study medication continued to be dispensed and collected while adverse events only continued to be assessed during Visits 8, 9, and 10.
**Visits 2 to 10 had ± 2-day visit window.
[1] IOP was measured in triplicate at 1-minute intervals at all visits without administration of any IOP lowering drug. IOPs were measured at 8 AM, 10 AM and 4 PM (±30 min) time points.
[2] These evaluations were not performed at this visit for subjects with end-of-study measures from Study CLR_09_12.
[3] Urine pregnancy test was performed at Visit 1 if not performed at end-of-study CLR_09_12.
[4] Visual fields must have been reliable (Fixation Loss ≤ 33%).

Number of Subjects:
Subjects from Study CLR_09_12 eligible for enrollment: 200
Enrolled: 161
Analyzed: 161

Diagnosis and Main Criteria for Inclusion:
Subjects had to be eligible to receive SPARC latanoprost 0.005% once daily as monotherapy for the treatment of elevated IOP. Each subject entering into this trial was diagnosed with ocular hypertension (OHT) or primary open angle glaucoma (POAG). Pseudoexfoliation or pigment dispersion component was acceptable.

Criteria for Evaluation:
This was a safety evaluation study. The following safety endpoints were assessed:

- Adverse events
- Intraocular pressure
- Slit lamp biomicroscopy
- Conjunctival hyperemia
- Dilated ophthalmoscopy
- Endothelial cell count
- Visual field (Humphrey 24-2/30-2)
- Iris and eyelash changes
- Vital signs (resting pulse rate and blood pressure)

Safety Analysis:
The safety population included all subjects who enrolled and received at least one dose of study medication. Safety endpoints were analyzed for both the study and non-study eye, and included analysis by prior treatment group (Xalatan or SPARC latanoprost) in previous Study CLR_09_12. A sufficient number of subjects were enrolled to obtain safety data from at least 100 subjects for 36 weeks (inclusive of exposure in Study CLR_09_12).

Summary tables were provided for all treatment-emergent adverse events (TEAEs). A TEAE was defined as any adverse event that existed before study drug administration and increased in severity or frequency, or any adverse event that occurred following study drug administration. The number and percentage of subjects reporting a TEAE were tabulated by system organ classification and preferred terms according to MedDRA (Version 12.0), by relationship to the study treatment, and by severity. SAEs were presented in the data listings and discussed individually. Ocular adverse events that were recorded in subjects' daily symptom diaries were transcribed in the eCRF, summarized, and listed. Separate analyses were performed for ocular and systemic adverse events.

Descriptive statistics, including the numbers, means, standard deviations, medians, maximums, minimums, and/or 95% CIs for continuous variables, and the numbers and percentages for categorical variables, at baseline and at each time point or visit measured, as well as change from baseline for all parameters, were provided for vital signs, IOP, SLE, VF, BCVA, conjunctival hyperemia, DFE, iris/eyelash changes, and endothelial cell count.

Reviewer's Comment:
Refer to Section 6.2 for the efficacy results of this study and Section 8 Review of Safety for the safety results of this study.

5.3.3 Protocol – CLR_08_01

Comparison of the efficacy and safety of Latanoprost 0.005% (Sun Pharma Advanced Research Company Ltd., Test) and Latanoprost 0.005% (Xalatan® Reference) administered once daily in open angle glaucoma and ocular hypertension.

Site No.	No. of Randomized Subjects	Principal Investigator Name and Address
01	3	Ruvit Nikam, DOMS, DNB, FCPS, MNAMS Aditya Jyot Eye Hospital Plot No. 153, Road No. 9, Major Parmeshwaran Road Wadal, Mumbai 400 031
02	0	Swaranjitshing Bhatti, MS, DOMS, DNB, FCPS Bhatti Eye Clinic, 22, Amar Mansion, Opposite Deonar Bus Depot, Sion-Trombay Road, Mumbai 400 088
03	20	Tejaswini Walimbe, DOMS, DNB Walimbe Eye Clinic, D-2, Aranyeshwar Park, Near Aranyeshwar Temple Sahakar Nagar, Pune 411 009
04	0	Roopali Nerlikar, DNB, FRCS Kelkar Nursing Home Prabhat Road, 1st Lane Corner, Deccan Gymkhana, Pune 411 004
05	2	Medha Prabhudesai, DOMS Prabhudesai Eye Clinic Laxmi Narasimha Apartment 1424 – Sadashiv Peth, Pune 411 030
06	3	Ajit Hazari, DOMS, MS Hazari Nursing Home Next to Vivekanand College Samarth Nagar, Aurangabad 431 001
07	27	*LEAD INVESTIGATOR*

Site No.	No. of Randomized Subjects	Principal Investigator Name and Address
		Pradeep Jain, DOMS Shri Ganapati Netralaya Near Janta High School Devalgaonraja-Mantha Road, Jalna 431 203
08	13	Yogesh Shah, MS, DOMS, FCPS Netra mandir Madona Colony Road Near Bhagwati Hospital Borivali (W), Mumbai 400 103
09	6	Sonika Shah, MS Navkar Eye Clinic Shop No. 1, Radharaman Society Opposite Telephone Exchange, Canada Corner Nashik 422 002
10	6	R.P. Gupta, MS, DOMS, FVRS Professor and Head Department of Ophthalmology Padmashree Dr. DY Patil Medical College Hospital & Research Centre Pimpri, Pune 411 018
11	24	Kalyani V,K,S,. M.S. Glaucoma Consultant PBMA's H.V. Desai Eye Hospital 93, Tarvade Vasti, Mohammadwadi Hadapsar, Pune 411 028

Study Objectives:
To compare the efficacy and safety of Latanoprost 0.005% ophthalmic (b) (4) (SPARC Ltd.) with Latanoprost 0.005% ophthalmic solution (Xalatan) in subjects with primary open angle glaucoma or ocular hypertension.

Methodology:
This was a randomized, open label, active –controlled, multicenter, parallel group study in which efficacy and safety of the latanoprost products in subjects with POAG or OHT was compared. This study consisted of 5 study visits. At Visit 1, Screening (Day -7 to -1) subjects were screened for inclusion/exclusion criteria. At Visit 2, Randomization (Day 0), following inclusion/exclusion evaluation, eligible subjects were randomized to a 4-week open label treatment period with one of two study treatments. Visit 3 (Days 8 to 10) and Visit 4 (Days 15 to

17) were follow-up visits and Visit 5 (Days 29 to 31) was the final study visit at which the end-of-study safety and efficacy evaluations were performed.

Study Schedule

Activities	Day -7 to-1 (visit 1) Screening	Day 0 (visit2) Randomization/ Baseline	Day 8-10 (visit 3) Follow-up	Day 15-17 (visit 4) Follow-up	Day 29-31 (visit 5) End-of-study visit
Informed consent	X	-	-	-	-
Medical history	X	-	-	-	-
Inclusion/Exclusion criteria	X	X	-	-	-
Demographic data, body weight	X	-	-	-	-
Pulse rate and blood pressure	X	X	X	X	X
Laboratory evaluation	X		-	-	X
Concomitant medication record	X	X	X	X	X
IOP measurement	X[1]	X[2]	X[3]	X[3]	X[3]
Study medication dispensing	-	X[4]	-	-	-
Adverse events recording	-	-	X	X	X
Ophthalmic examination	X[5]	-	-	-	X[6]
Subject's Global Impression of change	-	-	-	X	X
Investigator's Global Impression of change	-	-	-	X	X
Information about next visit	X	X	X	X	-

[1] IOP measured once at screening (day –7 to-1) without administration of any IOP lowering drug.
[2] IOP measured twice (evening and next morning) at baseline (visit 2) without administration of any IOP lowering drug.
[3] IOP measured twice: Before instillation of study medication in evening and 12-18 hours after instillation of study medication (next morning) at follow up visits (visit 3, visit 4 and end of study visit; visit 5).
[4] Study medication dispensed next morning after IOP measurement with instruction to start instillation from same day.
[5] Presenting and best-corrected visual acuity testing (Snellen's chart) with refraction, slit lamp examination, gonioscopy, dilated slit lamp stereo biomicroscopy, visual field (Humphrey 24-2 /30-2, SITA Standard or Octopus or Medmont), central corneal thickness measurement with ultrasound pachymetry (to correct IOP).
[6] Presenting and best-corrected visual acuity testing (Snellen's chart) with refraction, slit lamp examination, dilated slit lamp stereo biomicroscopy, visual field (Humphrey 24-2 /30-2, SITA Standard or Octopus or Medmont).

