CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207795Orig1s000

CLINICAL REVIEW(S)

Medical Officer's Review of NDA 207795
Class 2 Resubmission

NDA 207795	**Submission Date:** 8/17/2017
SDN-035	**Received Date:** 8/17/2017
	Review Date: 10/31/2017

Applicant: Bausch & Lomb, Inc.
c/o Valeant Pharmaceuticals North America LLC
400 Somerset Corporate Boulevard
Bridgewater, NJ 08807

Drug: Vyzulta (latanoprostene bunod ophthalmic solution) 0.024%

Pharmacologic Category: Prostaglandin analogue

Dosage Form and Route of Administration: Topical ophthalmic solution

Submitted:

Submitted is a resubmission of NDA 207795, Vyzulta (latanoprostene bunod ophthalmic solution) 0.024%. The original NDA was submitted on July 21, 2015. Complete Response (CR) letters dated July 21, 2016, and August 7, 2017, were issued. The Applicant has addressed the deficiency identified in the CR regarding the good manufacturing practice (GMP) status of the manufacturing facility in this submission. No new clinical data was provided in this submission.

Reviewer's Comments:

No new clinical information was provided in this resubmission. From a clinical perspective, the conclusions on the safety and efficacy of Vyzulta (latanoprostene bunod ophthalmic solution) 0.024% dosed once daily in the evening for the reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension are unchanged and the clinical data supports approval of the application. See Clinical reviews in DARRTS dated 4/21/16 and 8/1/2017.

The applicant has submitted proposed prescribing information. Based on a review of the application, the Review Team has recommended labeling consistent with the labeling of other prostaglandin analogs for ophthalmic use in lowering intraocular pressure. The labeling submitted on August 17, 2017, is acceptable and is attached at the end of this review.

Conclusion/Recommended Regulatory Action:

NDA 207795 is recommended for approval with the labeling identified in this review.

Lucious Lim, M.D., M.P.H.
Medical Officer

cc: NDA 207795
DTOP/Div/Files
DTOP/CSO/Almoza
DTOP/MO/Lim
DTOP/CTL/Boyd

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/s/

LUCIOUS LIM
11/01/2017

WILLIAM M BOYD
11/01/2017

Deputy Office Director Decisional Memo

Date	(electronic stamp)
From	John Farley, MD, MPH
Subject	Deputy Office Director Decisional Memo
NDA#	207795
Applicant Name	Bausch & Lomb Inc.
Date of Re-Submission	February 24, 2017
PDUFA Goal Date	August 24, 2017
Proprietary Name / Established (USAN) Name	Vyzulta (latanoprostene bunod ophthalmic solution) 0.024%
Dosage Forms / Strength	Topical ophthalmic solution, 0.024%
Applicant Proposed Indication(s)/Populations	Reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension
Action:	*Complete Response*

Material reviewed/consulted during this review cycle:	**Names of discipline reviewers**
Medical Officer Review	Lucious Lim, MD
Pharmacology Toxicology Review	Andrew J. McDougal, PhD
Labeling	Jane File, MD
CDTL and Deputy Division Director Review	William M. Boyd, MD Wiley Chambers, MD
Product Quality Review	
Drug Substance	Rohit Tiwari, Ph. D.
Drug Product	Chunchun Zhang, Ph.D.
Process	Sung Kim, Ph. D.
Microbiology	Daniel Schu, Ph. D.
Facility	Rose Xu, Ph.D.
Biopharmaceutics	Om Anand, Ph.D.
Application Technical Lead	Chunchun Zhang, Ph.D.
ORA Lead	Paul Perdue
Environmental Assessment (EA)	James Laurenson

CDTL=Cross-Discipline Team Leader

Background

Please refer to my Deputy Office Director Review including Benefit Risk Summary dated July 21, 2016 for this NDA 207795 supporting a Complete Response Letter issued that same day.

The Complete Response Letter of July 21, 2016 cited a single deficiency:
During a recent inspection of the Bausch & Lomb Inc. (FEI 1000113778) manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

The Complete Response Letter of July 21, 2016 also provided two comments/recommendations: In the resubmission, the Agency recommended that the Applicant include a copy of the protocol for the in-use stability of drug product and provide data from multiple batches analyzed for all quality attributes, including (b) (4), once every 2 weeks until the desired storage duration.

As the data concerning pregnancy risk were limited providing exposure margins based on dose multiples (on a mg/m^2 basis, presuming 100% absorption), the Agency recommended the Applicant consider conducting additional animal embryofetal toxicity studies.

This Memo summarizes pertinent updates to my Deputy Office Director Review of July 21, 2016.

At the time of original submission, this NDA was identified for review under the Program for Enhanced Review Transparency and Communication for NME NDAs and original BLAs (known as the Program and described in the PDUFA V goals letter). Further review of the application has indicated that NDA 207795 may not qualify for the Program, and the Agency continues to assess this matter. However, consistent with FDA policy, the review of the NDA has continued to be managed under the Program for process reasons. According to CDER's review process, the signatory authority for applications managed under the Program is generally at the office level. Because this application was managed under the Program, it will be signed at the office level to be consistent with OND practice.

Product Quality

Re-inspection of the drug product manufacturing facility again resulted in the Office of Process and Facilities recommending Withhold. Therefore, NDA 207795 was recommended for Complete Response by the Product Quality review team. I concur that satisfactory resolution of deficiencies at this manufacturing facility is required before this application can be approved and the deficiency cited on July 21, 2016 remains.

In this resubmission, thirty-six months of stability data at long term conditions (5°C) were updated for three commercial scale registration batches. All the quality attributes remained within the proposed specification. Additionally, the in-use stability data provided in the resubmission support the label storage statement of 25ºC for 8 weeks. Thus, the Product Quality team concluded that the first comment/recommendation listed in the Complete Response letter of July 21, 2016 had been adequately addressed.

Nonclinical Pharmacology/Toxicology

In this re-submission, the applicant did not submit additional animal embryofetal toxicity studies. The Pharmacology Toxicology Reviewer provided recommendations regarding the Applicant's proposed labeling concerning pregnancy, mechanism of action, and animal embryofetal toxicity studies. I concur that there are no Pharmacology Toxicology issues precluding approval.

Conclusion

NDA 207795 cannot be approved in its present form and a Complete Response letter will be issued with the following deficiency:

During a recent inspection of the Bausch & Lomb Inc (FEI#1000113778) manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

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/s/

JOHN J FARLEY
08/07/2017

Medical Officer's Review of NDA 207795
Class 2 Resubmission

NDA 207795 Resubmission	**Submission Date:** February 24, 2017 **Received Date:** February 24, 2017 **Review Date:** August 1, 2017
Applicant:	Bausch & Lomb, Inc. c/o Valeant Pharmaceuticals North America LLC 400 Somerset Corporate Boulevard Bridgewater, NJ 08807
Drug:	Vyzulta (latanoprostene bunod ophthalmic solution) 0.024%
Pharmacologic Category:	Prostaglandin analogue
Dosage Form and Route of Administration:	Topical ophthalmic solution

Submitted:

Submitted is a resubmission of NDA 207795, Vyzulta (latanoprostene bunod ophthalmic solution) 0.024%. The original NDA was submitted on July 21, 2015. A Complete Response (CR) letter dated July 21, 2016, was issued. Applicant now believes that the deficiency identified in the CR regarding the good manufacturing practice (GMP) status of the manufacturing facility has been rectified. No new clinical data was provided in this submission.

Reviewer's Comments:

No new clinical information was provided in this resubmission. From a clinical perspective, the conclusions on the safety and efficacy of Vyzulta (latanoprostene bunod ophthalmic solution) 0.024% dosed once daily in the evening for the reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension are unchanged. See original Clinical review in DARRTS dated 4/21/16.

The recommended revisions to the 7/24/17, labeling are attached to this review.

Conclusion/Recommended Regulatory Action:

NDA 207795 is recommended for approval with the labeling identified in this review.

Lucious Lim, M.D., M.P.H.
Medical Officer

cc: NDA 207795
DTOP/Div/Files
DTOP/CSO/Almoza
DTOP/MO/Lim
DTOP/CTL/Boyd
DTOP/Dep Div Director/Chambers

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/s/

LUCIOUS LIM
08/01/2017

WILLIAM M BOYD
08/01/2017

Deputy Office Director Decisional Memo

Date	(electronic stamp)
From	John Farley, MD, MPH
Subject	Deputy Office Director Decisional Memo
NDA#	207795
Applicant Name	Bausch & Lomb Inc.
Date of Submission	July 21, 2015
PDUFA Goal Date	July 21, 2016
Proprietary Name / Established (USAN) Name	Vyzulta (latanoprostene bunod ophthalmic solution) 0.024%
Dosage Forms / Strength	Topical ophthalmic solution, 0.024%
Applicant Proposed Indication(s)/Populations	Reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension
Action:	*Complete Response*

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**	
Medical Officer Review	Lucious Lim, MD	
Statistical Review	Abel Tilahun Eshete, PhD/Yan Wang, PhD/Dionne Price, PhD	
Pharmacology Toxicology Review	Andrew J. McDougal, PhD	
Clinical Pharmacology Review	Yongheng Zhang, PhD	
OPDP	Meena Ramachandra, PharmD	
OSI	Roy Blay, PhD/Janice K. Pohlman, MD, Kassa Ayalew, MD	
OSE/DMEPA	Michelle Rutledge, PharmD	
OSE/DRISK	Carolyn L. Yancey, MD	
PLLR Labeling Memorandum	Melissa Tassinari, PhD, DABT	
CDTL Review	William M. Boyd, MD	
Deputy Division Director Review	Wiley Chambers, MD	
Drug Substance	Gaetan Ladouceur, Ph. D.	ONDP/DNDAPI/NDBI
Drug Product	Chunchun Zhang, Ph.D.	ONDP/DNDP-I/Branch III
Process	Sung Kim, Ph. D.	OPF/DPAIII/PABVII
Microbiology	Daniel Schu, Ph. D.	OPF/DMA/MABIII
Facility	Denise DiGiulio	OPF/DIA2
Biopharmaceutics	Om Anand, Ph.D.	ONDP/DBP/Branch I
Regulatory Business Process Manager	Erin Andrews, Pharm D	OPRO/DRBPMI/RBPMBI
Application Technical Lead	Chunchun Zhang, Ph.D.	ONDP/DNDP-I/Branch III
ORA Lead	Paul Perdue	ORA/OO/OMPTO/DMPTPO/MDTP
Environmental Assessment (EA)	James Laurenson	OPQ/ONDP

OND=Office of New Drugs
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OSI=Office of Scientific Investigations
CDTL=Cross-Discipline Team Leader
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

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1. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Glaucoma is a progressive optic neuropathy which causes irreversible damage to the optic nerve and corresponding visual field loss. Glaucoma is usually associated with chronic elevation of IOP. In patients with glaucoma, lowering of the IOP is generally accepted to be of clinical benefit, and IOP is accepted as the clinical endpoint for establishing the efficacy of ocular hypotensive medications. There are many ophthalmic drug products approved for lowering IOP in patients with open-angle glaucoma and ocular hypertension

This NDA seeks approval of latanoprostene bunod ophthalmic solution 0.024%, a prostaglandin analog pro-drug, administered one drop once daily in the evening, for the reduction of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension. In two adequate and well-controlled trials, non-inferiority of latanoprostene bunod ophthalmic solution 0.024% to timolol maleate 0.5% was established for the primary efficacy endpoint of mean IOP in the study eye measured at specified time points: 8 AM, 12 PM, and 4 PM at Week 2, Week 6, and Month 3. These trials provide substantial evidence of efficacy.

At a recent inspection of the drug product manufacturing facility, GMP deficiencies were observed, resulting in the Office of Pharmaceutical Quality recommending a Complete Response. Related to these deficiencies is the need for investigation to determine the root cause for the observed out-of-specification for (b) (4) during in-use stability studies. Satisfactory resolution of these deficiencies is required before this NDA may be approved.

Based on studies with latanoprostene bunod in rabbits and rats, the Pharmacology Toxicology Reviewer concluded that the drug may cause miscarriage, abortion, and fetal harm at clinically relevant doses. Based on the data provided, this risk appears to be higher than that observed for other prostaglandin analog ophthalmic products. There are limitations in the embryofetal studies. We have provided the applicant with recommendations for additional animal studies that may be performed to better characterize pregnancy risk.

With the exception of the pregnancy risk, the risks for this drug appear to be similar to other prostaglandin analogs currently approved in the U.S. for the Indication proposed.

In summary, because of the GMP deficiencies, the Benefit Risk for latanoprostene bunod ophthalmic solution 0.024% is not favorable. This NDA cannot be approved until these deficiencies are resolved and a Complete Response Letter will be issued.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Glaucoma is a progressive optic neuropathy which causes irreversible damage to the optic nerve and corresponding visual field loss. Glaucoma is usually associated with chronic elevation of IOP. In open-angle glaucoma, the IOP elevation is thought to be caused by increased inflow and/or decreased outflow of aqueous humor. The mechanism whereby raised IOP injures the optic nerve is not known, and there may be "an interplay between IOP and abnormality of the retina and optic nerve".[1]	In patients with glaucoma, lowering of the IOP is generally accepted to be of clinical benefit. IOP is accepted as the clinical endpoint for establishing the efficacy of ocular hypotensive medications.
Current Treatment Options	• Ophthalmic drug products approved for lowering IOP in patients with open-angle glaucoma and ocular hypertension include: beta-adrenergic antagonists (beta-blockers), alpha-adrenergic agonists, parasympathomimetic (miotic) agents, carbonic anhydrase inhibitors, and prostaglandin analogs.	There are many approved drug products for the Indication proposed by the applicant for latanoprostene bunod ophthalmic solution 0.024%.
Benefit	• The primary evidence for the safety and efficacy of latanoprostene bunod ophthalmic solution 0.024% comes from two randomized, multicenter, double-masked, parallel-group trials (Trial 769 and Trial 770). The primary objective of the two trials was to demonstrate the non-inferiority of the test drug to timolol maleate 0.5% (Timolol) with respect to the reduction of IOP. The primary efficacy endpoint was the mean IOP in the study eye measured at the specified time points: 8 AM, 12 PM, and 4 PM at Week 2, Week 6, and Month 3. In each trial, 420 subjects were randomized in a 2:1 ratio to receive either test drug or Timolol. Both trials had a three month masked efficacy period. • The difference in the mean IOP between the treatment groups (latanoprostene bunod ophthalmic solution 0.024% minus Timolol) was determined based on the least square means from the ANCOVA model in the ITT population. Non-inferiority to Timolol was established if the upper limit of the 95% confidence interval for the	I concur with the review team, CDTL, and Deputy Division Director that Trials 769 and 770 demonstrated that latanoprostene bunod ophthalmic solution 0.024% was non-inferior to the active control timolol maleate ophthalmic solution 0.5% in reduction of IOP. Thus, substantial evidence of efficacy is provided.

[1] Cricks RP, Khaw PT. *A Textbook of Clinical Ophthalmology, 3rd Edition.* River Edge, NJ: World Scientific Publishing Co. Pte. Ltd., 2003.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	difference in the mean IOP was <1.5 mmHg at each of the nine post-baseline time points (Statistical Criterion) and was < 1 mmHg at the majority of time points (Clinical Criterion). • The mean baseline IOP values were comparable between the two treatment groups and both treatment groups demonstrated IOP reductions at each of the nine post-baseline time points in each trial. There was an IOP reduction between 7.5 to 9.0 mmHg in the latanoprostene bunod ophthalmic solution 0.024% arms compared to 6.5 to 7.9 mmHg in the Timolol arms. Because the upper limits of the 95% confidence intervals for the mean difference in IOP were less than 1.0 mmHg, both the statistical and clinical criteria for non-inferiority were met in both trials.	
Risk	• At a recent inspection of the drug product manufacturing facility, GMP deficiencies were observed, resulting in Office of Pharmaceutical Quality recommending a Complete Response. Related to these deficiencies is the need for investigation to determine the root cause for the observed out-of-specification for (b) (4) during in-use stability studies. As a result, the drug product in-use stability data does not support the label storage statement (b) (4) • Based on studies with latanoprostene bunod in rabbits and rats, the Pharmacology Toxicology Reviewer concluded that the drug may cause miscarriage, abortion, and fetal harm at clinically relevant doses. Based on the data provided, this risk appears to be higher than that observed for other prostaglandin analog ophthalmic products. For example, latanoprostene bunod was shown to be abortifacient to pregnant rabbits at exposures $\geq$ 0.28 times the clinical dose. Latanoprostene bunod was teratogenic in rabbits at doses $\geq$ 1.4 times the clinical dose.	Satisfactory resolution of these deficiencies is required before this NDA may be approved. The methods to be used in, and the facilities and controls used for, the manufacture, processing, packing or holding of the drug substance or the drug product must comply with the current good manufacturing practice regulations in 21 CFR 210 and 211. There are limitations in the embryofetal studies. The embryofetal studies for latanoprost bunod were conducted via the intravenous route (IV) rather than the intended human route of ophthalmic administration. Human dose equivalents, rather than human exposure equivalents, were calculated on body surface area. In addition, no data from a pre and post natal study were provided. We have provided

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• The total exposed safety population which includes all subjects exposed to at least one dose of latanoprostene ophthalmic solution 0.024% or higher, is 1,335 subjects. Two deaths occurred in the Phase 3 development program and were assessed by the review team as not related to study drug. SAE's were also assessed by the review team as not related to study drug. The most common ocular adverse reactions with incidence ≥ 2% were conjunctival hyperemia, eye irritation, eye pain, and installation site pain. If approved, usual Warnings and Precautions for the prostaglandin analog class including changes to pigmented tissues, eyelash changes, and macular edema are planned to be included in labeling.	the applicant with recommendations for additional animal studies that may be performed to better characterize pregnancy risk. I concur with the review team, CDTL, and Deputy Division Director that, based on the safety data from clinical trials provided, with the exception of the pregnancy risk, the risks for this drug appear to be similar to other prostaglandin analogs currently approved in the U.S. for the Indication proposed.
Risk Management	• Based on the review to date, there are no Post-Marketing Requirements or Commitments under consideration.	Based on the review to date, it is anticipated that routine post-marketing safety surveillance and reporting will be adequate.

2. Further discussion to support regulatory action

Background

Latanoprostene bunod is a pro-drug consisting of latanoprost acid covalently bound by an ester linkage to 4-hydroxybutyl nitrate (butanediol mononitrate); nitrooxy butyl alcohol. The applicant has shown that topical ocular administration of the drug product results in rapid appearance of latanoprost acid, a prostaglandin receptor agonist. The applicant proposes that the drug product is metabolized by esterases to latanoprost acid and free butanediol mononitrate. The applicant further proposes that butanediol monnitrate releases nitric oxide at sufficient local concentrations to relax the trabecular meshwork of the eye, but the review team concluded that the data submitted was inadequate to support this hypothesis.

At the time of submission, this NDA was identified for review under the Program for Enhanced Review Transparency and Communication for NME NDAs and original BLAs (known as the Program and described in the PDUFA V goals letter). Further review of the application during the review cycle has indicated that NDA 207795 may not qualify for the Program, and the Agency continues to assess this matter. However, consistent with FDA policy, the review of the NDA has continued to be managed under the Program for process reasons. According to CDER's review process, the signatory authority for applications managed under the Program is generally at the office level. Because this application was managed under the Program, it will be signed at the office level to be consistent with OND practice.

Product Quality

As described in the Benefit Risk Assessment, the NDA was recommended for Complete Response from the Product Quality perspective.

Nonclinical Pharmacology/Toxicology

The Pharmacology Toxicology Reviewer did not identify concerns that would preclude approval.

Based on studies with latanoprostene bunod in rabbits and rats, the Pharmacology Toxicology Reviewer concluded that the drug may cause miscarriage, abortion, and fetal harm at clinically relevant doses. Based on the data provided, this risk appears to be higher than that observed for other prostaglandin analog ophthalmic products. For example, latanoprostene bunod was shown to be abortifacient to pregnant rabbits at exposures $\geq$ 0.28 times the clinical dose. Latanoprostene bunod was teratogenic in rabbits at doses $\geq$ 1.4 times the clinical dose.

Both the Pharmacology Toxicology Reviewer and Consultant from the Division of Pediatric and Maternal Health noted limitations in the embryofetal studies. The embryofetal studies for latanoprost bunod were conducted via the intravenous route (IV) rather than the intended human route of ophthalmic administration. Human dose equivalents, rather than human

exposure equivalents, were calculated on body surface area due to the lack of interpretable exposure data in the animal studies and limitations in the human pharmacokinetic data with ophthalmic administration described below (no quantifiable plasma levels of the parent molecule, or the metabolite, butanediol mononitrate, and low plasma concentration levels of the metabolite latanoprost acid). The comparison of doses from the IV route in the animal studies to clinical topical ophthalmic doses to determine human dose equivalents presume 100% absorption and may overestimate the teratogenic risk due to the possible exposure differences resulting from the different routes of administration. In addition, no data from a pre and post natal study were provided. We have provided the applicant with recommendations for additional animal studies that may be performed to better characterize pregnancy risk.

Exposure of rats and mice to latanoprost acid, resulting from oral dosing with latanoprost in lifetime rodent bioassays, was not carcinogenic. In a 9 month topical ocular dose study in cynomolgus monkeys, pleural and subpleural chronic fibrosis/inflammation was observed in some animals at 7.9 and13.5 fold the clinical systemic exposure. Of note, the Pharmacology Toxicology Reviewer concluded that the nonclinical data overall indicate the systemic toxicities caused by latanoprostene bunod are due to systemic exposure to the parent compound and other metabolites and not entirely due to the latanoprost acid metabolite.

Clinical Pharmacology

The Clinical Pharmacology Reviewer did not identify concerns that would preclude approval. There were no quantifiable plasma concentrations of latanoprostene bunod (lower limit of quantitation, LLOQ, of 10.0 pg/mL) or butanediol mononitrate (LLOQ of 200 pg/mL) post ocular administration on Day 1 and Day 28. Latanoprost acid concentrations were quantifiable (LLOQ of 30.0 pg/mL) in the plasma samples of the majority of subjects, especially in the early time point (i.e., 5 min post dose). The mean time of maximal plasma concentration (Tmax) for latanoprost acid was approximately 5 min post ocular administration on both Day 1 and Day 28. The elimination of latanoprost acid from human plasma is rapid as latanoprost acid plasma concentration dropped below the LLOQ (30.0 pg/mL) in most of subjects by 15 min post the ocular administration of the drug product in humans.

Advisory Committee Meeting

As there were no efficacy or safety issues that would benefit from an Advisory Committee discussion, an Advisory Committee was not convened to discuss this NDA.

Pediatrics

Elevated IOP is rare in children. This application was presented at the Pediatric Review Committee (PeRC) during this review cycle. PeRC concurred that a waiver of required pediatric assessments was appropriate as necessary studies are impossible or highly impracticable due to the geographic distribution of potential pediatric study participants.

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/s/

JOHN J FARLEY
07/21/2016

Deputy Division Director Summary Review for NDA 207795

Date	June 17, 2016
From	Wiley A. Chambers, MD
Subject	Deputy Division Director Summary Review
NDA#	207795
Applicant	Bausch & Lomb Inc.
Date of Submission	July 21, 2016
Name	Vyzulta (latanoprostene bunod ophthalmic solution) 0.024%
Dosage Form(s) / Strength(s)	Topical ophthalmic solution, 0.024%
Applicant Proposed Indication(s)/Population(s)	Reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension
Recommended Action for NME:	*Complete Response*

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**	
Medical Officer Review	Lucious Lim, MD	
Statistical Review	Abel Tilahun Eshete, PhD/Yan Wang, PhD/Dionne Price, PhD	
Pharmacology Toxicology Review	Andrew J. McDougal, PhD	
Clinical Pharmacology Review	Yongheng Zhang, PhD	
OPDP	Meena Ramachandra, PharmD	
OSI	Roy Blay, PhD/Janice K. Pohlman, MD, Kassa Ayalew, MD	
CDTL Review	William M. Boyd, MD	
OSE/DMEPA	Michelle Rutledge, PharmD	
OSE/DRISK	Carolyn L. Yancey, MD	
Drug Substance	Gaetan Ladouceur, Ph. D.	ONDP/DNDAPI/NDBI
Drug Product	Chunchun Zhang, Ph.D.	ONDP/DNDP-I/Branch III
Process	Sung Kim, Ph. D.	OPF/DPAIII/PABVII
Microbiology	Daniel Schu, Ph. D.	OPF/DMA/MABIII
Facility	Denise DiGiulio	OPF/DIA2
Biopharmaceutics	Om Anand, Ph.D.	ONDP/DBP/Branch I
Regulatory Business Process Manager	Erin Andrews, Pharm D	OPRO/DRBPMI/RBPMBI
Application Technical Lead	Chunchun Zhang, Ph.D.	ONDP/DNDP-I/Branch III
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Environmental Assessment (EA)	James Laurenson	OPQ/ONDP

OND=Office of New Drugs
OPDP=Office of Prescription Drug Promotion
CDTL=Cross-Discipline Team Leader
DEPI= Division of Epidemiology
DRISK=Division of Risk Management
OPQ=Office of Pharmaceutical Quality
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis

1. Benefit-Risk Assessment

NDA 207795, Vyzulta (latanoprostene bunod ophthalmic solution) 0.024% is not recommended for approval for the reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension until all manufacturing facilities are found acceptable to be incompliance with current Good Manufacturing Practices (cGMPs).

The 505(b)(1) application includes adequate and well controlled clinical trials which support the safety and effectiveness of latanoprostene bunod ophthalmic solution 0.024% for the treatment of elevated intraocular pressure (IOP) in patients with open angle glaucoma or ocular hypertension.

Elevated intraocular pressure is a major risk factor for optic nerve damage, commonly described as glaucoma. This submission contains adequate and well controlled trials which support the safety and efficacy of latanoprostene bunod ophthalmic solution 0.024% dosed once daily in the evening for the treatment of elevated IOP in patients with open-angle glaucoma or ocular hypertension. Studies #769 and #770 demonstrate that the IOP lowering ability of latanoprostene bunod ophthalmic solution 0.024% is not inferior to the IOP lowering ability of timolol maleate ophthalmic solution 0.5%. The safety profile of latanoprostene bunod ophthalmic solution 0.024% is similar to other marketed topical prostaglandin analogues. The most common ocular adverse events are conjunctival/ocular hyperemia (10%) and ocular irritation upon instillation (5%).

Latanoprostene bunod ophthalmic solution 0.024%, if manufactured in a facility which complies with current good manufacturing practices, would be expected to have potential benefits which outweigh the potential risks for the treatment of elevated IOP in open-angle glaucoma or ocular hypertension. The risk for using this drug is consistent with the currently marketed prostaglandin analogs.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• 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 factor is elevated intraocular pressure (IOP).	Intraocular pressure is currently the accepted standard for establishing the efficacy of ocular hypotensive medications.
Current Treatment Options	• 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 analogues.	There are multiple beta-adrenergic antagonists (beta-blockers), alpha-adrenergic agonists, parasympathomimetic (miotic) agents, carbonic anhydrase inhibitors, and prostaglandin analogues approved in the U.S. to treat elevated IOP.
Benefit	• Intraocular pressure (IOP) is currently the accepted standard for establishing the efficacy of ocular hypotensive medications. The primary efficacy endpoint was mean IOP measured at multiple time points for studies #770 and #769. Studies #770 and #769 demonstrated that latanoprostene bunod ophthalmic solution 0.024% was non-inferior to timolol maleate 0.5% at all time points measured. The safety database was adequate.	Studies #770 and #769 demonstrated that latanoprostene bunod ophthalmic solution 0.024% was non-inferior to the active-control, timolol maleate ophthalmic solution 0.5%.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk	• The risk for using this drug is consistent with currently U.S. marketed prostaglandin analogues.	The safety database contained in this application established the safety of latanoprostene bunod ophthalmic solution 0.024% dosed once daily in the evening.
Risk Management	• No risk management activities are recommended beyond the routine monitoring and reporting of all adverse events. There are no recommended Postmarketing Requirements or Phase 4 Commitments.	Routine monitoring and reporting of all adverse events are adequate.

2. Background

Glaucoma is a progressive disease that is characterized by irreversible damage to the optic nerve and corresponding loss of visual field. It affects one person in 200 over the age of 40 and is a leading cause of irreversible blindness in the United States. 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. Prostaglandin analogues are believed to reduce IOP largely due to increased uveoscleral outflow of aqueous humor. The exact mechanism of action is unknown at this time.

Latanoprostene bunod is a new chemical entity. It is not currently marketed in the United States. The drug has no foreign regulatory and marketing history.

3. Product Quality

DESCRIPTION AND COMPOSITION

Latanoprostene Bunod Ophthalmic Solution, 0.024% drug product is a clear, colorless to slightly yellow, sterile, preserved ophthalmic solution formulated for topical delivery to the eye.

Component	Concentration (mg/mL)	Function
Latanoprostene bunod	0.24	Active
Benzalkonium chloride	0.20	(b) (4) preservative
Polysorbate 80	(b) (4)	(b) (4)
Edetate disodium	(b) (4)	
Sodium citrate	(b) (4)	Buffer
Citric acid,	(b) (4)	Buffer
Glycerin		(b) (4)
Water	(b) (4)	

Drug Substance Specifications

(NMT=Not more than)

Appearance		Colorless to pale yellow viscous oil	
Identification A	IR absorption	(b) (4)	
Identification B	UPLC		
Water Content	Karl Fischer	NMT (b) (4)%	
Residue on Ignition		NMT %	
Heavy Metals		NMT (b) (4)	
Assay		(b) (4)%	
Related Substances	UPLC	(b) (4)	NMT (b) (4)%
			NMT %
			NMT %
		Any other single unspecified impurity	NMT %
		Total unspecified impurities:	NMT %
Isometric impurities	HPLC	(b) (4)	NMT (b) (4)%
			NMT
Total Impurities	UPLC and HPLC	Sum of individual related substances	
		And isomeric impurities:	NMT (b) (4)%
Residual Solvents	GC	(b) (4)	(b) (4)
Specific rotation		(b) (4)	

Drug Product Specifications:

Test	Procedure	Shelf Life Criteria
Appearance	Visual	Clear and colorless to slightly yellow solution
Identification-A[a]	UPLC	Retention time matches reference
Identification-B[a]	UV	UV spectrum matches reference
Latanoprostene assay	(b) (4) UPLC[b]	(b) (4) % label claim
Related substances	UPLC	
(b) (4)		NMT (b) (4) %
Individual Related Substances		NMT %
Total Related Substances		NMT %
Benzalkonium chloride	UPLC	(b) (4) % of label claim
pH	USP	(b) (4)
Osmolality	USP	(b) (4) mOsm/kg
Particulate matter	USP	NMT (b) (4)
		NMT
		NMT
Antimicrobial effectiveness	USP	Meets USP requirement
Sterility	USP	Meets USP requirement
Weight loss/gain	Manual	NMT (b) (4) %
Fill volume[a,e]	Weight check	NLT label claim

[a] Required at time of release only

[c] (b) (4)

S

d

e

N

NLT= Not less than

USP= United States Pharmacopeia

The proposed specifications appear acceptable.

INSPECTIONS

Drug Substance Manufacturers

Facility Name	FEI	Profile Code	Responsibilities	Facility Sub-Score	Process Sub-Score	Product Sub-Score	Overall Initial Facility Risk Assessment	Recommendation
(b) (4)		CSN	drug substance manufacturer	low	low	med	**med**	**no PAI needed**

Drug Product Manufacturers

Facility Name	FEI	Profile Code	Responsibilities	Facility Sub-Score	Process Sub-Score	Product Sub-Score	Overall Initial Facility Risk Assessment	Recommendation
BAUSCH & LOMB INC	1000113778	SLQ	finished product manufacturer	high	high	high	**high**	**PAI needed; KTM will be written to address product specific concerns**
(b) (4)		CTL	ALT testing facility for compendial testing	med	low	low	**med**	**no PAI needed**
BAUSCH & LOMB INC	1313525	CTL	stability tester for clinical and submission batches; alt facility for analytical/micro release testing and stability testing	low	low	low	**low**	**no PAI needed**

Details for Bausch & Lomb finished product manufacturer inspections

BAUSCH & LOMB INC is located Tampa Florida and is the manufacturing site for the finished drug product for NDA 207795, lantanoprost bunod topical ophthalmic solution, 0.24%. This drug product is proposed to be (b) (4) at the manufacturing site.

Previous inspections/compliance history relevant to NDA 207795:

Date of Inspection	Findings	
3/2-6/2015	VAI	(b) (4)
6/20/13-7/12/13	VAI	
02/27-03/21/2012	VAI	

The last inspection dated 3/2/2015 included full coverage to the Quality and Materials Systems with limited coverage to the Facilities and Equipment, Production, Packaging and Labeling, and Laboratory Controls systems. A FDA 483 was issued and discussed with management in part for: (b) (4)

Inspection dated 6/20/13-7/12/13, covered portions of Quality, Materials, Production, Packaging and Labeling, and Facilities and Equipment Systems. A 483 was issued for deficiencies (b) (4)

Inspection dated 02/27-03/21/2012 was classified VAI. An FDA 483, Inspectional Observations Form, was issued regarding (b) (4)

Due to the high risk nature of this product and the questionable stability data submitted in the NDA, a pre-approval inspection was conducted. The inspection was conducted 2/8-25/2016. A 4-item 483 was issued at the close of the inspection. A withhold recommendation for NDA 207795 was forwarded to the ORA/FLA-DO Preapproval Manager. The withhold recommendation was due to unacceptable CGMP conditions that were uncovered during the inspection. Specifically, (b) (4)

A full assessment of the firm's corrective actions and capability to manufacture this NDA in accordance with CGMP cannot be completed until the consultants are finished their audits and training and a corrective action plan is submitted by the firm with resources allocated and timelines for completion. A pre- approval inspection will need to be conducted during the second review cycle for this submission, presuming all corrective actions have been implemented by that time. Review of the firm's response dated March 17, 2016 to the FDA 483 has raised a data integrity concern regarding the filed data.

In summary, the outcome of the most recent inspection of the Bausch & Lomb Inc. drug product manufacturing facility has resulted in Office of Process and Facilities recommending withhold. Therefore, NDA 207-795 is recommended for Complete Response from Product Quality perspective.

4. Nonclinical Pharmacology/Toxicology

Latanoprostene bunod (LBN, PF-0318707, BOL-303259-X) is a pro-drug consisting of latanoprost acid covalently bound by an ester linkage to 4- hydroxybutyl nitrate (butanediol mononitrate [BDMN]; nitrooxy butyl alcohol [NOBA]).

The Applicant has shown that topical ocular administration of LBN results in rapid appearance of latanoprost acid (a prostaglandin receptor agonist). LBN has IOP-lowering activity in animals attributable to latanoprost acid. The Applicant proposes that LBN is metabolized by esterases to latanoprost acid and to free BDMN and that BDMN releases nitric oxide (NO), at sufficient local concentrations to relax the trabecular meshwork of the eye, further lowering IOP. However, no experimental work was submitted to determine whether LBN releases any NO in ocular tissues.

Latanoprostene bunod was shown to be abortifacient and teratogenic when administered to pregnant rabbits (IV) at exposures ≥ 0.28 times the clinical dose, in the absence of maternal toxicity. Doses ≥

20 µg/kg/day (23 times the clinical dose) produced 100% embryofetal lethality. Structural abnormalities observed in rabbit fetuses included anomalies of the great vessels and aortic arch vessels, domed head, sternebral and vertebral skeletal anomalies, limb hyperextension and malrotation, abdominal distension and edema. Latanoprostene bunod was not teratogenic in the rat at clinically relevant doses.

Latanoprostene bunod has not been evaluated in patients for effect on fertility. Animal studies to evaluate the effects of latanoprostene bunod on fertility and reproductive performance have not been conducted.

5. Clinical Pharmacology

The systemic exposure of latanoprostene bunod, its metabolites latanoprost acid and butanediol mononitrate were evaluated in one study with 22 healthy subjects (Study #809) after topical ocular administration of Vyzulta once daily (one drop bilaterally in the morning) for 28 days. There were no quantifiable plasma concentrations of latanoprostene bunod (lower limit of quantitation, LLOQ, of 10.0 pg/mL) or butanediol mononitrate (LLOQ of 200 pg/mL) post dose on Day 1 and Day 28. Latanoprost acid concentrations were quantifiable (LLOQ of 30.0 pg/mL) in the plasma samples of the majority of subjects, especially in the early time point (i.e., 5 min post dose) The mean maximal plasma concentrations (Cmax) of latanoprost acid were 59.1 pg/mL and 51.1 pg/mL on Day 1 and Day 28, respectively. The mean time of maximal plasma concentration (Tmax) for latanoprost acid was approximately 5 min post administration on both Day 1 and Day 28. The elimination of latanoprost acid from human plasma is rapid as latanoprost acid plasma concentration dropped below the LLOQ (30.0 pg/mL) in most of subjects by 15 min post the ocular administration of Vyzulta in humans.

Systemic NO exposure was indirectly assessed in a separate study (#874) using a surrogate – the potential change in percentage of systemic methemoglobin (% MetHb), after a single and 7-day once-daily repeated topical bilateral ocular administration of LBN 0.024% in healthy subjects. There were no significant changes from baseline in %MetHb for LBN treated subjects on Day 1 and Day 7, and there was also no change in %MetHb between the vehicle- and LBN-treated groups when directly compared, indicating that the NO systemic exposure is likely to be limited and/or minimal following repeated once daily dosing of LBN 0.024%.

6. Clinical Microbiology

Not applicable. This product is not an anti-infective.

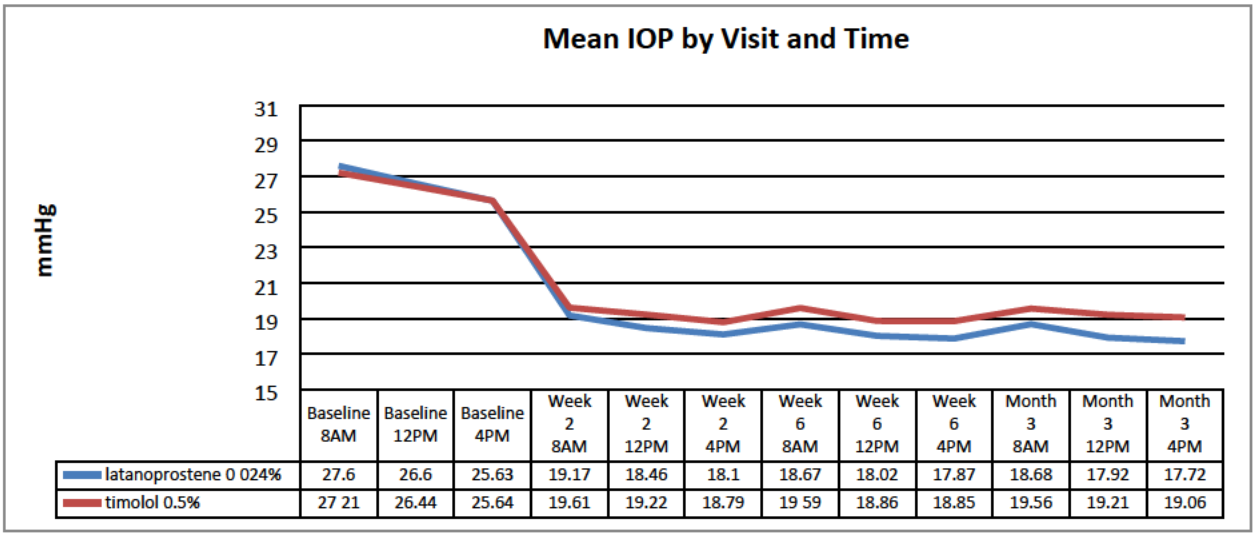
7. Clinical/Statistical-Efficacy

Study Identifier /Study Type	Study Design	Treatment and Dosing Regimen	1° Efficacy Endpoint	Treatment Duration	No. of Centers and Countries
770 Phase 3 Safety and Efficacy	Multicenter, double-masked, randomized, active-controlled, parallel-group efficacy phase (3 months) with an open-label safety extension phase (3 months)	Latanoprostene bunod 0.024% QD (PM) and vehicle QD (AM) 283 patients Timolol maleate 0.5% BID 137 patients	IOP at 8AM, 12PM and 4PM at Visit 4 (Week 2), Visit 5 (Week 6) and Visit 6 (Month 3)	6 months (latanoprostene 0.024% QD (PM) and vehicle QD (AM) for 3 months, then open-label latanoprostene 0.024% QD (PM) for 3 months) (timolol 0.5% BID for 3 months, , then open-label latanoprostene 0.024% QD (PM) for 3 months)	46 US (40), UK (3), Germany (2), Italy (1)
769 Phase 3 Safety and Efficacy	Multicenter, double-masked, randomized, active-controlled, parallel-group efficacy phase (3 months) with an open-label safety extension phase (9 months)	Latanoprostene bunod 0.024% QD (PM) and vehicle QD (AM) 286 patients Timolol maleate 0.5% BID 134 patients	IOP at 8AM, 12PM and 4PM at Visit 4 (Week 2), Visit 5 (Week 6) and Visit 6 (Month 3)	Up to 12 months (latanoprostene 0.024% QD (PM) and vehicle QD (AM) for 3 months, then open-label latanoprostene 0.024% QD (PM) for 9 months) (timolol 0.5% BID for 3 months, , then open-label latanoprostene 0.024% QD (PM) for 9 months)	45 US (40), Bulgaria (3), Czech Republic (2)
811 Phase 3 safety	Multicenter, open-label, single-arm	Latanoprostene bunod 0.024% QD (PM) 130 patients	NA	12 months	12 Japan

The safety and efficacy of the proposed drug product was supported by two adequate and well controlled studies in patients with elevated intraocular pressure. The control group in each study was timolol ophthalmic solution, 0.5% administered twice daily (BID). The safety and efficacy of timolol ophthalmic solution has been well established in prior studies reviewed by the Agency. Timolol ophthalmic solution can reliably be expected to lower intraocular pressure 4-7 mmHg in patients starting with a mean IOP of approximately 24 mmHg. The time period of peak efficacy for timolol ophthalmic solution is approximately 2 hours after administration.

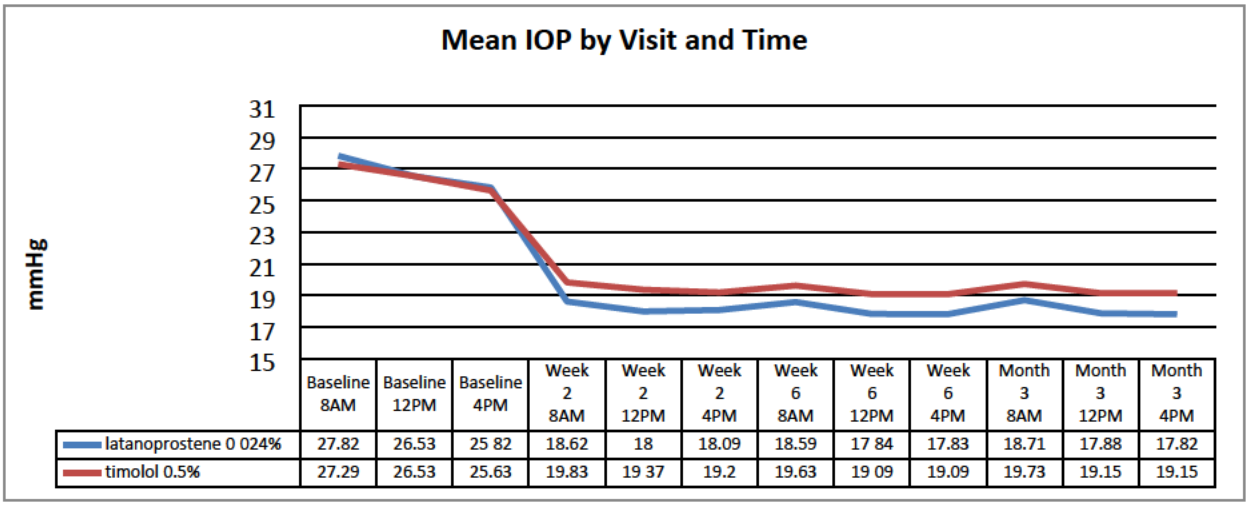
The patient population in these studies at baseline was approximately 25-27 mmHg. The Agency considers the non-inferiority margin for establishing efficacy to be a 95% confidence interval of 1.5 mmHg at all time points evaluated and expects the majority of time points to be within 1 mmHg. IOP reduction was not measured at the time when timolol would have been expected to have its maximal IOP lowering effect (i.e., 2 hours after administration).

Study #770 – ITT Population



	Baseline 8AM	Baseline 12PM	Baseline 4PM	Week 2 8AM	Week 2 12PM	Week 2 4PM	Week 6 8AM	Week 6 12PM	Week 6 4PM	Month 3 8AM	Month 3 12PM	Month 3 4PM
latanoprostene 0 024%	27.6	26.6	25.63	19.17	18.46	18.1	18.67	18.02	17.87	18.68	17.92	17.72
timolol 0.5%	27 21	26.44	25.64	19.61	19.22	18.79	19 59	18.86	18.85	19.56	19.21	19.06

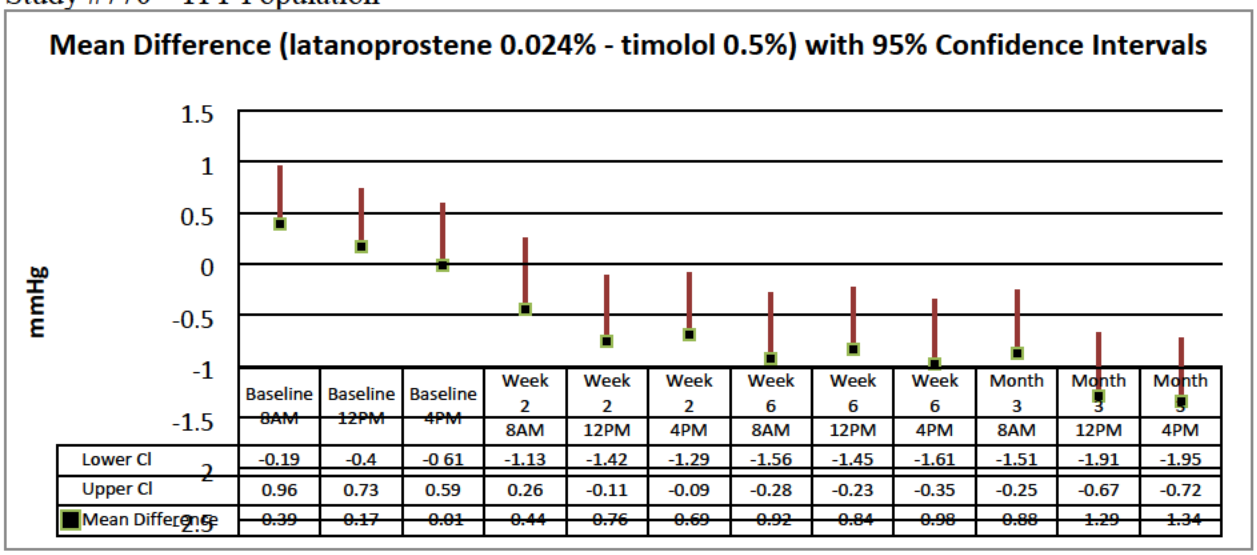
Study #769 – ITT Population



	Baseline 8AM	Baseline 12PM	Baseline 4PM	Week 2 8AM	Week 2 12PM	Week 2 4PM	Week 6 8AM	Week 6 12PM	Week 6 4PM	Month 3 8AM	Month 3 12PM	Month 3 4PM
latanoprostene 0 024%	27.82	26.53	25 82	18.62	18	18.09	18.59	17 84	17.83	18.71	17.88	17.82
timolol 0.5%	27.29	26.53	25.63	19.83	19 37	19.2	19.63	19 09	19.09	19.73	19.15	19.15

IOP lowering for latanoprostene was approximately 7-9 mmHg in each study at each time point. IOP lowering for timolol was approximately 6-8 mmHg in each study at each time point. Based on the time of expected maximal IOP lowering for other products in the prostaglandin analog class, peak effect of IOP reduction should have been demonstrated in this study for the latanorpostene group but not for the timolol group.