Number of Subjects
Screened: 119 Randomized: 104

Diagnosis and Main Criteria for Inclusion
Male and female subjects 18 years and above with ocular hypertension (OHT) or primary open angle glaucoma (POAG) with IOP ≥ 22 mmHg in one or both eyes, with no more than 5 mmHg inter-eye difference at Visit 1 (Screening).

Criteria for Evaluation:
Efficacy:
Primary Efficacy Variable: IOP was measured twice at each study visit: once before administration of drug product in the evening (trough effect) and once 12-18 hours after administration of drug product the following morning (peak effect).

Secondary Efficacy Variables:
1. Mean defect score on perimetery
2. Cup-to-disk ratio
3. Investigator's clinical global impression of change
4. Subject's global impression of change

Safety:
Primary Safety Variables: Treatment emergent adverse events (TEAEs)
Secondary Safety Variables: Clinically significant change in laboratory parameters, Vital signs and ophthalmic examination (including visual acuity)

5.3.4 Protocol CLR_10_01

Study to Evaluate Safety of Benzalkonium Chloride Free Latanoprost Ophthalmic (b) (4) *0.005% in Subjects with Glaucoma*

Site No.	No. of Randomized Subjects	Principal Investigator Name and Address
01	10	Dr. Purvi Bhagat Ahmedabad
02	18	Tejaswini Walimbe, Pune
03	18	Dr. Vidya Cherlekar Pune

Study Objectives:
To evaluate tear break-up time, inferior corneal staining, ocular surface disease, and intraocular pressure.

Methodology:
This was an open-label, single arm, multicenter, parallel groups study to quantify the changes in tear break-up time (TBUT), inferior corneal staining, and ocular surface disease in subjects with primary open angle glaucoma or ocular hypertension after switching therapy from Latanoprost containing 0.02% benzalkonium chloride to Latanoprost without benzalkonium chloride.

The study duration was 8 weeks and included 3 clinic visits. Subjects meeting inclusion criteria were to be dispensed latanoprost. Visit 2 (Days 28 to 30) and Visit 3 (Days 56 to 60) at which the safety evaluations were performed.

Number of Subjects
Planned: 40 Screened: 46 Enrolled: 46
Analyzed: 34 (Efficacy) Screened: 46 (Safety)

Diagnosis and Main Criteria for Inclusion
Male and female subjects 18 years and above, with TBUT less than 6 seconds. Taking Latanoprost 0.005% (containing BAK) monotherapy at least 12 months, willing to participate.

Criteria for Evaluation:

1. Tear break up time
2. Ocular surface disease index
3. Inferior corneal staining
4. Ocular hyperemia
5. Treatment Emergent Adverse Events as reported by subjects were recorded.

Statistical Methods:

Enough subjects were to be enrolled to obtain evaluable data from approximately 40 eyes. Data were to be summarized descriptively as counts and percentages.

Reviewer's Comment:

Refer to Section 8 Review of Safety for the results of this study.

6 Review of Efficacy

Efficacy Summary

6.1 Indication for Study CLR_09_12

For the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

6.1.1 Methods

The description of the clinical trial designs is contained in Section 5.3.1.

Clinical study reports, clinical protocols and literature references were submitted related to the two clinical trials submitted in support of the New Drug Application.

6.1.2 Demographics

Table 6.1.2-1
Demographics and Baseline Characteristics
ITT Population

Variables		Xalatan 0.005% (N=289)	Xelpros 0.005% (N=289)	Total (N=578)
Age (years)	Mean (SD)	63.1 (9.6)	63.8 (11.1)	63.4 (10.4)
	Median	63	65	64
	Range: Min, Max	34, 87	27, 88	27, 88
Sex: n (%)	Male	103 (35.6%)	101 (34.9%)	204 (35.3%)
	Female	186 (64.4%)	188 (65.1%)	374 (64.7%)
Race: n (%)	Caucasian	202 (69.9%)	198 (68.5%)	400 (69.2%)
	Black or African American	79 (27.3%)	82 (28.4%)	161 (27.9%)
	American Indian or Alaskan Native	1 (0.3%)	1 (0.3%)	2 (0.3%)
	Asian	6 (2.1%)	7 (2.4%)	13 (2.2%)
	Black or African American and American Indian or Alaskan Native	0 (0.0%)	1 (0.3%)	1 (0.2%)
	Other: Persian	1 (0.3%)	0 (0.0%)	1 (0.2%)
Ethnicity: n (%)	Hispanic or Latino	54 (18.7%)	53 (18.3%)	107 (18.5%)
	Not Hispanic or Latino	235 (81.3%)	236 (81.7%)	471 (81.5%)
Baseline IOP Group: n (%)	Low IOP (22-28 mmHg)	235 (81.3%)	235 (81.7%)	471 (81.5%)
	High IOP (29-35 mmHg)	54 (18.7%)	53 (18.3%)	107 (18.5%)
Source: Tables 14.1.2.1				

Table 6.1.2-2
Baseline Characteristics of the Study Eye
ITT Population

Baseline Characteristics	Statistics	Xalatan 0.005% (N=289)	Xelpros 0.005% (N=289)	Total (N=578)
Low IOP Group	N	235	236	471 (81.5%)
	Mean IOP (SD)	22.7 (2.7)	22.6 (2.7)	22.6 (2.7)
	Median	22.4	22.4	22.4
	Min, max	14.0, 34.6	14.0, 34.0	14.0, 34.6
High IOP Group	N	54	53	107 (18.5%)
	Mean IOP (SD)	27.8 (3.6)	28.3 (3.4)	28.1 (3.5)
	Median	28.0	28.0	28.0
	Min, max	19.0, 36.0	21.3, 37.2	19.0, 37.2
ETDRS Visual Acuity[a]	N	289	289	578
	Mean (SD)	0.08 (0.13)	0.09 (0.15)	0.09 (0.14)
	Median	0.06	0.08	0.08
	Min, max	-0.20, 0.72	-0.30, 0.58	-0.30, 0.72
Visual Field Mean Deviation	N	287	288	575
	Mean (SD)	-1.82 (3.12)	-2.48 (3.64)	-2.15 (3.40)
	Median	-0.97	-1.62	-1.23
	Min, max	-19.13, 4.3	-21.48, 2.57	-21.48, 4.33
Endothelial Cell Count	N	289	288	575
	Mean (SD)	2476.2 (404.34)	2458.9 (434.23)	2467.6 (419.25)
	Median	2525	2491	2506
	Min, max	942, 3750	778, 3624	778, 3750
Cup Disc Ratio	N	288	289	577
	Mean (SD)	0.5 (0.2)	0.5 (0.2)	0.5 (0.2)
	Median	0.5	0.5	0.5
	Min, max	0.1, 0.9	0.0, 0.9	0.0, 0.9
Iris Color	Blue/grey	43 (14.9%)	45 (15.6%)	88 (15.2%)
	Blue/grey with slightly brown usually around pupil	14 (4.8%)	24 (8.3%)	38 (6.6%)
	Blue/grey and brown (mixed color i.e. hazel)	11 (3.8%)	9 (3.1%)	20 (3.5%)
	Green	8 (2.8%)	6 (2.1%)	14 (2.4%)
	Green with slightly brown, usually around the pupil	6 (2.1%)	5 (1.7%)	11 (1.9%)
	Green/brown (mixed color i.e., hazel)	14 (4.8%)	18 (6.2%)	32 (5.5%)
	Yellow-brown (Caucasian mixed color i.e. hazel)	3 (1.0%)	1 (0.3%)	4 (0.7%)
	Brown (Caucasian)	104 (36.0%)	93 (32.2%)	197 (34.1%)
	Brown (Black)	78 (27.0%)	82 (28.4%)	160 (27.7%)
	Brown (Asian)	8 (2.8%)	6 (2.1%)	14 (2.4%)
Ocular hypertension diagnosis	Ocular hypertension	97 (33.6%)	104 (36.0%)	201 (34.8%)
	Pseudoexfoliation	2 (0.7%)	1 (0.3%)	3 (0.5%)
	Pigment dispersion	5 (1.7%)	3 (1.0%)	8 (1.4%)