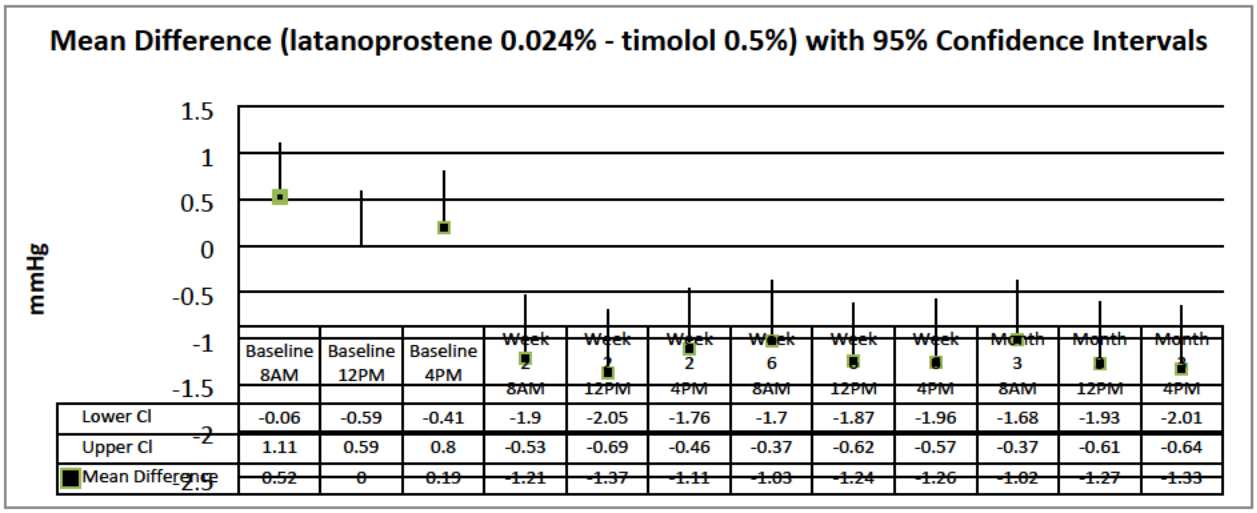
Study #770 – ITT Population



	Baseline 8AM	Baseline 12PM	Baseline 4PM	Week 2 8AM	Week 2 12PM	Week 2 4PM	Week 6 8AM	Week 6 12PM	Week 6 4PM	Month 3 8AM	Month 3 12PM	Month 3 4PM
Lower CI	-0.19	-0.4	-0 61	-1.13	-1.42	-1.29	-1.56	-1.45	-1.61	-1.51	-1.91	-1.95
Upper CI	0.96	0.73	0.59	0.26	-0.11	-0.09	-0.28	-0.23	-0.35	-0.25	-0.67	-0.72
Mean Difference	0.39	0.17	0.01	0.44	0.76	0.69	0.92	0.84	0.98	0.88	1.29	1.34

Appears this way on original

Study #769 – ITT Population



	Baseline 8AM	Baseline 12PM	Baseline 4PM	Week 2 8AM	Week 2 12PM	Week 2 4PM	Week 6 8AM	Week 6 12PM	Week 6 4PM	Month 3 8AM	Month 3 12PM	Month 3 4PM
Lower CI	-0.06	-0.59	-0.41	-1.9	-2.05	-1.76	-1.7	-1.87	-1.96	-1.68	-1.93	-2.01
Upper CI	1.11	0.59	0.8	-0.53	-0.69	-0.46	-0.37	-0.62	-0.57	-0.37	-0.61	-0.64
Mean Difference	0.52	0	0.19	-1.21	-1.37	-1.11	-1.03	-1.24	-1.26	-1.02	-1.27	-1.33

The group treated with latanoprostene demonstrated greater IOP reduction than the group treated with timolol, however, the time point when timolol would have been expected to demonstrate its largest clinical effect (i.e., 2 hours post-dosing, 10AM) was not evaluated. The amount of IOP reduction demonstrated these trials was consistent with the amount of IOP reduction generally seen in other prostaglandin analogs for ophthalmic use.

8. Safety

The safety database consists of two phase 1 studies (Studies 809, 849 and 874), four phase 2 studies (A9441001 and A9441003, Study 659, and Study 803), three phase 3 studies (Studies 769, 770, and 811). The total exposed safety population which includes all subjects exposed to at least one dose of latanoprostene ophthalmic solution 0.024% or higher, is 1,335 subjects (0.024% = 1165 and 0.040%=170). The total phase 2/3 pooled safety population is 1,289 subjects (0.024% = 1119 and 0.040%=170).

Deaths: There were two deaths in the safety database. Both patients had significant histories of cardiovascular disease prior to the initiation of the studies and both patients died of myocardial ischemia (one after exiting the study).

Serious Adverse Reactions: Approximately 30 serious adverse events were reported during the development program. There was no common pattern in the reported events and a review of these events by the Agency's clinical team considered it unlikely that these events were related to the use of latanoprostene bunod ophthalmic solution.

Common Adverse Reactions:

Treatment-Emergent Adverse Events Occurring in ≥ 2% of Subjects in Any Treatment Group (Phase2/3 Pooled)

Adverse Event	Latanoprostene Bunod 0.024% N=1119 n (%)	Latanoprost 0.005% N=185 n (%)	Timolol Maleate 0.005% N=294 n (%)
OCULAR			
Eye Disorders	**278 (25%)**	**28 (15%)**	**35 (12%)**
Conjunctival hyperemia	87 (8%)	5 (3%)	4 (1%)
Eye irritation	51 (5%)	4 (2%)	7 (2%)
Eye pain	33 (3%)	1 (0.5%)	6 (2%)
Ocular hyperemia	20 (2%)	9 (5%)	2 (1%)
Punctate keratitis	17 (2%)	3 (2%)	4 (1%)
General Disorders and Administration Site Conditions	**60 (5%)**	**5 (3%)**	**8 (3%)**
Instillation site pain	42 (4%)	5 (3%)	6 (2%)
NONOCULAR			
Infections and Infestations	**122 (11%)**	**5 (3%)**	**18 (6%)**
Nasopharyngitis	53 (5%)	2 (1%)	4 (1%)

The most common ocular adverse events were conjunctival/ocular hyperemia (10%) and eye irritation (5%). The most common non-ocular adverse event was nasopharyngitis (5%).

The safety profile of latanoprostene bunod ophthalmic solution 0.024% is similar to other marketed topical prostaglandin analogues.

9. Advisory Committee Meeting

The proposed product is a member of the prostaglandin analog class. The safety and efficacy of this product was consistent with other members of this class. There were no issues raised during the review of this application that were believed to benefit from discussion at an Advisory Committee meeting.

10. Pediatrics

Elevated intraocular pressure is a condition which is more common with advancing age. The applicant requested a waiver for conducting studies in the pediatric population for the proposed indication. This application was presented at the **Pediatric Review Committee (**PeRC) on December 2, 2015. PeRC agreed with the Division's assessment that a Full Waiver was appropriate because necessary studies would be impossible or highly impracticable because patients are geographically dispersed.

11. Other Relevant Regulatory Issues

The Office of Scientific Investigations conducted a review of two clinical sites. Based on the results of the clinical investigator inspections, the studies appear to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication.

The applicant has adequately disclosed financial arrangements with clinical investigators as recommended in the FDA guidance for industry on *Financial Disclosure by Clinical Investigators.*

The Division of Risk Management (DRISK) completed a Risk Evaluation and Mitigation Strategy (REMS) review on April 1, 2016. DRISK and the Division of Transplant and Ophthalmology Products agreed that the benefit-risk profile of this drug product is acceptable and, at this time, a REMS program is not necessary to ensure that the benefits of this proposed formulation outweigh its risks for the proposed treatment of reduction of intraocular pressure (IOP) in adult patients with open-angle glaucoma (OAG) or ocular hypertension (OHT).

The Division of Medication Error Prevention and Analysis (DMEPA) finalized a review of the proposed proprietary name, Vesneo, and found the name unacceptable. DMEPA finalized a review of the proposed proprietary name, Vyzulta, and granted conditional acceptance on January 15, 2016. Their proprietary name risk assessment did not find the name vulnerable to confusion that would lead to medication errors and did not consider the name promotional.

12. Labeling

The applicant has submitted proposed prescribing information. Based on a review of the application, the Review Team has recommended labeling consistent with the labeling of other prostaglandin analogs for ophthalmic use in lowering intraocular pressure. The recommended labeling is included in this review.

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

Valeant Pharmaceuticals North America LLC
Bridgewater, NJ 08807 USA

13. Postmarketing

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.

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/s/

WILEY A CHAMBERS
06/17/2016

Cross-Discipline Team Leader Review NDA 207795

Date	June 15, 2016
From	William M. Boyd, M.D.
Subject	Cross-Discipline Team Leader Review
NDA #	NDA 207795
Applicant	Bausch & Lomb Inc.
Date of Submission	July 21, 2015
PDUFA Goal Date	July 21, 2016
Proprietary Name / Non-Proprietary Name	Vyzulta (latanoprostene bunod ophthalmic solution) 0.024%
Dosage form(s) / Strength(s)	Topical ophthalmic solution
Applicant Proposed Indication	Reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension
Recommendation on Regulatory Action	Complete Response
Recommended Indication(s)/ Population(s) (if applicable)	Reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension

1. Benefit-Risk Assessment

NDA 207795 is not recommended for approval for the reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension until all manufacturing facilities are found to be incompliance with current Good Manufacturing Practices (cGMPs).

The 505(b)(1) application includes adequate and well controlled clinical trials which support the safety and effectiveness of latanoprostene bunod ophthalmic solution 0.024% for the treatment of elevated intraocular pressure (IOP) in patients with open angle glaucoma or ocular hypertension.

Established Name:	latanoprostene bunod ophthalmic solution 0.024%
Proposed Trade Name:	Vyzulta
Chemical Class:	new molecular entity
Pharmacological Class:	prostaglandin analogue, F2-α receptor agonist
Molecular formula:	$C_{27}H_{41}NO_8$
Chemical name:	4-(Nitrooxy) butyl (5Z)-7-{(1R,2R,3R,5S)-3,5-dihydroxy-2-[(3R)-3-hydroxy-5-phenylpentyl]cyclopentyl}hept-5-enoate
Dosing Regimen:	one drop in the affected eye(s) once daily in the evening
Age Groups:	patients 18 years or older

Benefit-Risk Summary and Assessment

Elevated intraocular pressure is a major risk factor for optic nerve damage, commonly described as glaucoma. This submission contains adequate and well controlled trials which support the safety and efficacy of latanoprostene bunod ophthalmic solution 0.024% dosed once daily in the evening for the treatment of elevated IOP in patients with open-angle glaucoma or ocular hypertension. Studies #769 and #770 demonstrate that the IOP lowering ability of latanoprostene bunod ophthalmic solution 0.024% is not inferior to the IOP lowering ability of timolol maleate ophthalmic solution 0.5% by a clinically significant amount.

The safety profile of latanoprostene bunod ophthalmic solution 0.024% is similar to other marketed topical prostaglandin analogues. The most common ocular adverse events are conjunctival/ocular hyperemia (10%) and eye irritation (5%).

Latanoprostene bunod ophthalmic solution 0.024%, if manufactured in a facility which complies with current good manufacturing practices, would be expected to have potential benefits which outweigh the potential risks for the treatment of elevated IOP in open-angle glaucoma or ocular hypertension. The risk for using this drug is consistent with the currently marketed prostaglandin analogs.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• 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 factor is elevated intraocular pressure (IOP).	Intraocular pressure is currently the accepted standard for establishing the efficacy of ocular hypotensive medications.
Current Treatment Options	• 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 analogues.	There are multiple beta-adrenergic antagonists (beta-blockers), alpha-adrenergic agonists, parasympathomimetic (miotic) agents, carbonic anhydrase inhibitors, and prostaglandin analogues approved in the U.S. to treat elevated IOP.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• Intraocular pressure (IOP) is currently the accepted standard for establishing the efficacy of ocular hypotensive medications. The primary efficacy endpoint was mean IOP measured at multiple time points for studies #770 and #769. Studies #770 and #769 demonstrated that latanoprostene bunod ophthalmic solution 0.024% was non-inferior to timolol maleate 0.5% at all time points measured. The safety database was adequate.	Studies #770 and #769 demonstrated that latanoprostene bunod ophthalmic solution 0.024% was non-inferior to the active-control, timolol maleate ophthalmic solution 0.5%.
Risk	• The risk for using this drug is consistent with currently U.S. marketed prostaglandin analogues.	The safety database contained in this application established the safety of latanoprostene bunod ophthalmic solution 0.024% dosed once daily in the evening.
Risk Management	• No risk management activities are recommended beyond the routine monitoring and reporting of all adverse events. There are no recommended Postmarketing Requirements or Phase 4 Commitments.	Routine monitoring and reporting of all adverse events are adequate.

2. Background

Glaucoma is a progressive disease that is characterized by irreversible damage to the optic nerve and corresponding loss of visual field. It affects one person in 200 over the age of 40 and is a leading cause of irreversible blindness in the United States. 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. Prostaglandin analogues are believed to reduce IOP largely due to increased uveoscleral outflow of aqueous humor. The exact mechanism of action is unknown at this time.

Latanoprostene bunod is a new chemical entity. It is not currently marketed in the United States. The drug has no foreign regulatory and marketing history.

Pfizer Inc. submitted an IND application for latanoprostene bunod ophthalmic solution (IND 73,435) on February 20, 2007. (b) (4) (b) (4). On November 2, 2009, ownership of the IND was transferred to Nicox S.A. No clinical studies were conducted during Nicox's ownership. Nicox transferred the ownership to Bausch & Lomb (B&L) on April 9, 2010. An End-of-Phase 2 meeting was held on September 26, 2012. The pre-NDA meeting was held on February 9, 2015.

3. Product Quality

DESCRIPTION AND COMPOSITION

Latanoprostene Bunod Ophthalmic Solution, 0.024% drug product is a clear, colorless to slightly yellow, sterile, preserved ophthalmic solution formulated for topical delivery to the eye.

Component	Concentration (mg/mL)	Function
Latanoprostene bunod	0.24	Active
Benzalkonium chloride	0.20	(b) (4) l preservative
Polysorbate 80	(b) (4)	(b) (4)
Edetate disodium (b) (4)		
Sodium citrate (b) (4)		Buffer
Citric acid, (b) (4)		Buffer
Glycerin		(b) (4)
Water (b) (4)		

Source: Module 3.2.P.1

DRUG SUBSTANCE

Table 3.2.S.4.1–1 Specifications for latanoprostene bunod at release and retest

Test	Procedure	Acceptance Criteria
Appearance[a]	Visual	Colorless to pale yellow viscous oil
Identification A	Current USP, IR absorption	(b) (4)
Identification B	UPLC, C-1928	
Water Content by Karl Fischer	Current USP	NMT (b) (4)%
Residue on Ignition	Current USP	NMT (b) (4)%
Heavy Metals	Current USP	NMT (b) (4)
Assay "as is"[a]	UPLC, C-1928	(b) (4)%
Related Substances[a]	UPLC, C-1928	(b) (4) NMT (b) (4)% NMT % NMT % Any other single unspecified impurity: NMT % Total unspecified impurities: NMT %
Isomeric Impurities[a]	HPLC, C-1929	(b) (4) NMT (b) (4)% NMT
Total Impurities[a]	UPLC, C-1928 and HPLC C-1929	Sum of individual related substances and isomeric impurities: NMT
Residual Solvents	GC, C-1952	(b) (4)
Specific Rotation	Current USP (b) (4)	(b) (4)

a These tests are also performed at retest to ensure suitability for use in manufacture of drug product.
NMT = not more than

Source: Module 3.2.S.4.1 Specification

DRUG PRODUCT

Test	Procedure	Shelf Life Criteria
Appearance	Visual	Clear and colorless to slightly yellow solution
Identification-A[a]	UPLC	Retention time matches reference
Identification-B[a]	UV	UV spectrum matches reference
Latanoprostene assay	(b) (4) UPLC[b]	(b) (4) % label claim
Related substances	UPLC	
(b) (4)		NMT (b) (4) %
Individual Related Substances		NMT %
Total Related Substances		NMT %
Benzalkonium chloride	UPLC	(b) (4) % of label claim
pH	USP	(b) (4)
Osmolality	USP	(b) (4) mOsm/kg
Particulate matter	USP	NMT (b) (4)
		NMT
		NMT
Antimicrobial effectiveness	USP	Meets USP requirement
Sterility	USP	Meets USP requirement
Weight loss/gain	Manual	NMT (b) (4) %
Fill volume[a,e]	Weight check	NLT label claim

[a] Required at time of release only

[c] (b) (4)

[d] (b) (4)

[e] (b) (4)

NMT= Not more than
NLT= Not less than
USP= United States Pharmacopeia

Source: Module 3.2.P.5.1 Specification

CONTAINER/CLOSURE

The packaging components summarized in the table below are used for the commercial product.

Table 3.2.P.7.1–1 Summary of primary packaging components

Components		Description	DMF Number
		5 mL Fill	
Bottle	Bottle Vendor	(b) (4)	(b) (4)
	Size	7.5 mL	
	Description	Natural, Boston Round, LDPE, (b) (4) (b) (4)	
	Cross-Reference to Drawing	Figure 3.2.P.7.1-1	
Tip	Tip Vendor	(b) (4)	
	Size		
	Description	(b) (4) Dropper Tip (b) (4) (b) (4) (b) (4)	
	Cross-Reference to Drawing	Figure 3.2.P.7.1-2	
Cap	Cap Vendor	(b) (4)	
	Size		
	Description	(b) (4)	
	Cross-Reference to Drawing	Figure 3.2.P.7.1-3	

LDPE = low density polyethylene

(b) (4)

Source: Module 3.2.P.7

From the original Quality Assessment addendum dated 4/14/16:

INSPECTIONS

Drug Substance Manufacturers

Facility Name	FEI	Profile Code	Responsibilities	Facility Sub-Score	Process Sub-Score	Product Sub-Score	Overall Initial Facility Risk Assessment	Recommendation
(b) (4)		CSN	drug substance manufacturer	low	low	med	**med**	**no PAI needed**

Drug Product Manufacturers

Facility Name	FEI	Profile Code	Responsibilities	Facility Sub-Score	Process Sub-Score	Product Sub-Score	Overall Initial Facility Risk Assessment	Recommendation
BAUSCH & LOMB INC	1000113778	SLQ	finished product manufacturer	high	high	high	**high**	**PAI needed; KTM will be written to address product specific concerns**
(b) (4)		CTL	ALT testing facility for compendial testing	med	low	low	**med**	**no PAI needed**
BAUSCH & LOMB INC	1313525	CTL	stability tester for clinical and submission batches; alt facility for analytical/micro release testing and stability testing	low	low	low	**low**	**no PAI needed**

The outcome of the most recent inspection of the Bausch & Lomb Inc. drug product manufacturing facility has resulted in Office of Process and Facilities recommending withhold.

QUALITY ASSESSEMENT SUMMARY RECOMMENDATIONS
From the original Quality Assessment addendum dated 4/14/16:

"Drug substance, process and biopharmaceutics reviewers have recommended approval of the NDA as documented in Review #1. As documented in this Addendum, all microbiological issues have been satisfactorily resolved. However, the drug product in-use stability data does not support the label storage statement (b) (4). Specifically, investigation to determine the root cause for the observed out-of-specification for (b) (4) during in-use stability studies has not been adequately addressed. Furthermore, there appears to be some discrepancy in explaining the OOS issue in the amendment submitted to the NDA as compared to what was observed during the recent inspection (as documented in the FDA 483 issued). Therefore, the NDA is deficient from the drug product perspective."

The outcome of the most recent inspection of the drug product manufacturing facility has resulted in Office of Process and Facilities recommending withhold. Therefore, NDA 207-795 is recommended for Complete Response from Product Quality perspective.

4. Nonclinical Pharmacology/Toxicology

From the original Pharmacology/Toxicology review dated 5/20/16:

Prostaglandin F2α analogues are a class of drugs which includes latanoprost, travoprost, bimatoprost, tafluprost (the ophthalmic prostaglandins), and carboprost (intramuscular administration for specific non-ophthalmic indications.

Latanoprostene bunod (LBN, PF-0318707, BOL-303259-X) is a pro-drug consisting of latanoprost acid covalently bound by an ester linkage to 4- hydroxybutyl nitrate (butanediol mononitrate [BDMN]; nitrooxy butyl alcohol [NOBA]).

The Applicant has shown that topical ocular administration of LBN results in rapid appearance of latanoprost acid (a prostaglandin receptor agonist). LBN has IOP-lowering activity in animals attributable to latanoprost acid. The Applicant proposes that LBN is metabolized by esterases to latanoprost acid and to free BDMN and that BDMN releases nitric oxide (NO), at sufficient local concentrations to relax the trabecular meshwork of the eye, further lowering IOP. However, no experimental work was submitted to determine whether LBN releases any NO in ocular tissues.

Latanoprostene bunod was shown to be abortifacient and teratogenic when administered to pregnant rabbits (IV) at exposures ≥ 0.28 times the clinical dose, in the absence of maternal toxicity. Doses ≥ 20 μg/kg/day (23 times the clinical dose) produced 100% embryofetal lethality. Structural abnormalities observed in rabbit fetuses included anomalies of the great vessels and aortic arch vessels, domed head, sternebral and vertebral skeletal anomalies, limb hyperextension and malrotation, abdominal distension and edema. Latanoprostene bunod was not teratogenic in the rat at clinically relevant doses.

Latanoprostene bunod has not been evaluated in patients for effect on fertility. Animal studies to evaluate the effects of latanoprostene bunod on fertility and reproductive performance have not been conducted.

5. Clinical Pharmacology

From the original Clinical Pharmacology review dated 4/7/16:

The Clinical Pharmacology information provided by the Applicant in the NDA submission is acceptable, and the Clinical Pharmacology review team recommends approval of Vyzulta.

The systemic exposure of latanoprostene bunod, its metabolites latanoprost acid and butanediol mononitrate were evaluated in one study with 22 healthy subjects (Study #809) after topical ocular administration of Vyzulta once daily (one drop bilaterally in the morning) for 28 days. There were no quantifiable plasma concentrations of latanoprostene bunod (lower limit of

quantitation, LLOQ, of 10.0 pg/mL) or butanediol mononitrate (LLOQ of 200 pg/mL) post dose on Day 1 and Day 28. Latanoprost acid concentrations were quantifiable (LLOQ of 30.0 pg/mL) in the plasma samples of the majority of subjects, especially in the early time point (i.e., 5 min post dose) The mean maximal plasma concentrations (Cmax) of latanoprost acid were 59.1 pg/mL and 51.1 pg/mL on Day 1 and Day 28, respectively. The mean time of maximal plasma concentration (Tmax) for latanoprost acid was approximately 5 min post administration on both Day 1 and Day 28. The elimination of latanoprost acid from human plasma is rapid as latanoprost acid plasma concentration dropped below the LLOQ (30.0 pg/mL) in most of subjects by 15 min post the ocular administration of Vyzulta in humans.

Systemic NO exposure was indirectly assessed in a separate study (#874) using a surrogate – the potential change in percentage of systemic methemoglobin (% MetHb), after a single and 7-day once-daily repeated topical bilateral ocular administration of LBN 0.024% in healthy subjects. There were no significant changes from baseline in %MetHb for LBN treated subjects on Day 1 and Day 7, and there was also no change in %MetHb between the vehicle- and LBN-treated groups when directly compared, indicating that the NO systemic exposure is likely to be limited and/or minimal following repeated once daily dosing of LBN 0.024%.