Baseline Characteristics	Statistics	Xalatan 0.005% (N=289)	Xelpros 0.005% (N=289)	Total (N=578)
	Primary open angle glaucoma	200 (69.2%)	193 (66.8%)	393 (68.0%)
Source: Tables 14.1.2.1, 14.1.2.2, 14.1.2.3				

a LogMAR (best-corrected) visual acuity was assessed for each eye using an ETDRS chart at each visit. LogMAR visual acuity was calculated as follows: LogMAR visual acuity = base logMAR + (N x 0.02), where base logMAR reading was the last line in which at least a letter was read correctly by the subject and N was the total number of letters missed up to and including the last line read.

6.1.3 Subject Disposition

Table 6.1.3-1
Subject Disposition
All Randomized Subjects

Subject Disposition	Xalatan 0.005% (N=289)	Xelpros 0.005% (N=289)	Total (N=578)
ITT Population	289 (100.0%)	289 (100.0%)	578 (100.0%)
Safety Population	289 (100.0%)	289 (100.0%)	578 (100.0%)
Per-Protocol Population	275 (95.2%)	270 (93.4%)	545 (94.3%)
Subjects Completed the Study	276 (95.5%)	274 (94.8%)	550 (95.2%)
Subjects Discontinued the Study	13 (4.5%)	15 (5.2%)	28 (4.8%)
Reasons for Discontinuation			
Withdrawal of consent	7 (2.4%)	3 (1.0%)	10 (1.7%)
Withdrawal of subject by investigator	1 (0.3%)	4 (1.4%)	5 (0.9%0
Protocol violation	0 (0.0%)	5 (1.7%)	5 (0.9%)
Study terminated at one site by Sponsor	2 (0.7%)	2 (0.7%)	4 (0.7%)
Adverse event	2 (0.7%)	1 (0.3%)	3 (0.5%)
Study medication failure	1 (0.3%)	0 (0.0%)	1 (0.2%)
Note: n = Number of subjects in each Treatment Group; N = Number of subjects in each category. Source: Adapted from Table 14.1.1.3, Listings 16.2.1.2, 16.2.2.3, 16.2.2.4, and 16.2.3.			

Table 6.1.3-2
Protocol Violations Reported on CRF
All Randomized Subjects

Violation Description	Xalatan 0.005% (N=289)	Xelpros 0.005% (N=289)	Total (N=578)
Focal laser OD within 6 months of screening	0	1	1
Improper washout	0	1	1
Subject given wrong replacement bottle of medication. Should have received bottle A0198-1 instead received bottle A0199-2	0	1	1
Visual field not qualified	0	2	2
Note: n = Number of subjects in each Treatment Group; subjects with more than one deviation appears in multiple rows. Source: Listing 16.2.2.4.			

6.1.4 Analysis of Primary Endpoint(s)

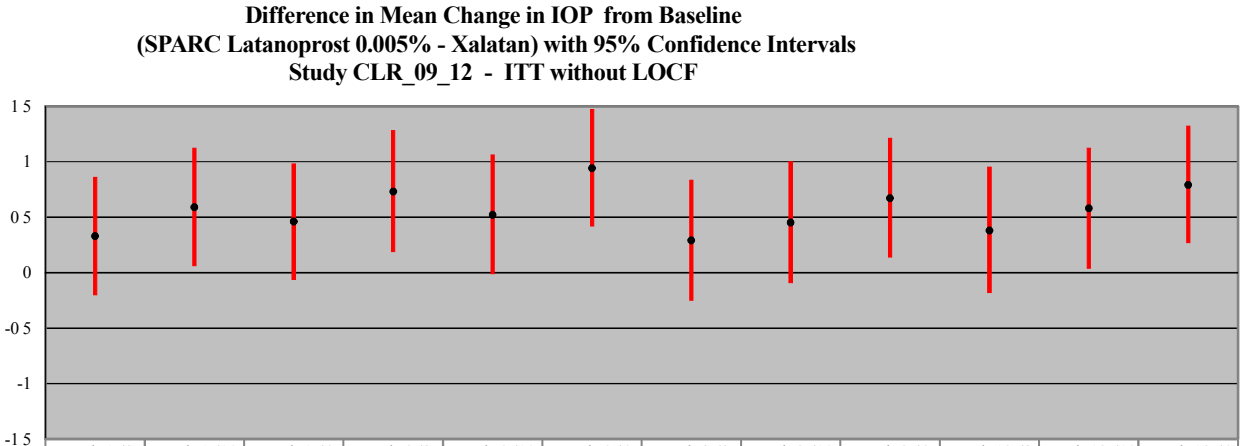
The primary efficacy endpoint in this study was the change from baseline in IOP at each of 12 time points as follows: 3 time points per visit (8 AM, 10 AM, and 4 PM) recorded during four post-baseline visits (Weeks 1, 4, 8, and 12).

The primary efficacy analysis was conducted on the ITT population without LOCF.

Non-inferiority was considered established if the following 3 steps were established simultaneously:

Step 1: 95% CI included 0 for all (12) time points.
Step 2: The upper limit of the 95% CI was <1.5 at all (12) time points.
Step 3: The upper limit of 95% CI was <1 at most (at least 7 of 12) time points

Chart 6.1.4-1



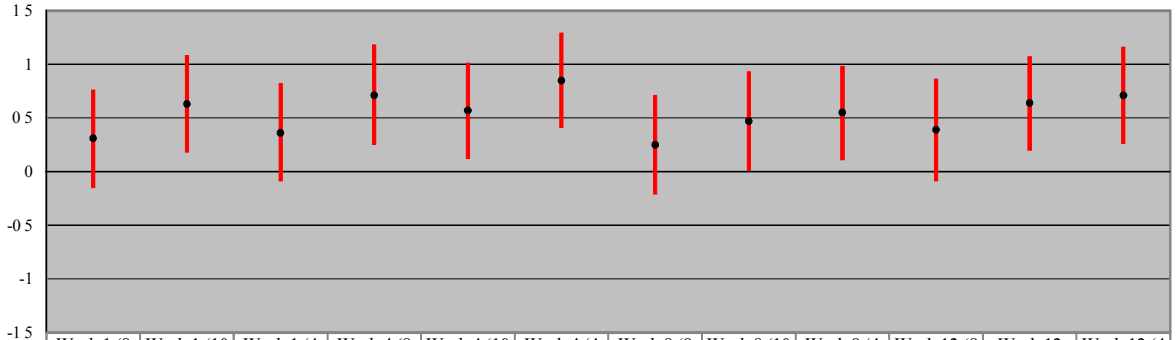
	Week 1 (8 AM)	Week 1 (10 AM)	Week 1 (4 PM)	Week 4 (8 AM)	Week 4 (10 AM)	Week 4 (4 PM)	Week 8 (8 AM)	Week 8 (10 AM)	Week 8 (4 PM)	Week 12 (8 AM)	Week 12 (10 AM)	Week 12 (4 PM)
Lower CI	-0 2	0 06	-0 06	0 19	-0 01	0 42	-0 25	-0 09	0 14	-0 18	0 04	0 27
Upper CI	0 86	1 12	0 98	1 28	1 06	1 47	0 83	1	1 21	0 95	1 12	1 32
Mean Difference	0 33	0 59	0 46	0 73	0 52	0 94	0 29	0 45	0 67	0 38	0 58	0 79

Reviewer's Comment:

For the ITT population without LOCF, the 95% confidence interval is within 1.5 mmHg for all time points, and the within 1.0 mmHg for 4 of 12 time points. Thus, SPARC latanoprost 0.005% has not demonstrated equivalence with Xalatan (latanoprost ophthalmic solution) 0.005%.

Chart 6.1.4-2

**Difference in Mean Change in IOP from Baseline - ANCOVA
(SPARC Latanoprost 0.005% - Xalatan) with 95% Confidence Intervals
Study CLR_09_12 - ITT Population - Observed Cases**



	Week 1 (8 AM)	Week 1 (10 AM)	Week 1 (4 PM)	Week 4 (8 AM)	Week 4 (10 AM)	Week 4 (4 PM)	Week 8 (8 AM)	Week 8 (10 AM)	Week 8 (4 PM)	Week 12 (8 AM)	Week 12 (10 AM)	Week 12 (4 PM)
Lower CI	-0 15	0 18	-0 09	0 25	0 12	0 41	-0 21	0 01	0 11	-0 09	0 2	0 26
Upper CI	0 76	1 08	0 82	1 18	1 01	1 29	0 71	0 93	0 98	0 86	1 07	1 16
Mean Difference	0 31	0 63	0 36	0 71	0 57	0 85	0 25	0 47	0 55	0 39	0 64	0 71

Reviewer's Comment:

For the ITT population Observed Cases, the 95% confidence interval is within 1.5 mmHg for all time points and the within 1.0 mmHg for 6 of 12 time points. Thus, SPARC latanoprost 0.005% has demonstrated equivalence with Xalatan (latanoprost ophthalmic solution) 0.005% using the Division's definition for this population.

Sensitivity Analyses were performed to assess the effect of missing data on the primary efficacy endpoint. Non-inferiority was not established for the ITT population analyzed with last observation carried forward, the ITT population with baseline observation carried forward or the ITT population with multiple imputations. The conclusions for these analyses were consistent with the primary analysis without imputations.

6.1.5 Analysis of Secondary Endpoints(s)

Interactions between treatment and baseline IOP, between treatment and site, and between treatment and baseline IOP group were investigated for the primary efficacy variable. All three types of interactions were found to be statistically significant when each was included in the primary ANCOVA model.

6.1.6 Other Endpoints

None.

6.1.7 Subpopulations

The efficacy results were consistent when examined by age, sex or race subgroups.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Not applicable.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

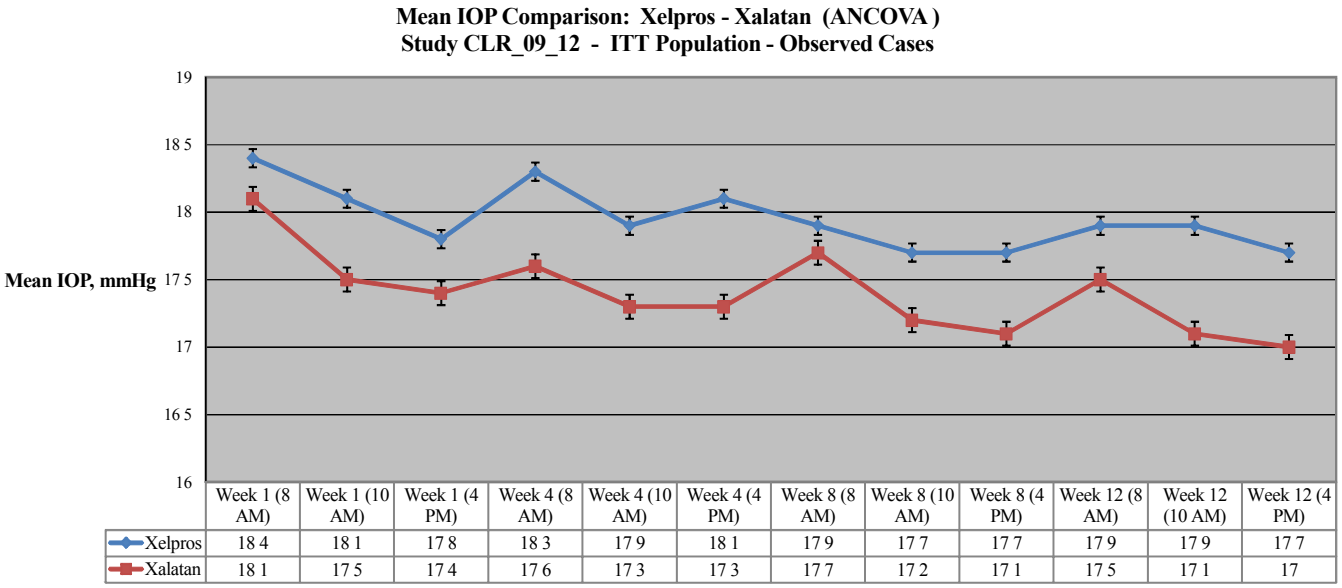
No evidence of tolerance or withdrawal effects has been detected in this trial or in previous trials with latanoprost ophthalmic (b) (4).

6.1.10 Additional Efficacy Issues/Analyses

A safety extension study of Study CLR_09_12, Study CLR_09_13, is reviewed in Section 7.

The study did not demonstrate the equivalence of Xelpros and Xalatan. Xelpros did demonstrate an IOP lowering effect in Study CLR_09_12. Mean IOP reductions for both drug products in Study CLR_09_12 are presented below.

Chart 6.1.4-3



	Week 1 (8 AM)	Week 1 (10 AM)	Week 1 (4 PM)	Week 4 (8 AM)	Week 4 (10 AM)	Week 4 (4 PM)	Week 8 (8 AM)	Week 8 (10 AM)	Week 8 (4 PM)	Week 12 (8 AM)	Week 12 (10 AM)	Week 12 (4 PM)
Xelpros	18 4	18 1	17 8	18 3	17 9	18 1	17 9	17 7	17 7	17 9	17 9	17 7
Xalatan	18 1	17 5	17 4	17 6	17 3	17 3	17 7	17 2	17 1	17 5	17 1	17

Reviewer's Comment:
The adjusted mean IOP ranged from 17.7 to 18.4 mmHg in the Xelpros group and from 17.0 to 18.1 mmHg in the Xalatan group. The mean IOP at each time point of each visit was lower in the Xalatan group. Xelpros was less effective in lowering IOP compared to Xalatan by about 0.5 mmHg.

6.2 Indication for Study CLR_08_01

For the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

6.2.1 Methods

The description of the clinical trial designs is contained in Section 5.3.3.

Clinical study reports, clinical protocols and literature references were submitted related to the clinical trials submitted in support of the New Drug Application.