6. Clinical Microbiology

Not applicable. This product is not an anti-infective.

7. Clinical/Statistical- Efficacy

The submitted clinical study reports and protocols identified in Table5.1-1 were reviewed and formed the primary basis of safety and efficacy for this application.

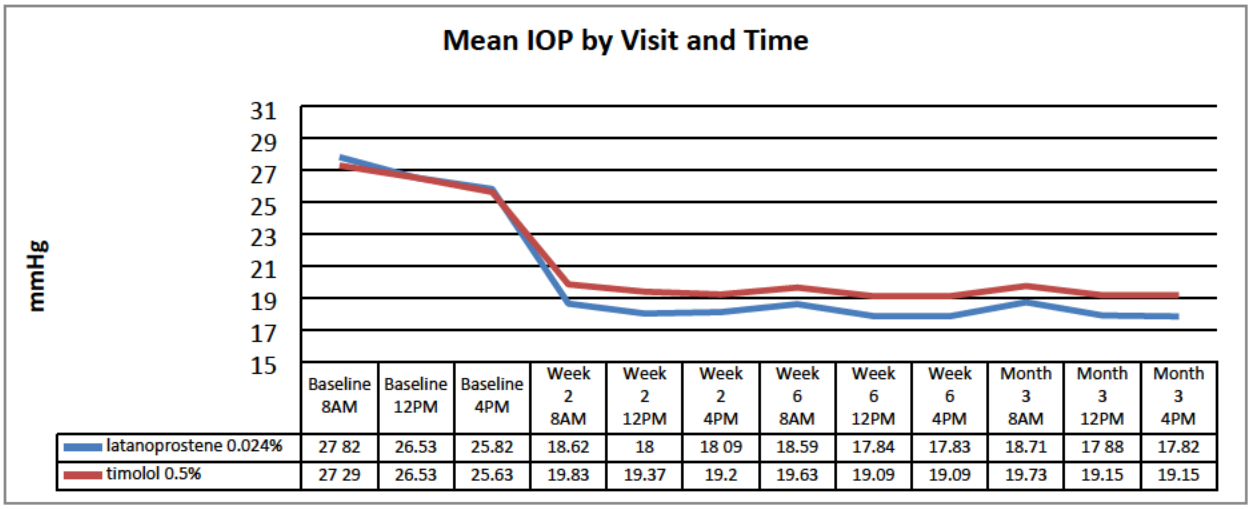
Table 5.1.-1
List of Clinical Studies

Study Identifier/Study Type	Study Design	Treatment and Dosing Regimen	1° Efficacy Endpoint	Treatment Duration	No. of Patients Enrolled	Study Population	No. of Centers and Countries
A9441001 Phase 2 Dose-finding	Adaptive, multicenter, double-masked, randomized, active-controlled, parallel-group	Stage 1: Latanoprostene bunod (0.003%, 0.006%, 0.012%, 0.024%) QD (AM) and vehicle QD (PM) Latanoprost 0.005% QD (PM) Stage 2: Latanoprostene bunod (0.024%, 0.040%) QD (AM) and vehicle QD (PM), 0.040% QD (PM) and vehicle QD (AM) Latanoprost 0.005% QD (AM) and vehicle QD (PM), 0.05% QD (PM) and vehicle QD (AM)	Reduction in mean diurnal IOP from baseline at Day 28	Latanoprostene bunod QD (AM) and (PM) for 28 days Latanoprost 0.005% QD (AM) and (PM) for 28 days	Stage 1: Latanoprostene 0.003%: 13 0.006%: 13 0.012%: 13 0.024%: 13 Latanoprost 0.005%: 14 Stage 2: Latanoprostene 0.024%: 30 0.040%: 60 Latanoprost 0.005%: 59	Patients 18 years or more with open-angle glaucoma or ocular hypertension	17 US
A9441003 Phase 2 Dose-finding	Multicenter, double-masked, randomized, active-controlled, parallel-group	Latanoprostene bunod (0.006%, 0.024%, 0.040%) QD (PM) and vehicle QD (PM) Latanoprost 0.005% QD (PM) and vehicle QD (PM) for 28 days	Reduction in mean in diurnal IOP from baseline at Day 28	Latanoprostene bunod QD (PM) and vehicle QD (PM) for 28 days Latanoprost 0.005% QD (PM) and vehicle QD (PM) for 28 days	Latanoprostene 0.006%: 29 0.024%: 29 0.040%: 29 Latanoprost 0.005%: 30	Patients 18 years or more with open-angle glaucoma or ocular hypertension	14 Japan
659 Phase 2 Dose-finding	Multicenter, investigator-masked, randomized, active-controlled, parallel-group	Latanoprostene bunod (0.006%, 0.012%, 0.024%, 0.040%) QD (PM) Latanoprost 0.005% QD (PM)	Reduction in mean diurnal IOP from baseline at Visit 6 (Day 28)	28 days	419 Latanoprostene 0.006%: 82 0.012%: 85 0.024%: 83 0.040%: 81 Latanoprost 0.005%: 82	Patients 18 years or more with open-angle glaucoma or ocular hypertension	23 US (15), Bulgaria (3), Poland (3), Czech Republic (2)
803 Phase 2 PD/PK	Single-center, open-label, randomized, crossover, active-controlled	Latanoprostene bunod 0.024% QD (PM) and vehicle QD (AM) Timolol maleate 0.5% BID	IOP measured Q2hr for 24hr period after 4 weeks of treatment	8 weeks (4 weeks with latanoprostene 0.024% QD (PM) and 4 weeks with timolol 0.5% BID)	46 Latanoprostene 0.024%: 23 Timolol 0.5%: 23	Patients 18 years or more with open-angle glaucoma or ocular hypertension	1 US
770 Phase 3 Safety and Efficacy	Multicenter, double-masked, randomized, active-controlled, parallel-group efficacy phase (3 months) with an open-label safety extension phase (3 months)	Latanoprostene bunod 0.024% QD (PM) and vehicle QD (AM) Timolol maleate 0.5% BID	IOP at 8AM, 12PM and 4PM at Visit 4 (Week 2), Visit 5 (Week 6) and Visit 6 (Month 3)	6 months (latanoprostene 0.024% QD (PM) and vehicle QD (AM) for 3 months, then open-label latanoprostene 0.024% QD (PM) for 3 months) (timolol 0.5% BID for 3 months, , then open-label latanoprostene 0.024% QD (PM) for 3 months)	420 Latanoprostene 0.024%: 283 Timolol 0.5%: 137	Patients 18 years or more with open-angle glaucoma or ocular hypertension	46 US (40), UK (3), Germany (2), Italy (1)
769 Phase 3 Safety and Efficacy	Multicenter, double-masked, randomized, active-controlled, parallel-group efficacy phase (3 months) with an open-label safety extension phase (9 months)	Latanoprostene bunod 0.024% QD (PM) and vehicle QD (AM) Timolol maleate 0.5% BID	IOP at 8AM, 12PM and 4PM at Visit 4 (Week 2), Visit 5 (Week 6) and Visit 6 (Month 3)	Up to 12 months (latanoprostene 0.024% QD (PM) and vehicle QD (AM) for 3 months, then open-label latanoprostene 0.024% QD (PM) for 9 months) (timolol 0.5% BID for 3 months, , then open-label	420 Latanoprostene 0.024%: 286 Timolol 0.5%: 134	Patients 18 years or more with open-angle glaucoma or ocular hypertension	45 US (40), Bulgaria (3), Czech Republic (2)

Study Identifier/Study Type	Study Design	Treatment and Dosing Regimen	1° Efficacy Endpoint	Treatment Duration	No. of Patients Enrolled	Study Population	No. of Centers and Countries
				latanoprostene 0.024% QD (PM) for 9 months)			
811 Phase 3 safety	Multicenter, open-label, single-arm	Latanoprostene bunod 0.024% QD (PM)	NA	12 months	130	Patients 18 years or more with open-angle glaucoma or ocular hypertension	12 Japan
849 Phase 1 PK	Single-center, open-label, single-arm	Latanoprostene bunod 0.024% QD (PM)	Change from baseline IOP measured at 12AM, 2AM, 4AM, 8AM, 10AM, 12PM, and 4PM for 24hr period after 14 days of treatment	14 days	24	Healthy male volunteers	1 Japan
809 Phase 1 PK	Single-center, open-label, single-arm	Latanoprostene bunod 0.024% QD (AM)	NA	28 days	20	Healthy volunteers	1 US

Efficacy Results – Primary Endpoint Study 769

Figure 6.2.2.-1 **Study #769 - ITT Population**

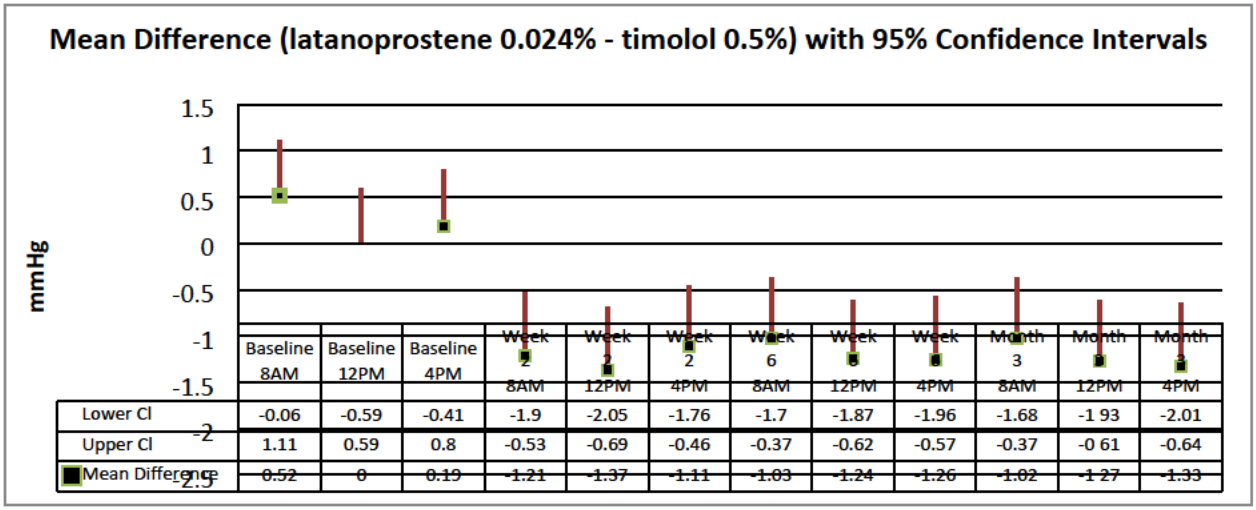


	Baseline 8AM	Baseline 12PM	Baseline 4PM	Week 2 8AM	Week 2 12PM	Week 2 4PM	Week 6 8AM	Week 6 12PM	Week 6 4PM	Month 3 8AM	Month 3 12PM	Month 3 4PM
latanoprostene 0.024%	27 82	26.53	25.82	18.62	18	18 09	18.59	17.84	17.83	18.71	17 88	17.82
timolol 0.5%	27 29	26.53	25.63	19.83	19.37	19.2	19.63	19.09	19.09	19.73	19.15	19.15

Source: Table 14.2.1.1.a

Baseline mean IOP of the two treatment groups are similar. The mean IOP for latanoprostene 0.024% and timolol 0.5% are similar at all time points measured.

Figure 6.2.2.-2 **Study #769 - ITT Population**



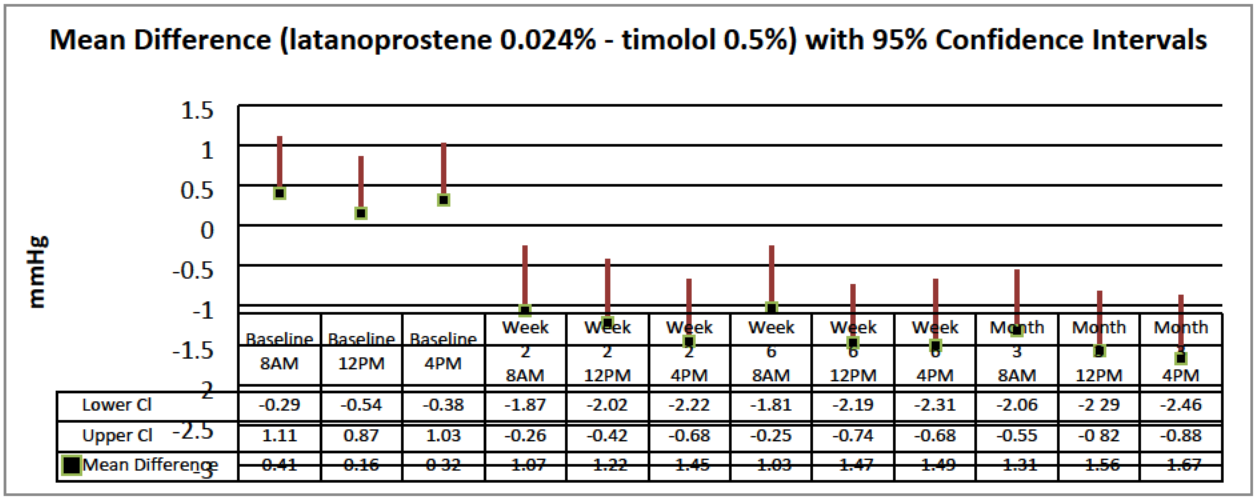
	Baseline 8AM	Baseline 12PM	Baseline 4PM	Week 2 8AM	Week 2 12PM	Week 2 4PM	Week 6 8AM	Week 6 12PM	Week 6 4PM	Month 3 8AM	Month 3 12PM	Month 3 4PM
Lower CI	-0.06	-0.59	-0.41	-1.9	-2.05	-1.76	-1.7	-1.87	-1.96	-1.68	-1 93	-2.01
Upper CI	1.11	0.59	0.8	-0.53	-0.69	-0.46	-0.37	-0.62	-0.57	-0.37	-0 61	-0.64
Mean Difference	0.52	0	0.19	-1.21	-1.37	-1.11	-1.03	-1.24	-1.26	-1.02	-1 27	-1.33

Source: Table 14.2.1.1.a

Appears this way on original

The mean IOP of the two treatment groups are comparable. The mean IOP values (latanoprostene 0.024% QD minus timolol 0.5% BID) and the upper confidence intervals are within 1 mmHg at a majority of the time points. The study demonstrates effective IOP lowering with the use of latanoprostene bunod but does not provide an unbiased comparison to timolol because the peak time point for IOP lowering with timolol maleate was not included.

Figure 6.2.2.-3 **Study #769 – PP Population**



	Baseline 8AM	Baseline 12PM	Baseline 4PM	Week 2 8AM	Week 2 12PM	Week 2 4PM	Week 6 8AM	Week 6 12PM	Week 6 4PM	Month 3 8AM	Month 3 12PM	Month 3 4PM
Lower CI	-0.29	-0.54	-0.38	-1.87	-2.02	-2.22	-1.81	-2.19	-2.31	-2.06	-2 29	-2.46
Upper CI	1.11	0.87	1.03	-0.26	-0.42	-0.68	-0.25	-0.74	-0.68	-0.55	-0 82	-0.88
Mean Difference	0.41	0.16	0 32	1.07	1.22	1.45	1.03	1.47	1.49	1.31	1.56	1.67

Source: Table 14.2.1.1.a

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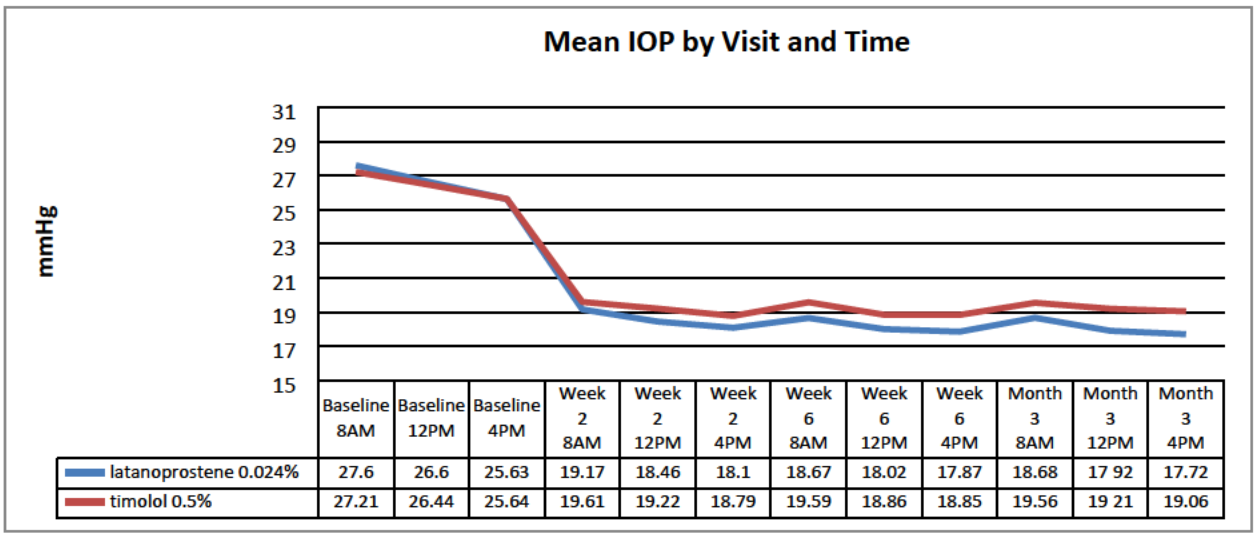
The analysis of the PP population is similar to that of the ITT population.

Efficacy Results – Primary Endpoint Study 770

Figure 6.1.2-1 **Study #770 - ITT Population**

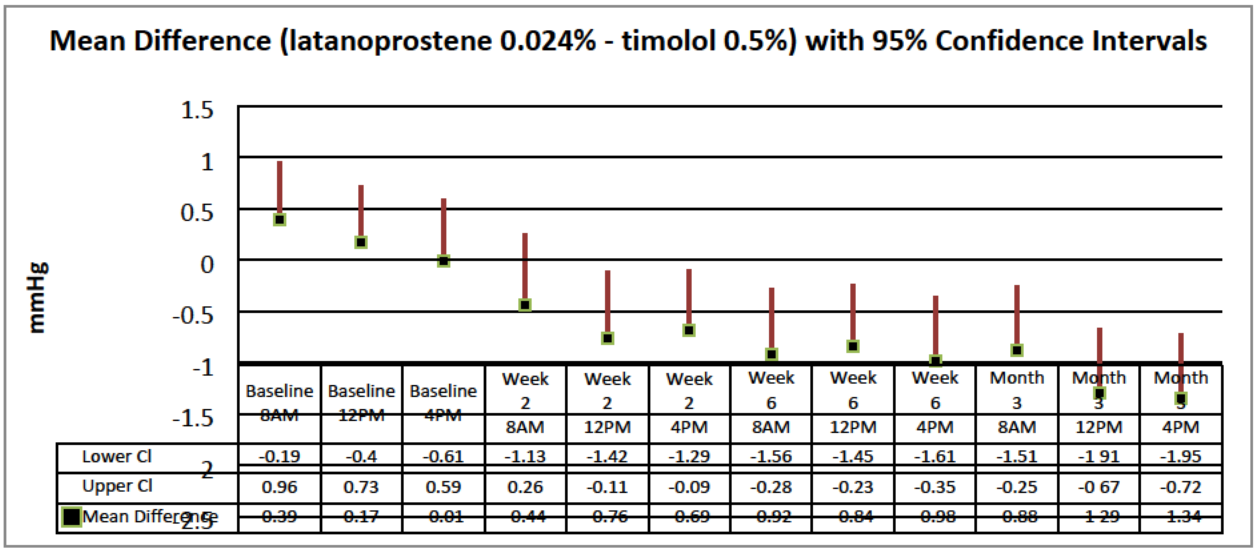


	Baseline 8AM	Baseline 12PM	Baseline 4PM	Week 2 8AM	Week 2 12PM	Week 2 4PM	Week 6 8AM	Week 6 12PM	Week 6 4PM	Month 3 8AM	Month 3 12PM	Month 3 4PM
latanoprostene 0.024%	27.6	26.6	25.63	19.17	18.46	18.1	18.67	18.02	17.87	18.68	17 92	17.72
timolol 0.5%	27.21	26.44	25.64	19.61	19.22	18.79	19.59	18.86	18.85	19.56	19 21	19.06

Source: Table 14.2.1.1.b

Baseline mean IOP of the two treatment groups are similar. The mean IOP for latanoprostene 0.024% and timolol 0.5% are similar at all time points measured.

Figure 6.1.2.-2 **Study #770 – ITT Population**



	Baseline 8AM	Baseline 12PM	Baseline 4PM	Week 2 8AM	Week 2 12PM	Week 2 4PM	Week 6 8AM	Week 6 12PM	Week 6 4PM	Month 3 8AM	Month 3 12PM	Month 3 4PM
Lower CI	-0.19	-0.4	-0.61	-1.13	-1.42	-1.29	-1.56	-1.45	-1.61	-1.51	-1 91	-1.95
Upper CI	0.96	0.73	0.59	0.26	-0.11	-0.09	-0.28	-0.23	-0.35	-0.25	-0 67	-0.72
Mean Difference	0.39	0.17	0.01	0.44	0.76	0.69	0.92	0.84	0.98	0.88	1 29	1.34

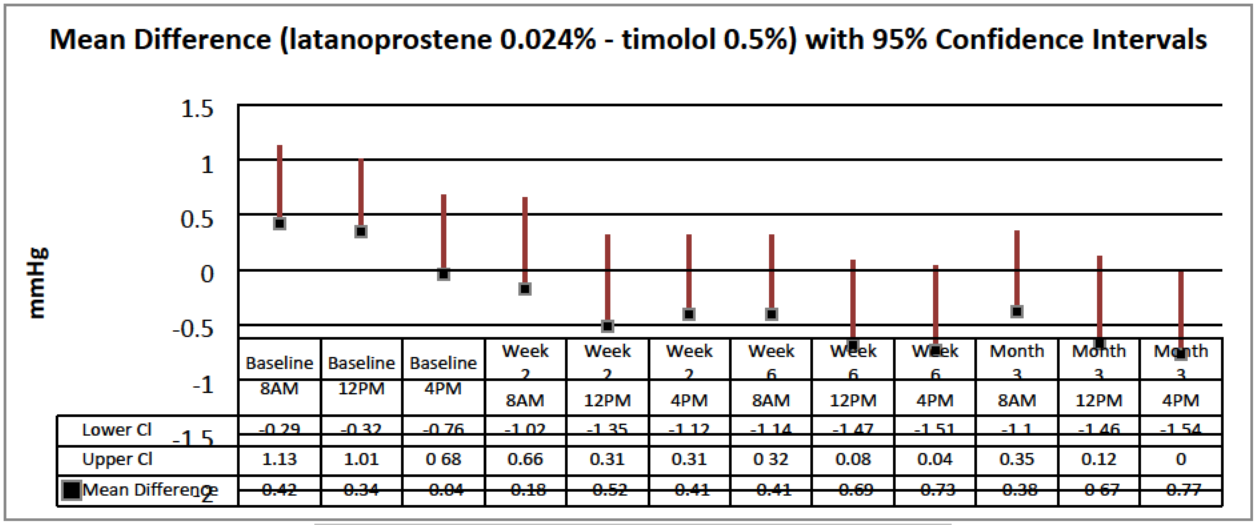
Source: Table 14.2.2.1.b

Appears this way on original

The mean IOP of the two treatment groups are comparable. The 95% confidence interval crosses zero at all time points measured at baseline. The mean IOP values (latanoprostene 0.024% QD minus timolol 0.5% BID) and upper end of the confidence intervals are within 1 mmHg at all of

the time points and within 1.5 mmHg at all time points. The study demonstrates effective IOP lowering with the use of latanoprostene bunod but does not provide a unbiased comparison to timolol because the peak time point for IOP lowering with timolol maleate was not included.

Figure 6.1.2.-3 **Study #770 – PP Population**



	Baseline 8AM	Baseline 12PM	Baseline 4PM	Week 2 8AM	Week 2 12PM	Week 2 4PM	Week 6 8AM	Week 6 12PM	Week 6 4PM	Month 3 8AM	Month 3 12PM	Month 3 4PM
Lower CI	-0.29	-0.32	-0.76	-1.02	-1.35	-1.12	-1.14	-1.47	-1.51	-1.1	-1.46	-1.54
Upper CI	1.13	1.01	0.68	0.66	0.31	0.31	0.32	0.08	0.04	0.35	0.12	0
Mean Difference	0.42	0.34	0.04	0.18	0.52	0.41	0.41	0.69	0.73	0.38	0.67	0.77

Source: Table 14.2.2.2.b

Appears this way on original

The analysis of the PP population is similar to that of the ITT population.

Efficacy Summary Statement

The data contained in this submission establishes the efficacy of latanoprostene bunod ophthalmic solution 0.024% dosed once daily in the evening for the treatment of elevated IOP in patients with open-angle glaucoma or ocular hypertension.

Studies #769 and #770 demonstrated that the IOP lowering ability of latanoprostene bunod ophthalmic solution 0.024% is not inferior to timolol maleate ophthalmic solution 0.5% at the time points evaluated. The study demonstrates effective IOP lowering with the use of latanoprostene bunod, but does not provide a comparison to timolol at the time point when timolol would be expected to have its peak efficacy (i.e., 2 hours post dosing). The IOP-lowering effect of Vyzulta (latanoprostene bunod ophthalmic solution), 0.024% given once daily (in the evening) was up to 7 to 9 mmHg. The efficacy of this drug is consistent with the currently marketed prostaglandin analogues.

The amount of reduction in IOP was consistent across all relevant subpopulations including age, sex, race/ethnicity, and geographic region.

8. Safety

The safety database consists of two phase 1 studies (Studies 809 and 849), four phase 2 studies (A9441001 and A9441003 [studies conducted by Pfizer], Study 659, and Study 803), three phase 3 studies (Studies 769, 770, and 811), and one ongoing phase 1 study (Study 874). The total exposed safety population which includes all subjects exposed to at least one dose of latanoprostene ophthalmic solution 0.024% or higher, is 1,335 subjects (0.024% = 1165 and 0.040%=170). The total phase 2/3 pooled safety population is 1,289 subjects (0.024% = 1119 and 0.040%=170).

Overall Exposure

Table 8.2.1-1
Safety Population (All Exposed Subjects[a])

Study	Latanoprostene Bunod			Latanoprost	Timolol Maleate
	0.024%	0.040%	ALL	0.005%	0.5%
849	24		24		
809	22		22		
A9441001 Stage 1 Stage 2	43	60	103	73	
A9441003	29	29	58	30	
659	83	81	164	82	
803	23		23		23
769	406		406		135
770	406		406		136
811	130		130		
Total Subjects	**1165**	**170**	**1336**	**185**	**294**

[a] All subjects who received at least 1 dose of latanoprostene ophthalmic solution 0.024% or higher.

Table 8.2.1.-2
Summary of Duration of Exposure (All Exposed Subjects[a])

Study				Latanoprost	Timolol Maleate
	Phase 1 0.024% (N=46)	0.024% (N=1119)	0.040% (N=170)	0.005% (N=185)	0.5% (N=294)
Duration of exposure (days)					
N	46	1119	170	185	294
Mean (SD)	19.9 (8.42)	213.2 (131.03)	28.3 (2.55)	27.9 (3.74)	85.6 (23.27)
Median	14.0	189.0	28.0	28.0	92.0
Min, Max	1, 29	1, 385	2, 36	1, 36	3, 117
Subject-year of exposure	2.5	653.7	13.2	14.0	68.9
Duration category (days) (n, %)					
1 to ≤ 28	27 (58.7)	146 (13.0)	103 (60.6)	115 (62.2)	18 (6.1)
29 to ≤ 66	19 (41.3)	73 (6.5)	67 (39.4)	70 (37.8)	21 (7.1)
67 to ≤ 135	0	148 (13.2)	0	0	255 (86.7)
136 to ≤ 225	0	263 (23.5)	0	0	0
226 to ≤ 318	0	119 (10.6)	0	0	0
≥ 319	0	370 (33.1)	0	0	0

[a] All subjects who received at least 1 dose of latanoprostene ophthalmic solution 0.024% or higher.

Deaths

One death was reported during study #770 (subject 7701307181748). One subject who was treated with latanoprostene in study #769 died of myocardial ischemia after exiting from the study (subject 7691307851321).

Table 8.4.1.-1
Deaths in the Safety Population

Study #	Patient #	Age (yrs)	Treatment	Time on treatment	Cause of death/Event
770	7701307181748	68	latanoprostene	4 months	Myocardial ischemia

Serious Adverse Events – Ocular and Nonocular

Table 8.4.2.-1
Ocular Serious Adverse Events
(Phase 2/3 Pooled)

Adverse Event	Latanoprostene Bunod 0.024% (N=1073) n (%)	Latanoprost 0.005% (N=162) n (%)	Timolol Maleate 0.5% (N=292) n (%)
OCULAR			
General disorders and administration site conditions	**1 (0.1)**	**0**	**0**
Device dislocation	1 (0.1)	0	0

Source: ISS Table 10-25

Table 8.4.2.-2
Non-Ocular Serious Adverse Events
(Phase 2/3 Pooled)

Adverse Event	Latanoprostene Bunod 0.024% (N=1119) n (%)	Latanoprost 0.005% (N=185) n (%)	Timolol Maleate 0.5% (N=294) n (%)
NONOCULAR			
Cardiac Disorders	**1 (0.1)**	**1 (0.5)**	**0**
Acute myocardial infarction	0	1 (0.5)	0
Coronary artery disease	1 (0.1)	0	0
Gastrointestinal Disorders	**0**	**1 (0.5)**	**0**
Gastric ulcer	0	0	0
Gastric ulcer hemorrhage	0	1(0.5)	0
Gastrointestinal hemorrhage	0	0	0
General Disorders and Administration Site Conditions	**2 (0.2)**	**0**	**0**
Chest pain	2 (0.2)	0	0
Hepatobiliary Disorders	**1 (0.1)**	**0**	**0**
Cholelithiasis	1 (0.1)	0	0
Immune System Disorder	**1 (0.1)**	**0**	**0**
Food allergy	1 (0.1)	0	0
Infections and Infestations	**2 (0.2)**	**0**	**0**
Pneumonia	1 (0.1)	0	0
Vestibular neuronitis	1 (0.1)	0	0
Injury, Poisoning and Procedural Complications	**14 (1.3)**	**0**	**1 (0.3)**
Ankle fracture	1 (0.1)	0	0
Arthropod bite	0	0	1 (0.3)
Fall	3 (0.3)	0	0
Femoral neck fracture	1 (0.1)	0	0
Fibula fracture	1 (0.1)	0	0

Adverse Event	Latanoprostene Bunod 0.024% (N=1119) n (%)	Latanoprost 0.005% (N=185) n (%)	Timolol Maleate 0.5% (N=294) n (%)
Head injury	1 (0.1)	0	0
Joint dislocation	2 (0.2)	0	0
Road traffic accident	1 (0.1)	0	0
Scapula fracture	1 (0.1)	0	0
Subdural hemorrhage	1 (0.1)	0	0
Tibia fracture	1 (0.1)	0	0
Ulna fracture	1 (0.1)	0	0
Musculoskeletal and Connective Tissue Disorders	**1 (0.1)**	**0**	**1 (0.3)**
Arthralgia	1 (0.1)	0	0
Rotator cuff syndrome	0	0	1 (0.3)
Neoplasms Benign, Malignant and Unspecified (including cysts and polyps)	**5 (0.4)**	**0**	**0**
Breast cancer recurrent	1 (0.1)	0	0
Gastric cancer	1 (0.1)	0	0
Lung adenocarcinoma	1 (0.1)	0	0
Lung neoplasm malignant	2 (0.2)	0	0
Nervous System Disorders	**5 (0.4)**	**0**	**0**
Aphasia	1 (0.1)	0	0
Convulsion	1 (0.1)	0	0
Coordination abnormal	1 (0.1)	0	0
Dizziness	1 (0.1)	0	0
Subarachnoid hemorrhage	1 (0.1)	0	0
Renal and Urinary Disorders	**1 (0.1)**	**0**	**0**
Hydronephrosis	1 (0.1)	0	0
Skin and Medical Procedures	**1 (0.1)**	**0**	**0**
Angioedema	1 (0.1)	0	0
Vascular Disorders	**1 (0.1)**	**0**	**0**
Hypertension	1 (0.1)	0	0

Source: ISS Table 10-24

Common Adverse Events

Table 8.4.5.-1
Treatment-Emergent Adverse Events
Occurring in ≥ 2% of Subjects in Any Treatment Group
(Phase2/3 Pooled)

Adverse Event	Latanoprostene Bunod 0.024% N=1119 n (%)	Latanoprost 0.005% N=185 n (%)	Timolol Maleate 0.005% N=294 n (%)
OCULAR			
Eye Disorders	**278 (25%)**	**28 (15%)**	**35 (12%)**
Conjunctival hyperemia	87 (8%)	5 (3%)	4 (1%)
Eye irritation	51 (5%)	4 (2%)	7 (2%)
Eye pain	33 (3%)	1 (0.5%)	6 (2%)
Ocular hyperemia	20 (2%)	9 (5%)	2 (1%)
Punctate keratitis	17 (2%)	3 (2%)	4 (1%)
General Disorders and Administration Site Conditions	**60 (5%)**	**5 (3%)**	**8 (3%)**
Instillation site pain	42 (4%)	5 (3%)	6 (2%)
NONOCULAR			
Infections and Infestations	**122 (11%)**	**5 (3%)**	**18 (6%)**
Nasopharyngitis	53 (5%)	2 (1%)	4 (1%)

Source: ISS Tables 10-1

The most common ocular adverse events (pooled) were conjunctival/ocular hyperemia (10%) and eye irritation (5%). The most common nonocular adverse event was nasopharyngitis (5%).

Safety Summary Statement

The data contained in this submission establishes the safety of latanoprostene bunod ophthalmic solution 0.024% dosed once daily in the evening for the treatment of elevated IOP in patients with open-angle glaucoma or ocular hypertension.

The safety profile of latanoprostene bunod ophthalmic solution 0.024% is similar to other marketed topical prostaglandin analogues. The most common ocular adverse events are conjunctival/ocular hyperemia (10%) and eye irritation (5%).

9. Advisory Committee Meeting

There were no issues raised during the review of this application that were believed to benefit from discussion at an Advisory Committee meeting.

10. Pediatrics

Bausch & Lomb requested a waiver for the pediatric population of birth to 17 years old for the proposed indication, reduction of intraocular pressure (IOP) in patients with open angle glaucoma (OAG) or ocular hypertension (OHT), for the following reason: necessary studies would be impossible or highly impracticable because patients are geographically dispersed.

This application was presented at the Pediatric Review Committee (PeRC) on 12/2/15. PeRC agreed with the Division's assessment that a Full Waiver was appropriate because necessary studies would be impossible or highly impracticable because patients are geographically dispersed.

11. Other Relevant Regulatory Issues

Office of Scientific Investigations (OSI)
Per the Office of Scientific Investigations review completed on 4/22/16:

The Applicant submitted this NDA to support the use of Vyzulta for the reduction of intraocular pressure (IOP) for patients with open-angle glaucoma or ocular hypertension.

Protocol 769 was conducted at 47 clinical sites in the United States (US), Bulgaria, and the Czech Republic with first enrollment on January 31, 2013, and an interim data cutoff date of December 19, 2014. The study analyzed a total of 417 subjects. Protocol 770 was conducted at 46 domestic and foreign sites comprising 420 randomized subjects with first subject enrollment on January 28, 2013, and the last subject completed on November 26, 2014.

The sites of Drs. Christie and Wirta were chosen for inspection based on relatively large study enrollments and a lack of recent inspections.

Site #/ Name of CI/ Address	**Protocol #/ # of Subjects (enrolled)**	**Inspection Dates**	**Classification**
130785/ William C. Christie, M.D. Scott & Christie and Associates, PC 1101 Freeport Road Pittsburgh, PA 15238 and 105 Brandt Drive Cranberry Township, PA 16066	769/ 35	6-14 Jan 2016	VAI
330042/ David L. Wirta, M.D. Eye Research Foundation 520 Superior Avenue, Suite 235 Newport Beach, CA 92663	770/ 49	17-20 Nov 2015	NAI

The final classification of the inspection of Dr. Christie was Voluntary Action Indicated (VAI) due to deviations from protocol in the protocol-specified storage temperature of the test article. The noted temperature excursions would not have affected the stability of the test article. The final classification of the inspection of Dr. Wirta was No Action Indicated (NAI).

Based on the results of the clinical investigator inspections, the study appears to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication.

Financial Disclosures
The applicant has adequately disclosed financial arrangements with clinical investigators as recommended in the FDA guidance for industry on *Financial Disclosure by Clinical Investigators.*

REMS
The Division of Risk Management (DRISK) completed a Risk Evaluation and Mitigation Strategy (REMS) review on 4/1/16, in the original NDA review cycle.

DRISK and DTOP agreed that the benefit-risk profile of this drug product is acceptable and, at this time, a REMS program is not necessary to ensure that the benefits of this proposed formulation outweigh its risks for the proposed treatment of reduction of intraocular pressure (IOP) in adult patients with open-angle glaucoma (OAG) or ocular hypertension (OHT).

DMEPA
In this review cycle, the Division of Medication Error Prevention and Analysis (DMEPA) finalized a review of the proposed proprietary name, Vesneo, and found the name unacceptable on 1/15/16. Their proprietary name risk assessment found the name vulnerable to confusion that would lead to medication errors. These findings differed from a previous review of the proposed proprietary name, Vesneo, as communicated in the Conditionally Acceptable letter dated June 4, 2014. DMEPA stated that it reached a different determination with respect to the safety of the proposed name based upon new safety information.

In this review cycle, the Division of Medication Error Prevention and Analysis (DMEPA) finalized a review of the proposed proprietary name, Vyzulta, and granted conditional acceptance on 1/15/16. Their proprietary name risk assessment did not find the name vulnerable to confusion that would lead to medication errors and did not consider the name promotional.

OPDP
The Office of Prescription Drug Promotion (OPDP) completed a formal review of the package insert and labeling on 4/21/16.

Biostatistics
Per the Biostatistics review completed on 4/22/16:

This NDA included data from two Phase 3 studies (769 and 770) to support the safety and efficacy of Vyzulta (latanoprostene ophthalmic solution, 0.024%) administered one drop once

daily for the reduction of intraocular pressure (IOP) in patients with open-angle glaucoma (OAG) or ocular hypertension (OH). Both studies had a three month masked efficacy period followed by an open-label safety extension period. The safety extension period was 9 months in Study 769 and 3 months in Study 770.

Based on the results of the two pivotal Phase 3 studies, there is adequate evidence of efficacy to support the indication of the reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension for once daily use of Vyzulta. Based on the results of the two pivotal Phase 3 studies, there is adequate evidence of efficacy to support the indication of the reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension for once daily use of Vyzulta.

12. Labeling

The applicant has submitted proposed prescribing information. Based on a review of the application, the Review Team has recommended labeling consistent with the labeling of other prostaglandin analogs for ophthalmic use in lowering intraocular pressure. The recommended labeling is attached to this review.

13. Postmarketing Recommendations

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.

14. Recommended Comments to the Applicant

1. As described in 21 CFR 314.125, the methods to be used in, and the facilities and controls used for, the manufacture, processing, packing, or holding of the drug substance and drug product must comply with current good manufacturing practice regulations. During a recent inspection of the Bausch & Lomb Inc (FEI 1000113778) manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

2. The in-use stability data does not support the label storage statement (b) (4) (b) (4)

8 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
06/15/2016

WILEY A CHAMBERS
06/17/2016

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	207795
Priority or Standard	Standard
Submit Date(s)	July 21, 2015
Received Date(s)	July 21, 2015
PDUFA Goal Date	July 21, 2016
Division/Office	DTOP/OAP
Reviewer Name(s)	Lucious Lim, M.D., M.P.H.
Review Completion Date	April 14, 2016
Established Name	Latanoprostene bunod ophthalmic solution 0.024%
(Proposed) Trade Name	Vyzulta
Applicant	Bausch & Lomb Inc.
Formulation(s)	Topical ophthalmic solution
Dosing Regimen	One drop in the affected eye(s) once daily in the evening
Applicant Proposed Indication(s)/Population(s)	Reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension
Recommendation on Regulatory Action	From a clinical perspective, it is recommended that NDA 207795 be approved.
Recommended Indication(s)/Population(s) (if applicable)	Reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension

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Table 8.4.5.-1 TEAEs Occurring in ≥ 2% of Subjects in Any Treatment Group (Phase 2/3 Pooled)

Table of Figures

Glossary

AC	advisory committee
AE	adverse event
BID	twice daily
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonization
IND	Investigational New Drug
IOP	intraocular pressure
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application

NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
QD	once daily
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction

Established Name:	latanoprostene bunod ophthalmic solution 0.024%
Proposed Trade Name:	Vyzulta
Chemical Class:	new molecular entity
Pharmacological Class:	prostaglandin analogue, F2-α receptor agonist
Proposed Indication:	reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension
Dosing Regimen:	one drop in the affected eye(s) once daily in the evening
Age Groups:	patients 18 years or older

1.2. Conclusions on the Substantial Evidence of Effectiveness

NDA 207795 is recommended for approval with the labeling revisions found in this review.

The application supports the safety and effectiveness of latanoprostene bunod ophthalmic solution 0.024% for the treatment of elevated intraocular pressure (IOP) in patients with open angle glaucoma or ocular hypertension.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

The data contained in this submission establishes the efficacy of latanoprostene bunod ophthalmic solution 0.024% dosed once daily in the evening for the treatment of elevated IOP in patients with open-angle glaucoma or ocular hypertension.

Studies #769 and #770 demonstrate that the IOP lowering ability of latanoprostene bunod ophthalmic solution 0.024% is not inferior to timolol maleate ophthalmic solution 0.5% and do not differ from timolol maleate 0.5% by a clinically significant amount.

The safety profile of latanoprostene bunod ophthalmic solution 0.024% is similar to other marketed topical prostaglandin analogues. The most common ocular adverse events are conjunctival/ocular hyperemia (10%) and eye irritation (5%).

The benefit of latanoprostene bunod ophthalmic solution 0.024% for the treatment of elevated IOP in open-angle glaucoma or ocular hypertension has been demonstrated in this NDA application. The risk for using this drug is consistent with the currently marketed prostaglandin analogs.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• 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 factor is elevated intraocular pressure (IOP).	Intraocular pressure is currently the accepted standard for establishing the efficacy of ocular hypotensive medications.
Current Treatment Options	• 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 analogues.	There are multiple beta-adrenergic antagonists (beta-blockers), alpha-adrenergic agonists, parasympathomimetic (miotic) agents, carbonic anhydrase inhibitors, and prostaglandin analogues approved in the U.S. to treat elevated IOP.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• Intraocular pressure (IOP) is currently the accepted standard for establishing the efficacy of ocular hypotensive medications. The primary efficacy endpoint was mean IOP measured at multiple time points for studies #770 and #769. Studies #770 and #769 demonstrated that latanoprostene bunod ophthalmic solution 0.024% was non-inferior to timolol maleate 0.5% at all time points measured. The safety database was adequate.	Studies #770 and #769 demonstrated that latanoprostene bunod ophthalmic solution 0.024% was non-inferior to the active-control, timolol maleate ophthalmic solution 0.5%.
Risk	• The risk for using this drug is consistent with currently U.S. marketed prostaglandin analogues.	The safety database contained in this application established the safety of latanoprostene bunod ophthalmic solution 0.024% dosed once daily in the evening.
Risk Management	• No risk management activities are recommended beyond the routine monitoring and reporting of all adverse events. There are no recommended Postmarketing Requirements or Phase 4 Commitments.	Routine monitoring and reporting of all adverse events are adequate.

2 Therapeutic Context

2.1. Analysis of Condition

Glaucoma is a life-long progressive disease that is characterized by irreversible damage to the optic nerve and corresponding loss of visual field. The various types of glaucoma are distinguished by the causative physiological defect. It affects one person in 200 over the age of 40. It is the leading cause of irreversible blindness in the United States. 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.

Treatment of glaucoma consists of both medical and surgical interventions. The treatments are designed to decrease the intraocular pressure by decreasing aqueous secretion or increasing aqueous outflow. Prostaglandin analogues are believed to reduce IOP largely due to increased uveoscleral outflow of aqueous humor. The exact mechanism of action is unknown at this time.

2.2. Analysis of Current Treatment Options

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.

Table 2.2.-1
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

Pharmacologic Class/ Applicant	Trade Name	Established Name
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 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 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Latanoprostene bunod is a new molecular entity. It is not currently marketed in the United States.

3.2. Summary of Presubmission/Submission Regulatory Activity

Pfizer Inc. submitted an IND application for latanoprostene bunod ophthalmic solution (IND

73,435) on February 20, 2007. (b) (4) (b) (4). On November 2, 2009, ownership of the IND was transferred to Nicox S.A. No clinical studies were conducted during Nicox's ownership. Nicox transferred the ownership to Bausch & Lomb (B&L) on April 9, 2010.

An end-of-phase 2 meeting was held on September 26, 2012. The pre-NDA meeting was held on February 9, 2015.

3.3. Foreign Regulatory Actions and Marketing History

The drug has no foreign regulatory and marketing history.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

No issues were identified in the review of the clinical portion of the NDA to suggest a problem with data integrity. Routine clinical inspections were requested from OSI. The final consult report is pending. See CDTL review for complete findings.

4.2. Product Quality

Table 4.2.-1
Qualitative and Quantitative Composition of
Latanoprostene Bunod Ophthalmic Solution 0.024%

Component	Reference to Quality Standard	Function	Concentration (mg/mL)
Latanoprostene bunod[a]	In-house	Active	0.24
Benzalkonium chloride (BAK), (b) (4)	NF	(b) (4) preservative	(b) (4)
Polysorbate 80 (b) (4)	NF	(b) (4)	
Edetate disodium (b) (4)	USP		
Sodium citrate (b) (4)	USP	Buffering agent	
Citric acid, (b) (4)	USP	Buffering agent	
Glycerin	USP	(b) (4)	
Water (b) (4)	USP		

[a] This ingredient is (b) (4).

[b] This amount is equivalent to 0.20 mg/mL BAK in the final formulation.

NF = National Formulary
USP = United States Pharmacopeia

The final Product Quality review is pending. See CDTL review for complete findings.

4.3. Clinical Microbiology

Not applicable. The drug product is not an antimicrobial.

4.4. Nonclinical Pharmacology/Toxicology

The final nonclinical pharmacology/toxicology review is pending. See CDTL review for complete findings.

4.5. Clinical Pharmacology

4.5.1. Mechanism of Action

On topical ocular administration, latanoprostene bunod is metabolized by esterases to two moieties. The first, latanoprost acid is an F2-α prostaglandin analogue, and the second nitric oxide is released from butanediol mononitrite. Prostaglandin analogues are believed to reduce IOP largely due to increased uveoscleral outflow of aqueous humor. Nitric oxide is believed to increase the second messenger cyclic guanosine monophosphate in the trabecular meshwork. The exact mechanism of action is unknown at this time.

4.5.2. Pharmacodynamics

Reduction of intraocular pressure starts approximately 1 to 3 hours after the first administration with the maximum effect reached after 11 to 13 hours in eyes with elevated intraocular pressure.

4.5.3. Pharmacokinetics

The systemic exposure of latanoprostene bunod, its metabolites latanoprost acid and butanediol mononitrate were evaluated in one study with 22 healthy subjects after topical ocular administration of latanoprostene bunod ophthalmic solution 0.024% once daily in the morning for 28 days. There were no quantifiable plasma concentrations latanoprost or butanediol mononitrate post dose on Day 1 and Day 28. The mean maximal plasma concentration (C_{max}) of latanoprost acid was 59.1 pg/mL and 51.1 pg/mL on Day 1 and Day 28, respectively. The mean time of maximal plasma concentration (T_{max}) for latanoprost acid was approximately 5 min post administration on both Day 1 and Day 28.