6.2.2 Demographics

Table 6.2.2-1
Demographics and Baseline Characteristics
ITT Population

Variables	Xelpros 0.005% (N=53)	Xalatan 0.005% (N=51)	Total (N=104)
Age (years)			
≤ 65	33 (62.3)	32 (62.8)	65 (62.5)
> 65 years	20 (37.7)	19 (37.3)	39 (37.5)
Mean (SD)	58.9 (10.61)	59.1 (11.21)	59.0 (10.85)
Min – Med - Max	34 – 61 – 81	26 – 61 – 74	26 – 61 – 81
Sex: n (%)			
Male	38 (71.7)	32 (62.8)	70 (67.3)
Female	15 (28.3)	19 (37.3)	34 (32.7)
Race: n (%)			
Asian	53 (100)	51 (100)	104 (100)
Iris n(%)			
Brown	51 (96.2)	48 (94.1)	99 (95.2)
Hazel	2 (3.8)	3 (5.9)	5 (4.8)
Diagnosis, n(%)			
OHT	11 (20.8)	18 (35.3)	29 (27.9)
POAG	35 (66.0)	29 (56.9)	64 (61.5)
OHT/PXF	1 (1.9)	1 (2.0)	2 (1.9)
POAG/PXF	6 (11.3)	3 (5.6)	9 (8.7)
Baseline IOP [a]			
Morning			
Mean (SD)	26.1 (6.00)	25.0 (5.48)	25.6 (5.75)
Min – Med - Max	14.7 – 25.0 – 55.3	16.0 – 24.3 – 44.0	14.7 – 24.7 – 55.3
Evening			
Mean (SD)	24.6 (4.67)	24.6 (4.66)	24.6 (4.65)
Min – Med - Max	15.0 – 24.3 – 36.3	17.0 – 24.0 – 41.0	15.0 – 24.3 – 41.0

Source: Table 11-2 of CSR
A Based on Statistical Reviewer's analysis

Reviewer's Comment:
The baseline morning IOP for the SPARC latanoprost group was 1.0 mm Hg higher than that of the Xalatan group. The population has predominantly dark colored irides.

6.2.3 Subject Disposition

Table 6.2.3-1
Subject Disposition – Study CLR_08_01
All Randomized Subjects

Subject Disposition	Xalatan 0.005% (N=51)	Xelpros 0.005% (N=53)	Total (N=578)
ITT Population	51 (100.0%)	53 (100.0%)	104 (100.0%)
Safety Population	51 (100.0%)	53 (100.0%)	104 (100.0%)
Subjects Who Completed the Study	48 (94.1%)	45 (84.9%)	93 (89.4%)
Subjects Who Discontinued the Study	3 (5.9%)	8 (15.1%)	11 (10.6%)
Reasons for Discontinuation			
Major Protocol Violation	1 (2.0%)	1 (1.9%)	2 (1.9%)
Withdrawal of consent	0 (0.0%)	2 (3.8%)	2 (1.9%)
Lost to follow-up	2 (3.9%)	4 (7.6%)	6 (5.8%)
Study medication failure	0 (0.0%)	1 (1.9%)	1 (1.0%)
Source: Table 10-2 of CSR			

Reviewer's Comment:
Eleven percent of subjects discontinued the study early. The Xelpros group discontinuation rate was almost twice that of the Xalatan group. The most common reason for study discontinuation was lost to follow-up (6%) which occurred almost twice as frequently in the Xelpros treatment group.

6.1.4 Analysis of Primary Endpoint(s)

The primary efficacy variable was intraocular pressure measured at trough (prior to study drug administration) and peak (12-18 hours after study drug administration) at each visit. The average trough IOP (morning) from baseline (day 0) to final visit (day 29) is presented.

Table 6.1.4-1
Mean IOP in the Study Eye per Visit and Time
(N=104)

Summary	Visit	Time Point	Xelpros			Xalatan		
			N	Mean (SD)	(95% CI)	N	Mean (SD)	(95% CI)
Actual IOP	Baseline	Morning	53	26.1 (6.00)	(24.5, 27.8)	51	25.0 (5.48)	(23.5, 26.6)
		Evening	53	24.6 (4.67)	(23.3, 25.9)	51	24.6 (4.66)	(23.3, 25.9)
	Day 8	Morning	50	18.8 (4.66)	(17.5, 20.1)	51	18.3 (4.13)	(17.1, 19.4)
		Evening	51	19.5 (4.89)	(18.2, 20.9)	51	19.1 (3.90)	(18.0, 20.2)
	Day 15	Morning	49	17.3 (3.86)	(16.1, 18.4)	50	17.0 (4.61)	(15.7, 18.3)
		Evening	49	17.0 (3.86)	(15.9, 18.2)	50	17.0 (4.02)	(15.9, 18.2)
	Day 29	Morning	45	17.3 (3.18)	(16.4, 18.3)	48	16.4 (3.67)	(15.3, 17.4)
		Evening	46	17.4 (3.27)	(16.4, 18.3)	49	16.9 (3.60)	(15.8, 17.9)
Change in IOP from Baseline	Day 8	Morning	50	-7.6 (6.50)	(-9.4, -5.7)	51	-6.7 (5.36)	(-8.2, -5.2)
		Evening	51	-5.4 (5.18)	(-6.8, -3.9)	51	-5.5 (4.26)	(-6.7, -4.3)
	Day 15	Morning	49	-9.0 (6.39)	(-10.8, -7.1)	50	-7.9 (4.90)	(-9.3, -6.5)
		Evening	49	-7.7 (4.84)	(-9.1, -6.3)	50	-7.5 (3.94)	(-8.6, -6.4)
	Day 29	Morning	45	-9.3 (6.62)	(-11.3, -7.3)	48	-8.6 (4.32)	(-9.9, -7.4)
		Evening	46	-7.4 (4.34)	(-8.7, -6.1)	49	-7.6 (3.86)	(-8.7, -6.5)
% Change in IOP from Baseline	Day 8	Morning	50	-27.3 (15.46)	(-31.7,-22.9)	51	-25.2 (16.73)	(-29.9,-20.5)
		Evening	51	-20.3 (19.33)	(-25.7,-14.9)	51	-21.3 (13.61)	(-25.1,-17.5)
	Day 15	Morning	49	-32.3 (16.41)	(-37.0,-27.6)	50	-30.8 (16.97)	(-35.6,-26.0)
		Evening	49	-29.7 (16.07)	(-34.3,-25.1)	50	-30.2 (12.30)	(-33.7,-26.7)
	Day 29	Morning	45	-32.8 (14.81)	(-37.3,-28.4)	48	-33.5 (11.69)	(-36.9,-30.1)
		Evening	46	-28.6 (14.16)	(-32.8,-24.4)	49	-30.6 (12.36)	(-34.1,-27.0)

Note: From Statistical Review Appendix 13.

Reviewer's Comment:
Study CLR_08_01 was a multicenter, randomized, open-label study. Patients were dosed once daily for 29 days. In order to make a determination of safety and efficacy for the IOP lowering indication, the Division recommends that studies be masked and conducted for 12 weeks or longer.

IOP reductions during the study were higher in the morning compared to the evening at each time point for both treatment groups.

This study demonstrated a statistically significant change in mean IOP from baseline to both time points at each study visit for both the Xelpros and Xalatan ($p<0.0001$) treatment groups. However, the study was not powered to meet the criterion for equivalence.

This study results are supportive of the Study CLR_09_12 results.

6.1.5 Analysis of Secondary Endpoints(s)

The planned secondary efficacy endpoints were descriptive presentation of the mean defect score on perimetry and cup-to-disk ratio.

Reviewer's Comment:
Secondary endpoints were not analyzed since the study did not meet its primary efficacy endpoint.

6.1.6 Other Endpoints

None.