4.6. Devices and Companion Diagnostic Issues

Not applicable. There is not a companion device or diagnostic.

4.7. Consumer Study Reviews

Not applicable. No consumer studies were conducted.

5 Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

The table below lists the clinical studies that were reviewed to evaluate safety and efficacy of latanoprostene bunod ophthalmic solution 0.024%.

Table 5.1.-1
List of Clinical Studies

Study Identifier/Study Type	Study Design	Treatment and Dosing Regimen	1° Efficacy Endpoint	Treatment Duration	No. of Patients Enrolled	Study Population	No. of Centers and Countries
A9441001 Phase 2 Dose-finding	Adaptive, multicenter, double-masked, randomized, active-controlled, parallel-group	Stage 1: Latanoprostene bunod (0.003%, 0.006%, 0.012%, 0.024%) QD (AM) and vehicle QD (PM) Latanoprost 0.005% QD (PM) Stage 2: Latanoprostene bunod (0.024%, 0.040%) QD (AM) and vehicle QD (PM), 0.040% QD (PM) and vehicle QD (AM) Latanoprost 0.005% QD (AM) and vehicle QD (PM), 0.05% QD (PM) and vehicle QD (AM)	Reduction in mean diurnal IOP from baseline at Day 28	Latanoprostene bunod QD (AM) and (PM) for 28 days Latanoprost 0.005% QD (AM) and (PM) for 28 days	Stage 1: Latanoprostene 0.003%: 13 0.006%: 13 0.012%: 13 0.024%: 13 Latanoprost 0.005%: 14 Stage 2: Latanoprostene 0.024%: 30 0.040%: 60 Latanoprost 0.005%: 59	Patients 18 years or more with open-angle glaucoma or ocular hypertension	17 US
A9441003 Phase 2 Dose-finding	Multicenter, double-masked, randomized, active-controlled, parallel-group	Latanoprostene bunod (0.006%, 0.024%, 0.040%) QD (PM) and vehicle QD (PM) Latanoprost 0.005% QD (PM) and vehicle QD (PM) for 28 days	Reduction in mean in diurnal IOP from baseline at Day 28	Latanoprostene bunod QD (PM) and vehicle QD (PM) for 28 days Latanoprost 0.005% QD (PM) and vehicle QD (PM) for 28 days	Latanoprostene 0.006%: 29 0.024%: 29 0.040%: 29 Latanoprost 0.005%: 30	Patients 18 years or more with open-angle glaucoma or ocular hypertension	14 Japan
659 Phase 2 Dose-finding	Multicenter, investigator-masked, randomized, active-controlled, parallel-	Latanoprostene bunod (0.006%, 0.012%, 0.024%, 0.040%) QD (PM)	Reduction in mean diurnal IOP from baseline at Visit 6 (Day 28)	28 days	419 Latanoprostene 0.006%: 82 0.012%: 85	Patients 18 years or more with open-angle glaucoma or ocular hypertension	23 US (15), Bulgaria (3), Poland (3), Czech Republic (2)

Study Identifier/Study Type	Study Design	Treatment and Dosing Regimen	1° Efficacy Endpoint	Treatment Duration	No. of Patients Enrolled	Study Population	No. of Centers and Countries
	group	Latanoprost 0.005% QD (PM)			0.024%: 83 0.040%: 81 Latanoprost 0.005%: 82		
803 Phase 2 PD/PK	Single-center, open-label, randomized, crossover, active-controlled	Latanoprostene bunod 0.024% QD (PM) and vehicle QD (AM) Timolol maleate 0.5% BID	IOP measured Q2hr for 24hr period after 4 weeks of treatment	8 weeks (4 weeks with latanoprostene 0.024% QD (PM) and 4 weeks with timolol 0.5% BID)	46 Latanoprostene 0.024%: 23 Timolol 0.5%: 23	Patients 18 years or more with open-angle glaucoma or ocular hypertension	1 US
770 Phase 3 Safety and Efficacy	Multicenter, double-masked, randomized, active-controlled, parallel-group efficacy phase (3 months) with an open-label safety extension phase (3 months)	Latanoprostene bunod 0.024% QD (PM) and vehicle QD (AM) Timolol maleate 0.5% BID	IOP at 8AM, 12PM and 4PM at Visit 4 (Week 2), Visit 5 (Week 6) and Visit 6 (Month 3)	6 months (latanoprostene 0.024% QD (PM) and vehicle QD (AM) for 3 months, then open-label latanoprostene 0.024% QD (PM) for 3 months) (timolol 0.5% BID for 3 months, , then open-label latanoprostene 0.024% QD (PM) for 3 months)	420 Latanoprostene 0.024%: 283 Timolol 0.5%: 137	Patients 18 years or more with open-angle glaucoma or ocular hypertension	46 US (40), UK (3), Germany (2), Italy (1)
769 Phase 3 Safety and Efficacy	Multicenter, double-masked, randomized, active-controlled, parallel-group efficacy phase (3 months) with an open-label safety extension phase (9 months)	Latanoprostene bunod 0.024% QD (PM) and vehicle QD (AM) Timolol maleate 0.5% BID	IOP at 8AM, 12PM and 4PM at Visit 4 (Week 2), Visit 5 (Week 6) and Visit 6 (Month 3)	Up to 12 months (latanoprostene 0.024% QD (PM) and vehicle QD (AM) for 3 months, then open-label latanoprostene 0.024% QD (PM) for 9 months) (timolol 0.5% BID for 3 months, , then open-label	420 Latanoprostene 0.024%: 286 Timolol 0.5%: 134	Patients 18 years or more with open-angle glaucoma or ocular hypertension	45 US (40), Bulgaria (3), Czech Republic (2)

Study Identifier/Study Type	Study Design	Treatment and Dosing Regimen	1° Efficacy Endpoint	Treatment Duration	No. of Patients Enrolled	Study Population	No. of Centers and Countries
				latanoprostene 0.024% QD (PM) for 9 months)			
811 Phase 3 safety	Multicenter, open-label, single-arm	Latanoprostene bunod 0.024% QD (PM)	NA	12 months	130	Patients 18 years or more with open-angle glaucoma or ocular hypertension	12 Japan
849 Phase 1 PK	Single-center, open-label, single-arm	Latanoprostene bunod 0.024% QD (PM)	Change from baseline IOP measured at 12AM, 2AM, 4AM, 8AM, 10AM, 12PM, and 4PM for 24hr period after 14 days of treatment	14 days	24	Healthy male volunteers	1 Japan
809 Phase 1 PK	Single-center, open-label, single-arm	Latanoprostene bunod 0.024% QD (AM)	NA	28 days	20	Healthy volunteers	1 US

5.2. Review Strategy

The submitted clinical study reports and protocols identified in section 5.1 were reviewed and formed the primary basis of safety and efficacy for this application.

6 Review of Relevant Individual Trials Used to Support Efficacy

6.1. A Randomized, Multicenter, Double-Masked, Parallel-Group Study Comparing the Safety and Efficacy of BOL-303259-X 0.024% (Latanoprostene Bunod) Ophthalmic Solution with Timolol Maleate Ophthalmic Solution 0.5% in Subjects with Open-Angle Glaucoma or Ocular Hypertension (Study #770)

6.1.1. Study Design

Overview and Objective

The primary objective of this study was to demonstrate that the mean IOP reduction after 3 months (90 days) of treatment with latanoprostene bunod ophthalmic solution 0.024% QD is non-inferior to timolol maleate 0.5% twice daily (BID).

Trial Design

This study was a prospective, multicenter (46 sites in US [40] and EU [6]), double-masked, randomized, active-controlled, parallel group study (3 months efficacy phase) with a 3 months open-label safety extension phase to evaluate the efficacy and safety of latanoprostene bunod ophthalmic solution 0.024%. The 0.024% dose was selected based on the results of a phase 2 dose-ranging study (Study #659). Subjects were randomized in a 2:1 ratio to receive either latanprostene bunod 0.024% once daily (QD) at 8 PM or timolol maleate 0.5% twice daily (BID) at 8 AM and 8 PM in subjects with open-angle glaucoma or ocular hypertension. Approximately 393 subjects were planned for enrollment in a 2:1 ratio in the efficacy phase. At the end of Visit 6 (Month 3), the safety extension phase started and all subjects converted to receive latanoprostene bunod 0.024% QD. Subjects received treatment for approximately 6 months.

Table 6.1.1.-1
Schedule of Visits and Parameters
(Study #770)

Activity	Visit 1[1] (Screening)	Washout Period (28 days), if applicable: Visit 2[1] (Mid-Washout Day −14 ± 1 day	Visit 3 (Eligibility) Day 1: 8 AM	Visit 3: 12 PM	Visit 3: 4 PM	Visit 4 Week 2 (Day 14) ± 2 days: 8 AM	Visit 4: 12 PM	Visit 4: 4 PM	Visit 5 Week 6 (Day 42) ± 3 days: 8 AM	Visit 5: 12 PM	Visit 5: 4 PM	Visit 6[2]; Month 3 (Day 90) + 10 days: 8 AM	Visit 6: 12 PM	Visit 6: 4 PM	Visit 7 Month 6 (Day 184) + 10 days: 8 AM	Visit 7: 12 PM	Visit 7: 4 PM
Informed consent and authorization as appropriate for local privacy regulations[a]	X																
Demographics	X																
Current and relevant medical and ocular history	X																
Concomitant medications	X																
Change in concomitant medications		X		X			X			X			X			X	
Randomization					X												
Urine pregnancy test, as applicable	X		X			X			X			X			X		
Vital signs (resting blood pressure and pulse)[b]	X	X	X			X			X			X			X		
Refraction[c]	X																
BCVA	X	X	X			X			X			X			X		
Conjunctival hyperemia assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Table 6.1.1.-1
Schedule of Visits and Parameters Continued
(Study #770)

Activity	Visit 1[a] (Screening)	Washout Period (28 days), if applicable: Visit 2[a] (Mid-Washout Day −14 ± 1 day)	Visit 3 (Eligibility) Day 1			Visit 4 Week 2 (Day 14) ± 2 days			Visit 5 Week 6 (Day 42) ± 3 days			Visit 6[m] Month 3 (Day 90) + 10 days			Visit 7 Month 6 (Day 184) + 10 days		
			8 AM	12 PM	4 PM	8 AM	12 PM	4 PM	8 AM	12 PM	4 PM	8 AM	12 PM	4 PM	8 AM	12 PM	4 PM
Slit-lamp examination (including iris color specification)[d]	X	X	X			X			X			X			X		
Pachymetry	X																
IOP[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Instill study drug						X			X			X					
Gonioscopy[f]	X																
Ophthalmoscopy	X				X									X			X
Discontinue current IOP medication	X																
Adverse Events[g]	X	X		X			X			X			X			X	
Dispense and collect study drug[h]					X[i]		X[k]			X[l]			X[n]			X	
Dispense and collect diary card[h]					X		X			X			X			X	

Abbreviations: BCVA, best-corrected visual acuity; IOP, intraocular pressure.

[a] Must be signed and dated before study procedures are performed.

[b] Performed in sitting position.

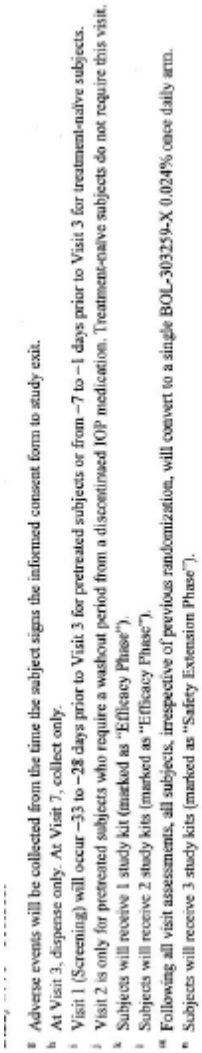
[c] Refraction must be repeated if a decrease in visual acuity of 10 or more letters as per the Early Treatment of Diabetic Retinopathy Study protocol occurs.

[d] Slit-lamp examination must be performed prior to IOP measurements, gonioscopy (if applicable), or instillation of the fluorescein agent.

[e] All IOP measurements should be ± 30 minutes of the required time.

[f] If gonioscopy was performed within 6 months prior to screening and was documented in the subject's records, no additional screening gonioscopy examination is necessary.

Table 6.1.1.-1
Schedule of Visits and Parameters Continued
(Study #770)



[a] Adverse events will be collected from the time the subject signs the informed consent form to study exit.
[b] At Visit 3, dispense only. At Visit 7, collect only.
[c] Visit 1 (Screening) will occur −33 to −28 days prior to Visit 3 for pretreated subjects or from −7 to −1 days prior to Visit 3 for treatment-naïve subjects.
[d] Visit 2 is only for pretreated subjects who require a washout period from a discontinued IOP medication. Treatment-naïve subjects do not require this visit.
[e] Subjects will receive 1 study kit (masked as "Efficacy Phase").
[f] Subjects will receive 2 study kits (marked as "Efficacy Phase").
[g] Following all visit assessments, all subjects, irrespective of previous randomization, will convert to a single BOL-303259-X 0.024% once daily arm.
[h] Subjects will receive 3 study kits (marked as "Safety Extension Phase").

Study Endpoints

The primary efficacy endpoint was IOP measured at 8 AM, 12 PM and 4 PM at Visit 4 (Week 2), Visit 5 (Week 6) and Visit 6 (Month 3).

Reviewer's Comment: *These time points capture the peak and trough times of latanoprostene bunod but not the peak time for timolol maleate (i.e., 2 hours after dosing).*

The key secondary efficacy endpoints were:

- Proportion of subjects with IOP ≤ 18 mmHg consistently at all 9 time points in the first 3 months
- Proportion of subjects with IOP ≥ 25 mmHg consistently at all 9 time points in the first 3 months

Additional secondary efficacy endpoints were as follows:

- Change from baseline (CFB) in IOP at specified time points (8 AM, 12 PM, and 4 PM) at Visit 4, 5, and 6 (Week 2, Week 6, and Month 3, respectively)
- Absolute and CFB in diurnal IOP at each postrandomization visit (Visits 4, 5, 6, 7, 8, and 9 [Week 2, Week 6, Month 3, Month 6, Month 9, and Month 12, respectively])
- Absolute and CFB in IOP at the specified time points: 8 AM, 12 PM, and 4 PM at Visit 7 (Month 6), Visit 8 (Month 9), and Visit 9 (Month 12)
- Standardized IOP area under the curve (AUC) (the AUC divided by the time period that the subject was observed) by treatment group from: 8 AM at Visit 4 (Week 2) to 4 PM at the following visits Visit 4 (Week 2), Visit 5 (Week 6), Visit 6 (Month 3), Visit 7 (Month 6), Visit 8 (Month 9), and Visit 9 (Month 12)
- For the timolol maleate 0.5% BID group (ie, the group of subjects randomized totimolol maleate 0.5% BID at Visit 3 [Eligibility, Day 0]), change in IOP fromVisit 6 (Month 3) at each time point at Visit 7 (Month 6), Visit 8 (Month 9), and Visit 9 (Month 12)
- For the timolol maleate 0.5% BID group (ie, the group of subjects randomized totimolol maleate 0.5% BID at Visit 3 [Eligibility, Day 0]), change in diurnal IOP from Visit 6 (Month 3) at Visit 7 (Month 6), Visit 8 (Month 9), and Visit 9 (Month 12)

The safety endpoints were:

- Vital signs (resting BP and pulse)
- BCVA
- Conjunctival hyperemia assessment
- Slit-lamp examination
- Gonioscopy
- Ophthalmoscopy
- Adverse events (AEs)

Statistical Analysis Plan

Analysis Populations

Intent-to-Treat (ITT) population**:** included all randomized subjects who received at least 1 dose of study drug and had a baseline and at least 1 post-baseline IOP assessment. Subjects were analyzed according to the treatment to which they were randomized.

Per-Protocol (PP) population: included all of the subjects in the ITT population who remained in the study through Visit 6 (Month 3) with non-missing post-baseline IOP assessment at any of the 9 time points and who did not have major protocol deviations. Subjects were analyzed according to the treatment they received.

Randomized population: included all randomized subjects.

Safety population: included all randomized subjects who received at least 1 dose of study drug. All subjects in the safety population were analyzed according to the treatment they received. All safety analyses were based on the safety population.

Efficacy Analysis

The primary efficacy analyses were performed using an ANCOVA based on the ITT population with missing data imputed using the LOCF method for the IOP in the study eye measured at the specified time points: 8 AM, 12 PM, and 4 PM at Visit 4 (Week 2), Visit 5 (Week 6), and Visit 6 (Month 3).

An ANCOVA for the IOP measurement at each time point and visit followed the below model.

$$Y_{ij} = \mu + \tau_i + \beta X_{ij} + \varepsilon_{ij}$$

Where

$\tau_i = i^{th}$ treatment group (BOL-303259-X 0.024% or timolol maleate 0.5%)
Y_{ij} = the IOP value for the j^{th} subject in the i^{th} treatment group,
μ = overall mean,
X_{ij} = the baseline IOP value for the j^{th} subject in the i^{th} treatment group,
β = a common slope of the regression line on baseline by treatment group,
ε_{ij} = a normally and independently distributed random error term with mean 0 and constant variance.

The 2 treatments, latanoprostene bunod ophthalmic solution 0.024% QD and timolol maleate ophthalmic solution 0.5% BID, were compared for each time point by visit. The least squares (LS) mean of each treatment group, the difference in the LS mean (latanoprostene bunod ophthalmic solution 0.024% minus timolol maleate ophthalmic solution 0.5%), and the 2-sided 95% CI for the difference were obtained. Non-inferiority was to be claimed if the upper limit of the CIs did not exceed 1.5 mmHg at all time points (8 AM, 12 PM, and 4 PM) at Visits 4, 5, and 6 (Week 2, Week 6, and Month 3, respectively) and did not exceed 1.00 mmHg for the majority (at least 5 out of the 9 time points) of the time points. If non-inferiority was determined,

superiority at each time point was to be claimed if the upper limit of the 95% CI did not exceed 0 mmHg at all time points of each of the 3 visits during the efficacy evaluation (Visits 4, 5, and 6).

To supplement the primary analyses, the analyses above were repeated for the PP population. Any discrepancy between the ITT and PP analyses was to be explained.

Safety Analysis

Safety analyses were based on the safety analysis set. The safety analyses set included all subjects who were confirmed to have received the study drug. All subjects in the safety analysis set were analyzed according to the treatment received.

Safety parameters included the following: recording of adverse events, vital sign measurements (resting blood pressure and pulse measured in the same arm at each visit), BCVA results, slit-lamp examination findings, conjunctival hyperemia assessment, ophthalmoscopy findings, and pachymetry results.

AEs were coded using Medical Dictionary for Regulatory Activities (MedDRA) dictionary version 13.0. All AEs collected with start dates following the first administration of study drug or that worsen following the first administration of study drug were considered treatment-emergent adverse events (TEAEs).

Treatment-emergent non-ocular AEs were summarized using discrete summaries at the subject and event level by system organ class (SOC) and preferred term (PT) for each treatment group. Treatment-emergent ocular AEs were summarized for study eyes, treated fellow eyes, and non-treated fellow eyes separately by treatment groups.

TEAEs were summarized by relationship to study drug. Relationship of AEs to study drug may have been classified as unrelated, unlikely, possibly, probably, or definitely related. Subjects with more than 1 occurrence of the same non-ocular PT were counted only once under the maximum relationship to the study drug. Ocular AEs were summarized for study eyes, treated fellow eyes, and non-treated fellow eyes separately. Eyes with more than 1 occurrence of the same PT were counted only once under the maximum relationship to the study drug.

TEAEs were summarized by severity. Severity of AEs may have been classified by the Investigator as “Mild”, “Moderate”, or ‘Severe”. Subjects with more than 1 occurrence of the same non-ocular PT were counted only once under the maximum severity. Ocular

AEs were summarized for study eyes, treated fellow eyes, and non-treated fellow eyes separately. Eyes with more than 1 occurrence of the same PT were counted only once under the maximum severity. AEs with unknown severity were counted as severe.

Systolic (SBP), diastolic (DBP), and heart rate (HR) were summarized by visit using descriptive statistics.

Other safety data, including BCVA, conjunctival hyperemia, slit lamp biomicroscopy, and ophthalmoscopy, were presented for study eyes, treated fellow eyes, and non-treated fellow eyes separately.

Protocol Amendments

The original protocol, dated November 8, 2012, was amended 3 times. None of the changes were considered to have impacted the results of the study.

Data Quality and Integrity: Sponsor's Assurance

Bausch & Lomb Global Clinical Operations representatives were to be allowed to visit all study site locations to assess the data, quality, and study integrity in a manner consistent with applicable health authority regulations and the procedures adopted by Bausch & Lomb Global Clinical Operations.

Monitoring visits and telephone consultations occurred as necessary during the course of the investigation to verify the following:

- The rights and well-being of subjects were protected.
- The conduct of the investigation was in compliance with the currently approved protocol/amendment, ICH GCPs, and IRB/EC requirements.
- The integrity of the data, including adequate study documentation.
- The facilities remained acceptable.
- The Investigator and site personnel remained qualified and able to conduct the study.
- Study drug accountability.

During the course of the study, if Bausch & Lomb determined that an Investigator was non-compliant with the study plan and/or applicable regulatory requirements, Bausch & Lomb were to take action to secure compliance.

6.1.2. Study Results

Compliance with Good Clinical Practices

This study was conducted in compliance with the study protocol and in accordance with Good Clinical Practices (GCPs), as described in the International Conference on Harmonization (ICH) Harmonized Tripartite Guidelines for GCP, the US Code of Federal Regulations dealing with clinical studies (21 CFR Parts 11, 50, 54, 56, and 312), the ethical principles in the Declaration of Helsinki, and applicable local regulations.

Financial Disclosure

The applicant has adequately disclosed financial arrangements with clinical investigators as recommended in the FDA guidance for industry on *Financial Disclosure by Clinical Investigators.*

There is no evidence to suggest that any of the investigators/sub-investigators had any financial interests or arrangements with the applicant.

Patient Disposition

Table 6.1.2.-1
Subject Disposition
and Primary Reason for Discontinuation

Subject Disposition	Latanoprostene 0.024%	Timolol Maleate 0.5% Crossover to Latanoprostene 0.024%	Total
Randomized Population[a], N	283	137	420
Efficacy Phase			
Completed, n (%)	259 (91.5)	128 (93.4)	387 (92.1)
Discontinued, n (%)	24 (8.5)	9 (6.6)	33 (7.9)
Entire Study[b]			
Completed, n (%)	253 (89.4)	125 (91.2)	378 (90.0)
Discontinued, n (%)	30 (10.6)	12 (8.8)	42 (10.0)
ITT Population, N	278	136	414
Efficacy Phase			
Completed, n (%)	259 (93.2)	128 (94.1)	387 (93.5)
Discontinued, n (%)	19 (6.8)	8 (5.9)	27 (6.5)
Entire Study			
Completed, n (%)	253 (91.0)	125 (91.9)	378 (91.3)
Discontinued, n (%)	25 (9.0)	11 (8.1)	36 (8.7)
Per-Protocol Population, N	183	87	270
Efficacy Phase			
Completed, n (%)	182 (99.5)	87 (100.0)	269 (99.6)
Discontinued, n (%)	1 (0.5)	0	1 (0.4)

Subject Disposition	Latanoprostene 0.024%	Timolol Maleate 0.5% Crossover to Latanoprostene 0.024%	Total
Entire Study			
Completed, n (%)	178 (97.3)	84 (96.6)	262 (97.0)
Discontinued, n (%)	5 (2.7)	3 (3.4)	8 (3.0)
Safety Population, N	279	136	415
Efficacy Phase			
Completed, n (%)	259 (92.8)	128 (94.1)	387 (93.3)
Discontinued, n (%)	20 (7.2)	8 (5.9)	28 (6.7)
Entire Study			
Completed, n (%)	253 (90.7)	125 (91.9)	378 (91.1)
Discontinued, n (%)	26 (9.3)	11 (8.1)	37 (8.9)
Reasons for Discontinuation (ITT Population)			
Withdrew consent, n (%)	3 (1.1)	2 (1.5)	5 (1.2)
Lost to follow-up, n (%)	1 (0.4)	1 (0.7)	2 (0.5)
Adverse event, n (%)	5 (1.8)	4 (2.9)	9 (2.2)
Investigator decision, n (%)	1 (0.4)	0	1 (0.2)
Failure to follow the required study procedures, n (%)	6 (2.2)	2 (1.5)	8 (1.9)
Other, n (%)	9 (3.2)	2 (1.5)	11 (2.7)

[a] The randomized population comprised of all randomized subjects; 5 subjects were randomized but did not receive any instillation of study medication.
[b] Both efficacy and safety phases.
Source: Table 10-1

Protocol Violations/Deviations

There were 198 major protocol violations in the efficacy phase. The most common protocol violation was that the subject's visit fell outside the visit window (101 subjects [24%]). The percentages of major protocol violations were comparable between treatment groups.