6.1.7 Subpopulations

None.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Not applicable.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

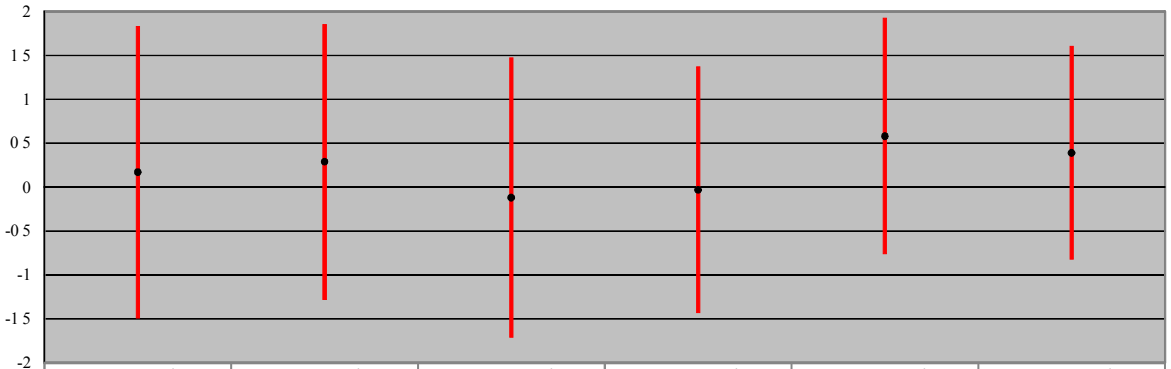
No evidence of tolerance or withdrawal effects has been detected in this trial or in previous trials with latanoprost ophthalmic (b) (4).

6.1.10 Additional Efficacy Issues/Analyses

None.

Chart 6.1.10-1

**Difference in Mean Change in IOP from Baseline - ANCOVA
(Xelpros - Xalatan) with 95% Confidence Intervals
Study CLR_08_01 - ITT Population - Observed Cases**



	Day 8 Morning	Day 8 Evening	Day 15 Morning	Day 15 Evening	Day 29 Morning	Day 29 Evening
Lower CI	-1 49	-1 28	-1 71	-1 43	-0 76	-0 82
Upper CI	1 83	1 85	1 47	1 37	1 92	1 6
Mean Difference	0 17	0 29	-0 12	-0 03	0 58	0 39

Reviewer's Comment:
Study CLR_08_01 was conducted for 29 days. In order to make a determination of safety and efficacy for the IOP lowering indication, the Division recommends that studies be conducted for 12 weeks or longer. For the ITT population Observed Cases, the 95% confidence interval is within 1.5 mmHg at only the Day 15 Evening time point and not within 1.0 mmHg for any time point.

The study was not powered to establish equivalence.

7 Review of Safety

Safety Summary

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The following studies were included in the Integrated Summary of Safety for Xelpros (latanoprost ophthalmic emulsion) 0.005%. The safety analysis dataset for the Integrated Safety Summary included all subjects that were included in the safety analyses in each study.

Table 7.1.1 Studies Used to Evaluate Safety

Study Number / Study Phase	Study Design	Treatment Groups (Numbers of Subjects Treated)	Duration of Treatment / Age
Study CLR_08_01 (India) Phase 3	Multicenter, open-label, randomized, active-controlled, parallel group. Visits on Days -7, 0, 8, 15, and 29.	SPARC latanoprost (N=53) Xalatan (N=51)	Once daily for 4 weeks Age ≥ 18 years
Study CLR_10_01 (India) Pilot	Multicenter, open-label, randomized, active-controlled, parallel group Visits on Days 0, 28, and 56.	Subjects previously treated with Xalatan were switched over to SPARC latanoprost (N=25 subjects, 46 eyes)	Once daily for 8 weeks Age ≥ 18 years
Study CLR_09_12 (US, IND 102,842) Phase 3	Multicenter, assessor-masked, randomized, active-controlled, parallel group, non-inferiority study. Visits on Days -35, -7, 0, 7, 28, 56, and 84	SPARC latanoprost (N=289) Xalatan (N=289)	Once daily for 12 weeks Age ≥ 18 years
Study CLR_09_13 (US, IND 102,842) Phase 3	Multicenter, open-label, non-randomized, uncontrolled, single group assignment. Visits at Weeks 1, 4, 8, 12, 16, 20, 24, 28, 32, and 36.	Single group, all subjects received SPARC latanoprost (open label extension of prior Study CLR_09_12) (N=161)	Once daily for 36 weeks Age ≥ 18 years

Note: SPARC latanoprost 0.005% is the name used by the applicant during product development. SPARC latanoprost 0.005% and Xelpros (latanoprost ophthalmic emulsion) are interchangeable terms.

7.1.2 Categorization of Adverse Events

The adverse event summary focused on treatment emergent adverse events (TEAE). The definition of treatment emergent adverse event from each study was used as defined in the study protocol. Similarly, adverse events were mapped using the MedDRA in each study as follows:

Study	*MedDRA Version*
CLR_09_12	*MedDRA 12.0*
CLR_09_13	*MedDRA 12.0*
CLR_08_01	*MedDRA 12.1*
CLR_10_01	*MedDRA 12.0*

All adverse events were coded using a MedDRA dictionary and received independent causality assessments from the Investigator and the Medical Monitor.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The safety populations of the four clinical studies listed are pooled in this analysis.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Four-hundred and forty-eight subjects were exposed to SPARC latanoprost 0.005% ophthalmic (b) (4) for a mean of 131.2 days.

Table 7.2.1-1
Summary of Duration of Exposure to SPARC latanoprost by Study
Safety Populations

Study	Duration of Exposure to Xelpros [1]	N
Study CLR_08_01	> 1 day	53
	> 1 day and < 7 days	2
	> 7 days and < 29 days	5
	Completed 29 days	46
Study CLR_10_01	> 1 day	46
	> 1 day and < 28 days	6
	> 28 days and < 56 days	6
	Completed 56 days	34

Study	Duration of Exposure to Xelpros [1]	N
Study CLR_09_12	> 1 day	289
	> 1 day and < 12 weeks	15
	Completed 12 weeks	274
Study CLR_09_13 [2]	24 weeks	153
	36 weeks	153
	48 weeks	37

1 All dosing was once per day in the study eye. All numbers refer to study eyes treated.
2 Total exposure from studies CLR_09_12 and the open label extension study CLR_09_13.
Source: ISS, Table 5

Table 7.2.1-2 Summary of Duration of Exposure
ISS Analysis Set

	Statistics	Treatment Group [1]	
		Xelpros 0.005% (n=448)	Reference Drug (n=340)
Duration of Exposure to Study Drug (Days)	n	448	340
	Mean (SD)	131.9 (96.6)	74.2 (21.8)
	95% CI of Mean	122.9, 1408.	71.9, 76.5
	Median	84.0	84.0
	Min, Max	1, 345	5, 140
Total Exposure	Person-Day	59074	25233
	Person-Year [2]	161.7	69.1

1 81 subjects switched therapy from the Reference drug in Study CLR_09_12 to the Test drug in Study CLR_09_13. They both contributed data to both treatment groups.
2 Person-year = Person-day / 365.25
Source: ISS Table 14.3.1.1.1

Reviewer's Comment:
The vast majority of patients exposed to Xelpros were dosed for at least 12 weeks.

Table 7.2.1-3
Summary of Overall Demographics and Baseline Characteristics of Study Eye
ISS Analysis Set

	Statistics	Treatment Group [1]	
		Xelpros 0.005% (n=448)	Reference Drug (n=340)
Age (years)	n	448	340
	Mean (SD)	62.8 (11.0)	62.5 (9.94)
	95% CI of Mean	61.8, 63.8	61.4, 63.5
	Median	64.0	63.0
	Min, Max	27, 89	26, 87
Age group	< 65 years	230 (51.3%)	194 (57.1%)
	≥ 65 years	218 (48.7%)	146 (42.9%)
Sex	Male	180 (40.2%)	135 (39.7%)
	Female	268 (59.8%)	205 (60.3%)
Race	American Indian/ Alaskan Native	1 (0.2%)	1 (0.3%)
	Asian	86 (19.2%)	57 (16.8%)
	Native Hawaiian / Other Pacific Islander	0	0
	White	259 (57.8%)	202 (59.4%)
	Black / African American	101 (22.5%)	79 (23.2%)
	Other	1 (0.2%)	1 (0.3%)
Untreated Baseline IOP (mmHg)	n	447	340
	Mean (SD)	23.3 (4.20)	23.8 (3.76)
	95% CI of Mean	22.9, 23.7	23.4, 24.2
	Median	23.0	23.0
	Min, Max	12, 46	14, 41
Untreated Baseline IOP Group	Very Low (<22 mmHg)	125 (28.0%)	81 (23.8%)
	Low (22-28 mmHg)	279 (62.4%)	227 (66.8%)
	High (29-35 mmHg)	41 (9.2%)	28 (8.2%)
	Very High (>35 mmHg)	2 (0.4%)	4 (1.2%)

1 81 subjects switched therapy from the Reference drug in Study CLR_09_12 to the Test drug in Study CLR_09_13. They both contributed data to both treatment groups.
Source: ISS Table 14.1.2.1

7.2.2 Explorations for Dose Response

Xelpros 0.005% was administered in one dosage regimen in each of the clinical studies. One drop was instilled once daily in the affected eyes for varying time periods. See Table 7.1.1 for details. No dose response information was submitted in this application.

7.2.3 Special Animal and/or In Vitro Testing

No special toxicology studies were conducted with SPARC latanoprost 0.005%. Adequate nonclinical investigations of SPARC latanoprost 0.005% were performed for and submitted in this application.

7.2.4 Routine Clinical Testing

The routine clinical testing required to evaluate safety concerns for SPARC latanoprost 0.005% was adequately addressed in the design and conduct of this clinical trial.

7.2.5 Metabolic, Clearance, and Interaction Workup

Adequate nonclinical investigations of SPARC latanoprost 0.005% were submitted in this NDA. Refer to the nonclinical reviews for details.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The adverse events reported during the development of SPARC latanoprost 0.005% are consistent with other prostaglandin analogs. The assessment of these adverse events within the clinical trials was adequate.

7.3 Major Safety Results

The Integrated Summary of Safety analyzes the reported treatment-emergent adverse events. These were defined as adverse events that existed before study drug administration and increased in severity during treatment or adverse events that only occurred after study drug administration.

7.3.1 Deaths

There were no deaths in any study.

7.3.2 Nonfatal Serious Adverse Events

Thirteen treatment-emergent serious adverse events were reported in the four studies. None were reported in studies CLR_08_01 and CLR_10_01. Eight serious adverse events occurred in Study CLR_09_12. Five serious adverse events occurred in Study CLR_09_13.

Table 7.3.2
Treatment Emergent Serious Adverse Events
ISS Analysis Set

System Organ Class / Preferred Term	Xelpros 0.005% (N = 448)	Xalatan® 0.005% (N = 340)
Subjects with ≥ 1 Serious Adverse Event	**10 (2.2%)**	**3 (0.9%)**
Eye disorders		
Macular edema	1 (0.2%)	0 (0.0%)
Gastrointestinal disorders		
Abdominal pain	1 (0.2%)	0 (0.0%)
Colitis	1 (0.2%)	0 (0.0%)
General disorders and administration site conditions		
Chest pain	0 (0.0%)	1 (0.3%)
Infections and infestations		
Orchitis	1 (0.2%)	0 (0.0%)
Investigations		
Blood pressure increased	0	1 (0.3%)
Musculoskeletal and connective tissue		
Back pain	0 (0.0%)	1 (0.3%)
Rotator cuff syndrome	1 (0.2%)	0 (0.0%)
Nervous system disorders		
Carotid artery stenosis	1 (0.2%)	0 (0.0%)
Syncope	1 (0.2%)	0 (0.0%)
Tension headache	1 (0.2%)	0 (0.0%)
Retinal and urinary disorders		
Renal failure	1 (0.2%)	0 (0.0%)
Vascular disorders		
Peripheral vascular disorder	1 (0.2%)	0 (0.0%)

1 81 subjects switched therapy from the Reference drug in Study CLR_09_12 to the Test drug in Study CLR_09_13. They both contributed data to both treatment groups.
2 N = number of subjects with at least one event. Each subject was counted once per event if the subject had more than one occurrence of the same event. However, all events were included in the event counts.
Source: ISS Table 14.3.3.1

Reviewer's Comment:
There was an imbalance in reported serious adverse events between the treatment groups. None of the events occurred at ≥ 1%. No new safety signal was identified by these reported non-serious adverse events.

7.3.3 Dropouts and/or Discontinuations

Table 7.3.3-1
Subject Disposition
All Screened Subjects

Subject Disposition	Treatment Group [1]		
	Xelpros 0.005%	Xalatan 0.005%	Total
Subjects screened	---	---	867
Screening failures	---	---	160
Subjects randomized	---	---	707
Subjects not treated	---	---	0
Subjects Included in ISS Analysis Set	448	340	707
Subjects with ≥ 1 dose study drug [2]	448	340	707
Subjects completed study	334 (74.6%)	324 (95.3%)	577 (81.6%)
Subjects discontinued from the study	114 (25.4%)	16 (4.7%)	130 (18.4%)
Reasons for Discontinuation			
Withdrawal of Consent	76 (17.0%)	7 (2.1%)	83 (11.7%)
Protocol Violation	7 (1.6%)	1 (0.3%)	8 (1.1%)
Adverse Event	5 (1.1%)	2 (0.6%)	7 (1.0%)
Withdrawal of Subject by Investigator	10 (2.2%)	1 (0.3%)	11 (1.6%)
Lost to follow up	6 (1.3%)	2 (0.6%)	8 (1.1%)
Study Terminated by Sponsor	7 (1.6%)	2 (0.6%)	9 (1.3%)
Study Medication Failure	3 (0.7%)	1 (0.3%)	4 (0.6%)

1 81 subjects switched therapy from the Reference drug in Study CLR_09_12 to the Test drug in Study CLR_09_13. They both contributed data to both treatment groups. All subjects were counted once in the Total column.
2 Percentage was calculated based on the number of subjects treated with ≥ 1 dose of study drug in each group.
Source: ISS Table 14.1.1.1

Reviewer's Comment:
The percentage of subjects who withdrew from the study was 18.4% overall but the dropout rate was higher in the Xelpros group (25.4%) compared to the Xalatan group (4.7%). The number of subjects who discontinued was higher in the Xelpros group in every category.

Table 7.3.3
Subject Discontinuations
ISS Analysis Population

Reason for Discontinuation	Treatment	Patient Number	Study Number
Adverse event – eye irritation, asthenopia	Xelpros	(b) (6)	CLR_10_01
Adverse event – eye pain, headache	Xelpros		CLR_10_01
Adverse event – headache	Xelpros		CLR_10_01
Adverse event – cystoid macular edema	Xelpros		CLR_09_12
Adverse event – iritis	Xalatan		CLR_09_12
Adverse event – meibomianitis	Xalatan		CLR_09_12
Adverse event – conjuncitivitis	Xalatan		CLR_09_13
Adverse event – ocular hyperemia, eyelid rash, eye pain, eyelid erythema, ocular discharge	Xelpros		CLR_09_12
Adverse event – visual field defect, increased depression	Xalatan		CLR_09_13
Adverse event – ocular hyperemia	Xalatan		CLR_09_13
Adverse event – eye pain	Xalatan		CLR_09_13
Adverse event – allergic conjunctivitis	Xalatan		CLR_09_13

Source: ISS Sections 7.5.1 and 7.5.2.

Reviewer's Comment:
For the highlighted subjects above, the reason for discontinuation was listed as "withdrawal of subject by investigator" or "withdrawal of consent" not adverse event. No new safety signal was identified by the subject discontinuations.

7.3.4 Significant Adverse Events

Refer to Section 7.3.2.