Table 6.1.2.-2
Major Protocol Violations in the Efficacy Phase
Randomized Population

Violation Description	Latanoprostene 0.024% N=283 n (%)	Timolol Maleate 0.5% N=137 n (%)	Total N=420 n (%)
Subject's visit fell outside visit window	66 (23.3)	35 (25.5)	101 (24.0)
Subject missed IOP assessment before month 3	24 (8.5)	11 (8.0)	35 (8.3)
Subject took disallowed medication	14 (4.9)	4 (2.9)	18 (4.3)
Subject missed doses	11 (3.9)	3 (2.2)	14 (3.3)

Violation Description	Latanoprostene 0.024% N=283 n (%)	Timolol Maleate 0.5% N=137 n (%)	Total N=420 n (%)
Inclusion/exclusion violation	8 (2.8)	4 (2.9)	12 (2.9)
Subject's treatment compliance <80% or >120%	8 (2.8)	3 (2.2)	11 (2.6)
Subject had disallowed change to concomitant medication	5 (1.8)	3 (1.5)	7 (1.7)
Source Table 10-3			

Table of Demographic Characteristics

Table 6.1.2.-3
Demographics and Baseline Characteristics
ITT Population

Demographic Variable		Latanoprostene 0.024% N=278	Timolol Maleate 0.5% Crossover to Latanoprostene 0.024% N=136	Total N=414
Age (years)				
	n	278	136	414
	Mean (SD)	65.0 (9.77)	64.1 (9.71)	64.7 (9.75)
	Median	66.0	65.0	65.0
	Range: Min, Max	23, 87	37, 88	23, 88
Age Group, n (%)				
	< 65 years	127 (45.7)	64 (47.1)	191 (46.1)
	≥ 65 years	151 (54.3)	72 (52.9)	223 (53.9)
Sex, n (%)				
	Male	116 (41.7)	57 (41.9)	173 (41.8)
	Female	162 (58.3)	79 (58.1)	241 (58.2)
Race, n (%)				
	White	204 (73.4)	89 (65.4)	293 (70.8)
	Black/African American	69 (24.8)	46 (33.8)	115 (27.8)
	American Indian/ Alaskan Native	1 (0.4)	0	1 (0.2)
	Asian	4 (1.4)	1 (0.7)	5 (1.2)
	Native Hawaiian/Pacific Islander	0	0	0
Ethnicity, n (%)				
	Hispanic or Latino	36 (12.9)	19 (14.0)	55 (13.3)
	Not Hispanic and not Latino	242 (87.1)	117 (86.0)	359 (86.7)
Treatment-				

Demographic Variable		Latanoprostene 0.024% N=278	Timolol Maleate 0.5% Crossover to Latanoprostene 0.024% N=136	Total N=414
Naïve[a] Subject, n (%)				
	Yes	82 (29.5)	34 (25.0)	116 (28.0)
	No	196 (70.5)	102 (75.0)	298(72.0)

[a] A subject was considered treatment-naïve if he or she did not require a washout period (i.e., had no documented IOP lowering medication in the medical history 30 days prior to Visit 1)
Source: Table 10-1

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Baseline study eye characteristics are presented for the ITT population in Table 6.1.2-4.

Table 6.1.2-4
Baseline Study Eye Characteristics
ITT Population

Baseline Characteristic		Latanoprostene 0.024% N=277	Timolol Maleate 0.5% Crossover to Latanoprostene 0.024% N=135	Total N=412
Mean Corneal Thickness (microns)				
	Mean (SD)	550.17 (31.11)	551.18 (32.67)	550.50 (31.59)
	Median	551.33	556.33	553.66
	Range: Min, Max	470, 598.66	436, 598.66	436, 589.66
Refraction sphere (diopters)				
	Mean (SD)	-0.919 (2.78)	-0.430 (2.21)	-0.758 (2.61)
	Median	-0.250	0.000	-0.250
	Range: Min, Max	-15.25, 5.5	-7.25, 4.25	-15.25, 5.5
Refraction Cylinder (diopter)				
	Mean (SD)	0.366 (1.05)	0.256 (1.10)	0.330 (1.06)
	Median	0.250	0.250	0.250
	Range: Min, Max	-2.75, 4.25	-3,3	-3, 4.25
Source: Table 11-2				

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

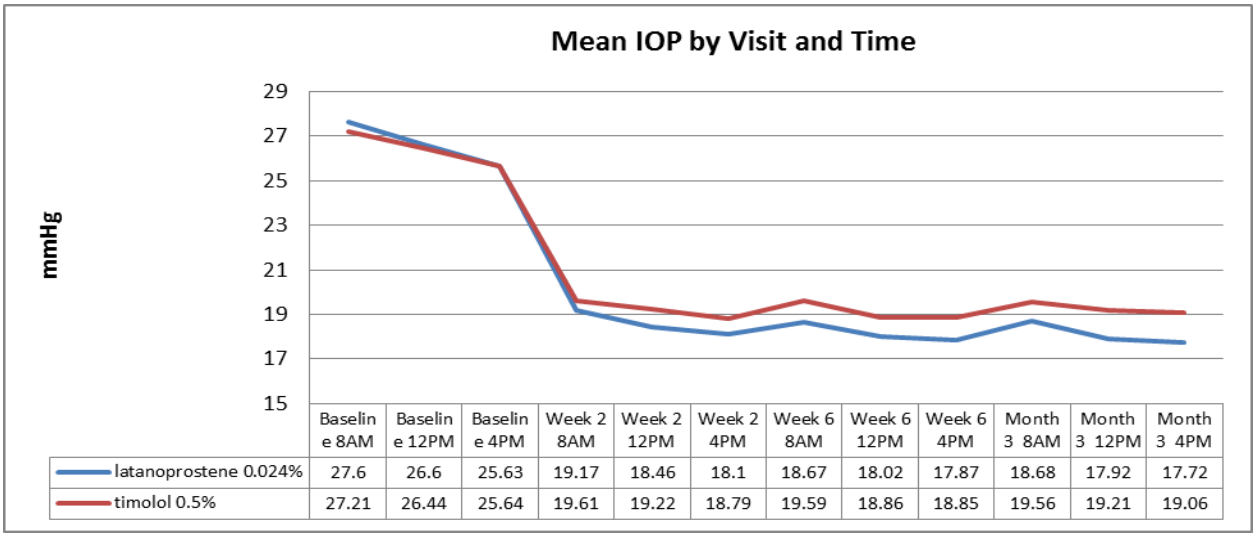
Treatment compliance between the two treatment groups was similar.

The majority of subjects (390 subjects; 94.0%) in the safety population reported receiving at least 1 concomitant medication. The most commonly reported concomitant medications included 3-hydroxy-3-methylgutaryl-coenzyme A (HMG CoA) reductase inhibitors (154 subjects; 37.1%), platelet aggregation inhibitors (excluding heparin) (117 subjects; 28.2%), and ACE inhibitors (plain) (99 subjects; 23.9%).

Rescue medications were not used in this study.

Efficacy Results – Primary Endpoint

Figure 6.1.2-1 Study #770 - ITT Population

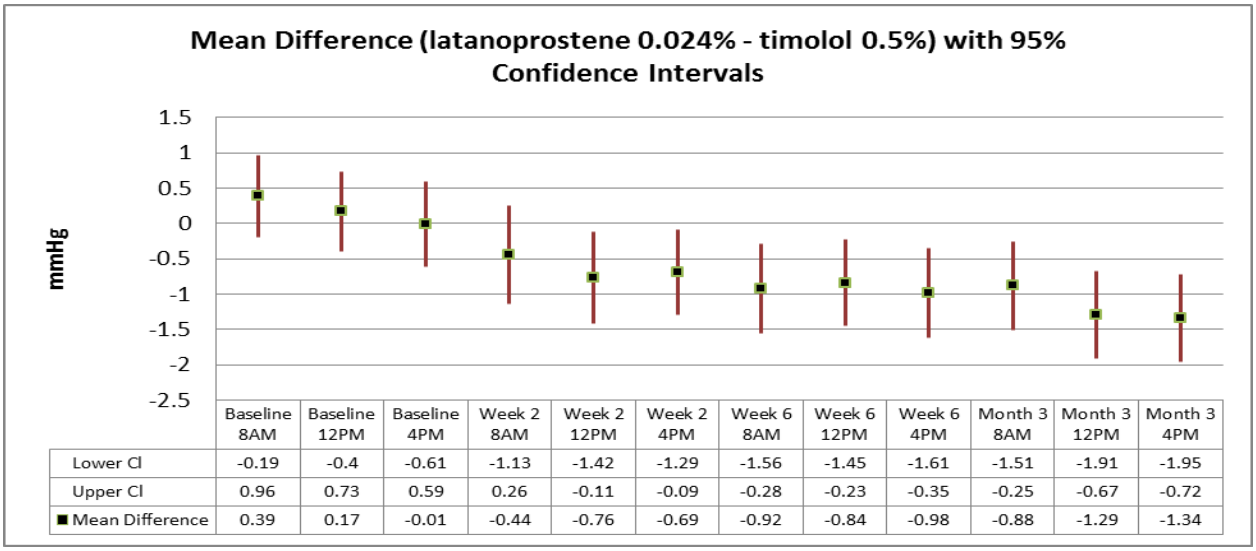


	Baseline 8AM	Baseline 12PM	Baseline 4PM	Week 2 8AM	Week 2 12PM	Week 2 4PM	Week 6 8AM	Week 6 12PM	Week 6 4PM	Month 3 8AM	Month 3 12PM	Month 3 4PM
latanoprostene 0.024%	27.6	26.6	25.63	19.17	18.46	18.1	18.67	18.02	17.87	18.68	17.92	17.72
timolol 0.5%	27.21	26.44	25.64	19.61	19.22	18.79	19.59	18.86	18.85	19.56	19.21	19.06

Source: Table 14.2.1.1.b

Reviewer's Comment: *Baseline mean IOP of the two treatment groups are similar. The mean IOP for latanoprostene 0.024% and timolol 0.5% are similar at all time points measured.*

Figure 6.1.2.-2 Study #770 – ITT Population

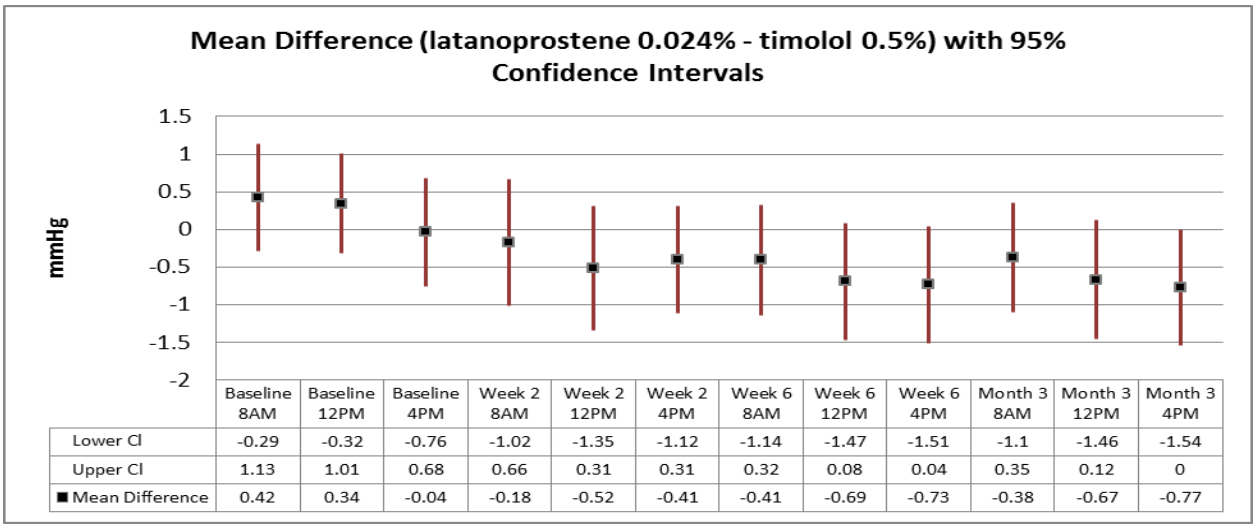


	Baseline 8AM	Baseline 12PM	Baseline 4PM	Week 2 8AM	Week 2 12PM	Week 2 4PM	Week 6 8AM	Week 6 12PM	Week 6 4PM	Month 3 8AM	Month 3 12PM	Month 3 4PM
Lower CI	-0.19	-0.4	-0.61	-1.13	-1.42	-1.29	-1.56	-1.45	-1.61	-1.51	-1.91	-1.95
Upper CI	0.96	0.73	0.59	0.26	-0.11	-0.09	-0.28	-0.23	-0.35	-0.25	-0.67	-0.72
Mean Difference	0.39	0.17	-0.01	-0.44	-0.76	-0.69	-0.92	-0.84	-0.98	-0.88	-1.29	-1.34

Source: Table 14.2.2.1.b

Reviewer's Comment: *The mean IOP of the two treatment groups are comparable. The 95% confidence interval crosses zero at all time points measured at baseline. The mean IOP values (latanoprostene 0.024% QD minus timolol 0.5% BID) and upper end of the confidence intervals are within 1 mmHg at all of the time points and within 1.5 mmHg at all time points. The study demonstrates effective IOP lowering with the use of latanoprostene bunod but does not provide a valid comparison to timolol because the peak time point for IOP lowering with timolol maleate was not included.*

Figure 6.1.2.-3 Study #770 – PP Population



	Baseline 8AM	Baseline 12PM	Baseline 4PM	Week 2 8AM	Week 2 12PM	Week 2 4PM	Week 6 8AM	Week 6 12PM	Week 6 4PM	Month 3 8AM	Month 3 12PM	Month 3 4PM
Lower CI	-0.29	-0.32	-0.76	-1.02	-1.35	-1.12	-1.14	-1.47	-1.51	-1.1	-1.46	-1.54
Upper CI	1.13	1.01	0.68	0.66	0.31	0.31	0.32	0.08	0.04	0.35	0.12	0
Mean Difference	0.42	0.34	-0.04	-0.18	-0.52	-0.41	-0.41	-0.69	-0.73	-0.38	-0.67	-0.77

Source: Table 14.2.2.2.b

Reviewer's Comment: *The analysis of the PP population is similar to that of the ITT population.*

Data Quality and Integrity – Reviewers' Assessment

This submission is of sufficient quality to allow for a substantive review. No issues related to data quality or data integrity were identified in this review.

Efficacy Results – Secondary and other relevant endpoints

The key endpoint to evaluate reduction of intraocular pressure is mean IOP. This was performed in the primary efficacy endpoint analyses. The secondary endpoint analyses are exploratory. The Applicant does not plan to make labeling claims based on pre-specified secondary and other endpoints.

Dose/Dose Response

Study #659 was a dose-ranging study that evaluated four doses (0.006%, 0.012%, 0.024%, and 0.040%) of latanoprostene bunod ophthalmic solution compared to latanoprost 0.005% in subjects with open-angle glaucoma or ocular hypertension. The study identified the 0.024% dose as the optimal dose to develop based on a risk-benefit analysis.

Durability of Response

The mean IOP reduction for each of the time points 8AM, 12PM, and 4PM over the three month evaluation period were similar. For more details, see Figure 6.1.2-1.

Persistence of Effect

Latanoprostene is intended to treat a chronic condition.

Additional Analyses Conducted on the Individual Trial

The key endpoint to evaluate reduction of intraocular pressure is mean IOP. This was performed in the primary efficacy endpoint analyses. Additional analyses are not necessary.

6.2. A Randomized, Multicenter, Double-Masked, Parallel-Group Study Comparing the Safety and Efficacy of BOL-303259-X 0.024% (Latanoprostene Bunod) Ophthalmic Solution with Timolol Maleate Ophthalmic Solution 0.5% in Subjects with Open-Angle or Ocular Hypertension (Study #769)

6.2.1. Study Design

Overview and Objective

The primary objective of this study was to demonstrate that the mean IOP reduction after 3 months (90 days) of treatment with latanoprostene bunod ophthalmic solution 0.024% QD is non-inferior to timolol maleate ophthalmic solution 0.5% twice daily (BID).

Trial Design

This study was a prospective, multicenter (45 sites in US [40], Bulgaria [3], and Czech Republic [2]), double-masked, randomized, active-controlled, parallel group study (3 months efficacy phase) with a 9 months open-label safety extension phase to evaluate the efficacy and safety of latanoprostene bunod ophthalmic solution 0.024%. The 0.024% dose was selected based on the results of a phase 2 dose-ranging study (Study #659). Subjects were randomized in a 2:1 ratio to receive either latanprostene once daily (QD) at 8 PM or timolol maleate 0.5% twice daily (BID) at 8 AM and 8 PM in subjects with open-angle glaucoma or ocular hypertension. Approximately 393 subjects were planned for enrollment in a 2:1 ratio in the efficacy phase. At the end of Visit 6 (Month 3), the safety extension phase started and all subjects converted to receive latanoprostene QD. Subjects received treatment for approximately 12 months.

Table 6.2.1.-1
Schedule of Visits and Parameters
(Study #669)

Activity	Visit 1[j] (Screening)	Washout Period (28 days), if applicable	Visit 3 (Eligibility) Day 1			Visit 4 Week 2 (Day 14) ± 2 days			Visit 5 Week 6 (Day 42) ± 3 days			Visit 6[e] Month 3 (Day 90) + 10 days			Visit 7 Month 6 (Day 180) + 10 days Visit 8 Month 9 (Day 270) + 10 days Visit 9 Month 12 (Day 366) + 10 days		
		Visit 2[k] (Mid-Washout Day −14 ± 1 day	8 AM	12 PM	4 PM	8 AM	12 PM	4 PM	8 AM	12 PM	4 PM	8 AM	12 PM	4 PM	8 AM	12 PM	4 PM
Informed consent and authorization as appropriate for local privacy regulations[a]	X																
Demographics	X																
Current and relevant medical and ocular history	X																
Concomitant medications	X																
Change in concomitant medications		X		X			X			X			X			X	
Randomization					X												
Urine pregnancy test, as applicable	X		X			X			X			X			X		
Vital signs (resting blood pressure and pulse)[b]	X	X	X			X			X			X			X		
Refraction[c]	X																
BCVA	X	X	X			X			X			X			X		

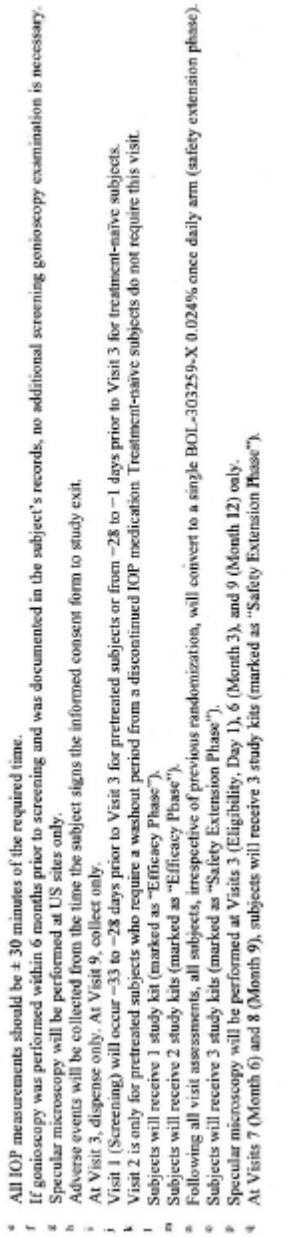
Table 6.2.1.-1
Schedule of Visits and Parameters Continued
(Study #669)

Activity	Visit 1[j] (Screening)	Washout Period (28 days), if applicable		Visit 3 (Eligibility) Day 1			Visit 4 Week 2 (Day 14) ± 2 days			Visit 5 Week 6 (Day 42) ± 3 days			Visit 6[n] Month 3 (Day 90) + 10 days			Visit 7 Month 6 (Day 180) + 10 days Visit 8 Month 9 (Day 270) + 10 days Visit 9 Month 12 (Day 366) + 10 days		
		Visit 2[k] (Mid-Washout) Day −14 ± 1 day		8 AM	12 PM	4 PM	8 AM	12 PM	4 PM	8 AM	12 PM	4 PM	8 AM	12 PM	4 PM	8 AM	12 PM	4 PM
Conjunctival hyperemia assessment	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Slit-lamp examination (including iris color specification)[a]	X	X		X			X			X			X			X		
Pachymetry	X																	
IOP[m]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Instill study drug				X			X			X			X					
Gonioscopy[c]	X																	
Ophthalmoscopy	X					X									X			X
Specular Microscopy[g]						X									X			X[p]
Discontinue Current IOP medication	X																	
Adverse Events[h]	X	X			X			X			X			X			X	
Dispense and collect study drug[i]						X[l]		X[l]			X[m]			X[o]			X[q]	
Dispense and collect diary card[f]						X		X			X			X			X	

Abbreviations: BCVA, best-corrected visual acuity; IOP, intraocular pressure.

a. Must be signed and dated before study procedures are performed.
b. Performed in sitting position.
c. Refraction must be repeated if a decrease in visual acuity of 10 or more letters per the Early Treatment of Diabetic Retinopathy Study protocol occurs.
d. Slit-lamp examination must be performed prior to IOP measurements, gonioscopy (if applicable), or instillation of the fluorescein agent.

Table 6.2.1-1
Schedule of Visits and Parameters Continued
(Study #669)



e All IOP measurements should be ± 30 minutes of the required time.
f If gonioscopy was performed within 6 months prior to screening and was documented in the subject's records, no additional screening gonioscopy examination is necessary.
g Specular microscopy will be performed at US sites only.
h Adverse events will be collected from the time the subject signs the informed consent form to study exit.
i At Visit 3, dispense only. At Visit 9, collect only.
j Visit 1 (Screening) will occur −33 to −28 days prior to Visit 3 for pretreated subjects or from −28 to −1 days prior to Visit 3 for treatment-naïve subjects.
k Visit 2 is only for pretreated subjects who require a washout period from a discontinued IOP medication Treatment-naïve subjects do not require this visit.
l Subjects will receive 1 study kit (marked as "Efficacy Phase").
m Subjects will receive 2 study kits (marked as "Efficacy Phase").
n Following all visit assessments, all subjects, irrespective of previous randomization, will convert to a single BOL-303259-X 0.024% once daily arm (safety extension phase).
o Subjects will receive 3 study kits (marked as "Safety Extension Phase").
p Specular microscopy will be performed at Visits 3 (Eligibility, Day 1), 6 (Month 3), and 9 (Month 12) only.
q At Visits 7 (Month 6) and 8 (Month 9), subjects will receive 3 study kits (marked as "Safety Extension Phase").

Study Endpoints

The primary efficacy endpoint was IOP measured at 8 AM, 12 PM and 4 PM at Visit 4 (Week 2),

Visit 5 (Week 6) and Visit 6 (Month 3).