7.3.5 Submission Specific Primary Safety Concerns

No specific primary safety concerns were identified for the submission.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Treatment-Emergent Adverse Events[a] Occurring in ≥ 1% of Subjects in Any Treatment Group ISS Analysis Population

System Organ Class / Preferred Term	Xelpros 0.005% (N = 448)	Xalatan® (N = 340)
Eye disorders	**238 (82.4%)**	**231 (79.9%)**
Eye pain	185 (64.0%)	136 (47.1%)
Ocular hyperemia	135 (46.7%)	143 (49.5%)
Conjunctival hyperemia	58 (20.1%)	55 (19.0%)
Eye discharge	39 (13.5%)	41 (14.2%)
Growth of eyelashes	27 (9.3%)	36 (12.5%)
Eyelash thickening	15 (5.2%)	17 (5.9%)
Eye pruritus	16 (5.5%)	14 (4.8%)
Visual acuity reduced	11 (3.8%)	12 (4.2%)
Erythema of eyelid	9 (3.1%)	13 (4.5%)
Dry eye	12 (4.2%)	5 (1.7%)
Foreign body sensation in eyes	6 (2.1%)	5 (1.7%)
Punctate keratitis	1 (0.3%)	9 (3.1%)
Vision blurred	3 (1.0%)	7 (2.4%)
Chalazion	2 (0.7%)	7 (2.4%)
Blepharitis	3 (1.0%)	4 (1.4%)
Eyelash discoloration	5 (1.7%)	2 (0.7%)
Lacrimation increased	2 (0.7%)	4 (1.4%)
Meibomianitis	3 (1.0%)	1 (0.3%)
Eyelid margin crusting	4 (1.4%)	1 (0.3%)
Eyelid edema	5 (1.7%)	0 (0.0%)
Conjunctival edema	3 (1.0%)	1 (0.3%)
Conjunctival hemorrhage	0 (0.0%)	3 (1.0%)
Infections and infestations	**20 (6.9%)**	**12 (4.2%)**
Upper respiratory tract infection	8 (2.8%)	0 (0.0%)
Sinusitis	4 (1.4%)	0 (0.0%)
Nasopharyngitis	0 (0.0%)	3 (1.0%)
Investigations	**4 (1.4%)**	**5 (1.7%)**
Corneal staining	1 (0.3%)	3 (1.0%)
Musculoskeletal and connective tissue	7 (2.4%)	2 (0.7%)
Rotator cuff syndrome	3 (1.0%)	0 (0.0%)
Nervous system disorders	**4 (1.4%)**	**7 (2.4%)**
Headache	3 (1.0%)	5 (1.7%)

System Organ Class / Preferred Term	Xelpros 0.005% (N = 448)	Xalatan® (N = 340)
Psychiatric disorders	**2 (0.7%)**	**4 (1.4%)**
Anxiety	2 (0.7%)	3 (1.0%)
Skin and subcutaneous tissue disorders	**10 (3.5%)**	**5 (1.7%)**
Rash	3 (1.0%)	0 (0.0%)
Vascular disorders	**1 (0.3%)**	**6 (2.1%)**
Hypertension	1 (0.3%)	6 (2.1%)

Source: ISS Table 14.3.3.2
a Adverse events that existed before study drug administration and increased in severity or adverse events that only occurred after study drug administration were considered TEAEs.

Reviewer's Comment:
Treatment-emergent adverse events which occurred in ≥ 5 % of subjects and more frequently in the Xelpros group compared to the Xalatan group (highlighted above) were: eye pain (64.0%), conjunctival hyperemia (46.7%), and eye pruritus (5.5%).

Treatment-emergent adverse events which occurred in between 1 % and 5 % of subjects and more frequently in the Xelpros group compared to the Xalatan group (highlighted above) were: dry eye (4.2%), upper respiratory tract infection (2.8%), foreign body sensation in the eyes (2.1%), eyelash discoloration (1.7%), eyelid edema (1.7%), eyelid margin crusting (1.4%), sinusitis (1.4%), conjunctival edema (1.0%), meibomianitis (1.0%), rash (1.0%) and rotator cuff syndrome (1.0%).

7.4.2 Laboratory Findings

Clinical laboratory assessments were not conducted in this study.

7.4.3 Vital Signs

Vital signs were evaluated in Study CLR_09_12. For systolic blood pressure, 52 subjects (18.0%) in the Xelpros group and 44 subjects (15.2%) in the Xalatan group has potentially clinically significant post-baseline values or changes from baseline.

7.4.4 Electrocardiograms (ECGs)

Electrocardiograms were not conducted in this study.

7.4.5 Special Safety Studies/Clinical Trials

No special safety studies were performed during the clinical development program.

7.4.6 Immunogenicity

Latanoprost is contraindicated in patients with previously demonstrated hypersensitivity to any ingredients in the formulation or to other prostaglandin analogs. There is no known potential to cause immunogenicity.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Studies to evaluate dose dependency in the occurrence of adverse events were not performed.

7.5.2 Time Dependency for Adverse Events

Studies to evaluate time dependency in the occurrence of adverse events were not performed.

7.5.3 Drug-Demographic Interactions

Studies to evaluate drug-demographic interactions in the occurrence of adverse events were not performed.

7.5.4 Drug-Disease Interactions

Studies to evaluate drug-disease interactions in the occurrence of adverse events were not performed.

7.5.5 Drug-Drug Interactions

Studies to evaluate drug-drug interactions in the occurrence of adverse events were not performed.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

There have been no latanoprost clinical studies performed and no post-marketing data which suggest any tumorigenic potential.

7.6.2 Human Reproduction and Pregnancy Data

There have been no clinical studies in human reproduction or pregnancy performed. No clinical study or post-marketing data suggest an effect on human reproduction or pregnancy.

7.6.3 Pediatrics and Assessment of Effects on Growth

Effects on growth were not evaluated.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There is no evidence for the potential for overdose or potential abuse with latanoprost.

7.7 Additional Submissions / Safety Issues

None.

8 Postmarket Experience

Since Xelpros is not a marketed product, there is no post-marketing experience with this product.

9 Appendices

9.1 Literature Review/References

The medical reviewer conducted a PubMed electronic literature search to supplement the submitted review of the relevant literature. There was no significant new information found in the published literature.

9.2 Advisory Committee Meeting

No Advisory Committee Meeting was scheduled for this NDA.

9.3 Clinical Investigator Financial Disclosure

Clinical Investigator Financial Disclosure
Review Template

Application Number: NDA 206-185

Submission Date(s): January 31, 2014

Applicant: Sun Pharma Advanced Research Co., Ltd.

Product: Latanoprost 0.005% Ophthalmic (b) (4)

Reviewer: Rhea A. Lloyd, MD, Medical Officer

Date of Review: February 20, 2014

Covered Clinical Study (Name and/or Number):

- SPARC Multicenter Efficacy Study CLR_08_01
- SPARC Multicenter Efficacy Study CLR_10_01
- SPARC Multicenter Efficacy Study CLR_09_12
- SPARC Multicenter Efficacy Study CLR_09_13

Was a list of clinical investigators provided:	Yes ×	No ☐ (Request list from applicant)
Total number of investigators identified: 61		
Number of investigators who are sponsor employees (including both full-time and part-time employees): None		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3454): None		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): None. Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from applicant)

Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) None		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

Discuss whether the applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*.[1] Also discuss whether these interests/arrangements, investigators who are sponsor employees, or lack of disclosure despite due diligence raise questions about the integrity of the data:

- If not, why not (e.g., study design (randomized, blinded, objective endpoints), clinical investigator provided minimal contribution to study data)
- If yes, what steps were taken to address the financial interests/arrangements (e.g., statistical analysis excluding data from clinical investigators with such interests/arrangements)

Briefly summarize whether the disclosed financial interests/arrangements, the inclusion of investigators who are sponsor employees, or lack of disclosure despite due diligence affect the approvability of the application.

Not applicable.

9.4 Labeling Recommendations

Following is the applicant's proposed labeling submitted in the July 9, 2014 submission.

The reviewer's additions are noted in underline and deletions by.

13 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

RHEA A LLOYD
11/03/2014

WILLIAM M BOYD
11/03/2014