Reviewer's Comment: *The time points capture the peak and trough times of latanoprostene bunod but not the peak time for timolol maleate (i.e., 2 hours after dosing).*

The key secondary efficacy endpoints were:

- Proportion of subjects with IOP ≤ 18 mmHg consistently at all 9 time points in the first 3 months
- Proportion of subjects with IOP ≥ 25 mmHg consistently at all 9 time points in the first 3 months

Additional secondary efficacy endpoints were as follows:

- Change from baseline (CFB) in IOP at specified time points (8 AM, 12 PM, and 4 PM) at Visit 4, 5, and 6 (Week 2, Week 6, and Month 3, respectively)
- Absolute and CFB in diurnal IOP at each postrandomization visit (Visits 4, 5, 6, 7, 8, and 9 [Week 2, Week 6, Month 3, Month 6, Month 9, and Month 12, respectively])
- Absolute and CFB in IOP at the specified time points: 8 AM, 12 PM, and 4 PM at Visit 7 (Month 6), Visit 8 (Month 9), and Visit 9 (Month 12)
- Standardized IOP area under the curve (AUC) (the AUC divided by the time period that the subject was observed) by treatment group from: 8 AM at Visit 4 (Week 2) to 4 PM at the following visits Visit 4 (Week 2), Visit 5 (Week 6), Visit 6 (Month 3), Visit 7 (Month 6), Visit 8 (Month 9), and Visit 9 (Month 12)
- For the timolol maleate 0.5% BID group (ie, the group of subjects randomized totimolol maleate 0.5% BID at Visit 3 [Eligibility, Day 0]), change in IOP fromVisit 6 (Month 3) at each time point at Visit 7 (Month 6), Visit 8 (Month 9), and Visit 9 (Month 12)
- For the timolol maleate 0.5% BID group (ie, the group of subjects randomized totimolol maleate 0.5% BID at Visit 3 [Eligibility, Day 0]), change in diurnal IOP from Visit 6 (Month 3) at Visit 7 (Month 6), Visit 8 (Month 9), and Visit 9 (Month 12)

The safety endpoints were:

- Vital signs (resting BP and pulse)
- BCVA
- Slit-lamp examination
- Conjunctival hyperemia assessment
- Ophthalmoscopy
- Pachymetry
- Specular microscopy (at select U.S. sites only)
- Adverse events (AEs)

Statistical Analysis Plan

Analysis Populations

Intent-to-Treat (ITT) population**:** included all randomized subjects who received at least 1 dose of study drug and had a baseline and at least 1 post-baseline IOP assessment. Subjects were analyzed according to the treatment to which they were randomized.

Per-Protocol (PP) population: included all of the subjects in the ITT population who remained in the study through Visit 6 (Month 3) with non-missing post-baseline IOP assessment at any of the 9 time points and who did not have major protocol deviations. Subjects were analyzed according to the treatment they received.

Randomized population: included all randomized subjects.

Safety population: included all randomized subjects who received at least 1 dose of study drug. All subjects in the safety population were analyzed according to the treatment they received. All safety analyses were based on the safety population.

Efficacy Analysis

The primary efficacy analyses were performed using an ANCOVA based on the ITT population with missing data imputed using the LOCF method for the IOP in the study eye measured at the specified time points: 8 AM, 12 PM, and 4 PM at Visit 4 (Week 2), Visit 5 (Week 6), and Visit 6 (Month 3).

An ANCOVA for the IOP measurement at each time point and visit followed the model below.

$$Y_{ij} = \mu + \tau_i + \beta X_{ij} + \varepsilon_{ij}$$

Where

τ_i = i^{th} treatment group (BOL-303259-X 0.024% or timolol maleate 0.5%)
Y_{ij} = the IOP value for the j^{th} subject in the i^{th} treatment group,
μ = overall mean,
X_{ij} = the baseline IOP value for the j^{th} subject in the i^{th} treatment group,
β = a common slope of the regression line on baseline by treatment group,
ε_{ij} = a normally and independently distributed random error term with mean 0 and constant variance.

The 2 treatments, latanoprostene bunod ophthalmic solution 0.024% QD and timolol maleate 0.5% BID, were compared for each time point by visit. The least squares (LS) mean of each treatment group, the difference in the LS mean (latanoprostene bunod ophthalmic solution 0.024% minus timolol maleate 0.5%), and the 2-sided 95% CI for the difference were obtained.

Non-inferiority was to be claimed if the upper limit of the CIs did not exceed 1.5 mmHg at all time points (8 AM, 12 PM, and 4 PM) at Visits 4, 5, and 6 (Week 2, Week 6, and Month 3, respectively) and did not exceed 1.00 mmHg for the majority (at least 5 out of the 9 time points) of the time points. If non-inferiority was determined, superiority at each time point was to be claimed if the upper limit of the 95% CI did not exceed 0 mmHg at all time points of each of the 3 visits during the efficacy evaluation (Visits 4, 5, and 6).

To supplement the primary analyses, the analyses above were repeated for the PP population. Any discrepancy between the ITT and PP analyses was to be explained.

Safety Analysis

Safety analyses were based on the safety analysis set. The safety analyses set included all subjects who were confirmed to have received the study drug. All subjects in the safety analysis set were analyzed according to the treatment received.

Safety parameters included the following: recording of adverse events, vital sign measurements (resting blood pressure and pulse measured in the same arm at each visit), BCVA results, slit-lamp examination findings, conjunctival hyperemia assessment, ophthalmoscopy findings, pachymetry results, and specular microscopy (at select US sites only).

AEs were coded using Medical Dictionary for Regulatory Activities (MedDRA) dictionary version 13.0. All AEs collected with start dates following the first administration of study drug or that worsen following the first administration of study drug were considered treatment-emergent adverse events (TEAEs).

Treatment-emergent non-ocular AEs were summarized using discrete summaries at the subject and event level by system organ class (SOC) and preferred term (PT) for each treatment group. Treatment-emergent ocular AEs were summarized for study eyes, treated fellow eyes, and non-treated fellow eyes separately by treatment groups.

TEAEs were summarized by relationship to study drug. Relationship of AEs to study drug may have been classified as unrelated, unlikely, possibly, probably, or definitely related. Subjects with more than 1 occurrence of the same non-ocular PT were counted only once under the maximum relationship to the study drug. Ocular AEs were summarized for study eyes, treated fellow eyes, and non-treated fellow eyes separately. Eyes with more than 1 occurrence of the same PT were counted only once under the maximum relationship to the study drug.

TEAEs were summarized by severity. Severity of AEs may have been classified by the Investigator as “Mild”, “Moderate”, or ‘Severe”. Subjects with more than 1 occurrence

of the same non-ocular PT were counted only once under the maximum severity. Ocular AEs were summarized for study eyes, treated fellow eyes, and non-treated fellow eyes separately. Eyes with more than 1 occurrence of the same PT were counted only once under the maximum severity. AEs with unknown severity were counted as severe. Systolic (SBP), diastolic (DBP), and heart rate (HR) were summarized by visit using descriptive statistics.

Other safety data, including BCVA, conjunctival hyperemia, slit lamp biomicroscopy, and ophthalmoscopy were presented for study eyes, treated fellow eyes, and non-treated fellow eyes separately.

Protocol Amendments

The original protocol, dated September 8, 2012, was amended 3 times. None of the changes was considered to have impacted the results of the study.

Data Quality and Integrity: Sponsor's Assurance

Bausch & Lomb Global Clinical Operations representatives were to be allowed to visit all study site locations to assess the data, quality, and study integrity in a manner consistent with applicable health authority regulations and the procedures adopted by Bausch & Lomb Global Clinical Operations.

Monitoring visits and telephone consultations occurred as necessary during the course of the investigation to verify the following:

- The rights and well-being of subjects were protected.
- The conduct of the investigation was in compliance with the currently approved protocol/amendment, ICH GCPs, and IRB/EC requirements.
- The integrity of the data, including adequate study documentation.
- The facilities remained acceptable.
- The Investigator and site personnel remained qualified and able to conduct the study.
- Study drug accountability.

During the course of the study, if Bausch & Lomb determined that an Investigator was non-compliant with the study plan and/or applicable regulatory requirements, Bausch & Lomb were to take action to secure compliance.

6.2.2. Study Results

Compliance with Good Clinical Practices

This study was conducted in compliance with the study protocol and in accordance with

Good Clinical Practices (GCPs), as described in the International Conference on Harmonization (ICH) Harmonized Tripartite Guidelines for GCP, the US Code of Federal Regulations dealing with clinical studies (21 CFR Parts 11, 50, 54, 56, and 312), the ethical principles in the Declaration of Helsinki, and applicable local regulations.

Financial Disclosure

The applicant has adequately disclosed financial arrangements with clinical investigators as recommended in the FDA guidance for industry on *Financial Disclosure by Clinical Investigators.*

There is no evidence to suggest that any of the investigators/sub-investigators had any financial interests or arrangements with the applicant.

Patient Disposition

Table 6.2.2.-1
Subject Disposition
and Primary Reason for Discontinuation

Subject Disposition	Latanoprostene 0.024%	Timolol Maleate 0.5% Crossover to Latanoprostene 0.024%	Total
Randomized Population[a], N	286	134	420
Efficacy Phase[b]			
Completed, n (%)	264 (92.3)	123 (91.8)	387 (92.1)
Discontinued, n (%)	22 (7.7)	11 (8.2)	33 (7.9)
Entire Study[c]			
Completed, n (%)	250 (87.4)	110 (82.1)	360 (85.7)
Discontinued, n (%)	36 (12.6)	24 (17.9)	60 (14.3)
ITT Population, N	284	133	417
Efficacy Phase			
Completed, n (%)	264 (93.0)	123 (92.5)	387 (92.8)
Discontinued, n (%)	20 (7.0)	10 (7.5)	30 (7.2)
Entire Study			
Completed, n (%)	250 (88.0)	110 (82.7)	360 (86.3)
Discontinued, n (%)	34 (12.0)	23 (17.3)	57 (13.7)
Per-Protocol Population, N	192	80	272
Efficacy Phase			
Completed, n (%)	191 (99.5)	80 (100.0)	271 (99.6)
Discontinued, n (%)	1 (0.5)	0	1 (0.4)
Entire Study			
Completed, n (%)	182 (94.8)	69 (86.3)	251 (92.3)
Discontinued, n (%)	10 (5.2)	11 (13.8)	21 (7.7)
Safety Population, N	283	135	418

Subject Disposition	Latanoprostene 0.024%	Timolol Maleate 0.5% Crossover to Latanoprostene 0.024%	Total
Efficacy Phase			
Completed, n (%)	263 (92.9)	124 (91.9)	387 (92.6)
Discontinued, n (%)	20 (7.1)	11 (8.1)	31 (7.4)
Entire Study			
Completed, n (%)	249 (88.0)	111 (82.2)	360 (86.1)
Discontinued, n (%)	34 (12.0)	24 (17.8)	58 (13.9)
Reasons for Discontinuation in Efficacy Phase (ITT Population)			
Withdraw consent, n (%)	9 (3.2)	4 (3.0)	7 (1.7)
Lost to follow-up, n (%)	2 (0.7)	1 (0.8)	3 (0.7)
Adverse event, n (%)	7 (2.5)	8 (6.0)	15 (3.6)
Investigator decision, n (%)	2 (0.7)	2 (1.5)	4 (107)
Failure to follow the required study procedures, n (%)	3 (1.1)	2 (1.5)	5 (1.2)
Other, n (%)	11 (3.9)	6 (4.5)	17 (4.1)

[a] The randomized population comprised of all randomized subjects.
[b] The efficacy phase spanned from Visit 3 (eligibility, day of first dose) up to and including Visit 6 (Month 3). For the Safety and PP populations, the actual treatment group in the efficacy phase was the treatment received the most in the efficacy phase.
[c] Both efficacy and safety phases.
Source: Table 10-1

Protocol Violations/Deviations

Table 6.2.2.-2
Major Protocol Violations in the Efficacy Phase
Randomized Population

Violation Description	Latanoprostene 0.024% N=286 n (%)	Timolol Maleate 0.5% N=134 n (%)	Total N=420 n (%)
Subject's visit fell outside visit window	66 (23.1)	47 (35.1)	113 (26.9)
Subject missed IOP assessment before month 3	21 (7.3)	11 (8.2)	32 (7.6)
Subject took disallowed medication	9 (3.1)	3 (2.2)	12 (2.9)
Subject missed doses	5 (1.7)	3 (2.2)	8 (1.9)
Subject's treatment compliance <80% or >120%	4 (1.4)	3 (2.2)	7 (1.7)
Subject had disallowed change to concomitant medication	4 (1.4)	1 (0.7)	5 (1.2)
Other violations	4 (1.4)	1 (0.7)	5 (1.2)
Inclusion/exclusion violation	2 (0.7)	0	2 (0.5)
Subject received wrong treatment	1 (0.3)	0	1 (0.2)

Source: Table 10-3

Table of Demographic Characteristics

Table 6.2.2.-3
Demographics and Baseline Characteristics
ITT Population

Demographic Variable		Latanoprostene 0.024% N=284	Timolol Maleate 0.5% Crossover to Latanoprostene 0.024% N=133	Total N=417
Age (years)				
	n	284	133	417
	Mean (SD)	64.7 (10.32)	63.1 (11.23)	64.2 (10.63)
	Median	65.0	64.0	65.0
	Range: Min, Max	22, 88	23, 83	23, 88
Age Group, n (%)				
	< 65 years	138 (48.6)	67 (50.4)	205 (49.2)
	≥ 65 years	146 (51.4)	66 (49.6)	212 (50.8)
Sex, n (%)				
	Male	118 (41.5)	56 (42.1)	174 (41.7)
	Female	166 (58.5)	77 (57.9)	243 (58.3)
Race, n (%)				
	White	217 (76.4)	108 (81.2)	325 (77.9)
	Black/African American	64 (22.5)	24 (18.0)	88 (21.1)
	American Indian/ Alaskan Native	0	0	0
	Asian	1 (0.4)	1 (0.8)	2 (0.5)
	Native Hawaiian/Pacific Islander	0	0	0
	Other	2 (0.7)	0	2 (0.5)
Ethnicity, n (%)				
	Hispanic or Latino	30 (10.6)	13 (9.8)	43 (10.3)
	Not Hispanic and not Latino	254 (89.4)	120 (90.2)	374 (89.7)
Treatment-Naïve[a] Subject, n (%)				
	Yes	83 (29.2)	34 (25.6)	117 (28.1)
	No	201 (70.8)	99 (74.4)	300(71.9)

[a] A subject was considered treatment-naïve if he or she did not require a washout period (i.e., had no documented IOP lowering medication in the medical history 30 days prior to Visit 1)
Source: Table 10-1

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Baseline study eye characteristics are presented for the ITT population in Table 6.2.2.-4.

Table 6.2.2.-4
Baseline Study Eye Characteristics
ITT Population

Baseline Characteristic		Latanoprostene 0.024% N=284	Timolol Maleate 0.5% Crossover to Latanoprostene 0.024% N=133	Total N=417
Mean Corneal Thickness (microns)				
	Mean (SD)	546.32 (31.77)	549.64 (31.10)	547.38 (31.56)
	Median	548.66	550.66	549.00
	Range: Min, Max	409, 598.66	461, 597.00	409, 598.66
Refraction sphere (diopters)				
	Mean (SD)	-0.45 (2.57)	-0.76 (2.63)	-0.55 (2.59)
	Median	0	-0.250	0
	Range: Min, Max	-18.00, 5.50	-12.25, 4.25	-18.00, 5.5
Refraction Cylinder (diopter)				
	Mean (SD)	0.13 (1.05)	0.25 (1.06)	0.17 (1.06)
	Median	0	0.250	0
	Range: Min, Max	-5.50, 3.25	-3.00, 4.00	-5.50, 4.00
Iris Color				
	Blue	68 (23.9)	41 (30.8)	109 (26.1)
	Brown	171 (60.2)	68 (51.1)	239 (57.3)
	Green	12 (4.2)	6 (4.5)	18 (4.3)
	Hazel	32 (11.3)	17 (12.8)	49 (11.8)
	Other	1 (0.4)	1 (0.8)	2 (0.5)
Source: Table 11-2				

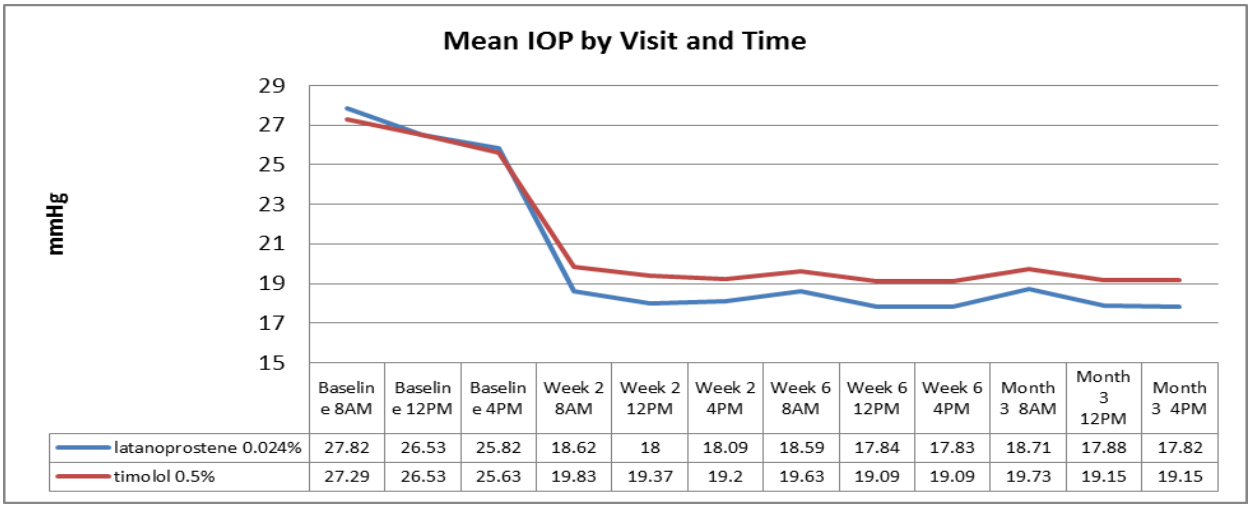
Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment compliance between the two treatment groups was comparable.

The majority of subjects (384 subjects; 91.9%) in the safety population reported receiving at least 1 concomitant medication. The most commonly reported concomitant medications included 3-hydroxy-3-methylgutaryl-coenzyme A (HMG CoA) reductase inhibitors (161 subjects; 38.5%), platelet aggregation inhibitors (excluding heparin) (123 subjects; 29.4%), ACE inhibitors (plain) (104 subjects; 24.9%), multivitamins (plain) (73 subjects; 17.5%), and biguanides (67 subjects; 16.0%).
Rescue medications were not used in this study.

Efficacy Results – Primary Endpoint

Figure 6.2.2.-1 Study #769 - ITT Population

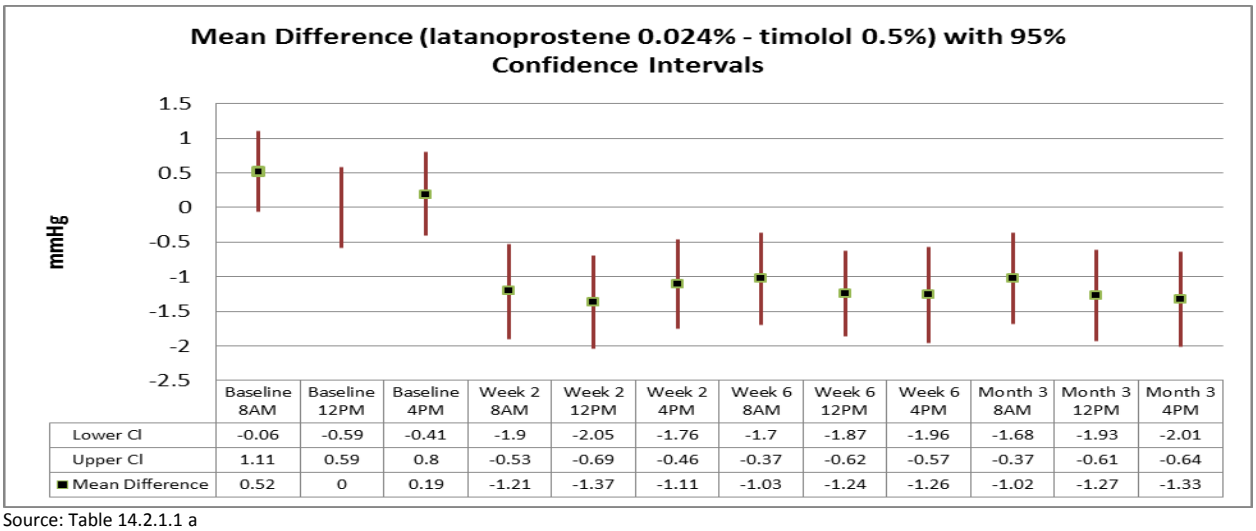


	Baseline 8AM	Baseline 12PM	Baseline 4PM	Week 2 8AM	Week 2 12PM	Week 2 4PM	Week 6 8AM	Week 6 12PM	Week 6 4PM	Month 3 8AM	Month 3 12PM	Month 3 4PM
latanoprostene 0.024%	27.82	26.53	25.82	18.62	18	18.09	18.59	17.84	17.83	18.71	17.88	17.82
timolol 0.5%	27.29	26.53	25.63	19.83	19.37	19.2	19.63	19.09	19.09	19.73	19.15	19.15

Source: Table 14.2.1.1 a

Reviewer's Comment: *Baseline mean IOP of the two treatment groups are similar. The mean IOP for latanoprostene 0.024% and timolol 0.5% are similar at all time points measured.*

Figure 6.2.2.-2 Study #769 - ITT Population

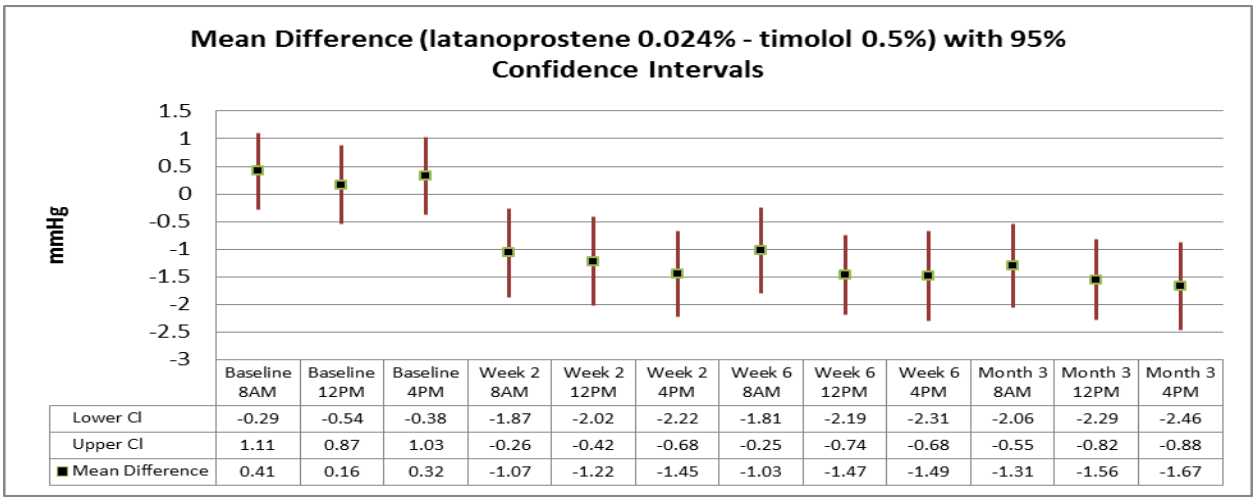


	Baseline 8AM	Baseline 12PM	Baseline 4PM	Week 2 8AM	Week 2 12PM	Week 2 4PM	Week 6 8AM	Week 6 12PM	Week 6 4PM	Month 3 8AM	Month 3 12PM	Month 3 4PM
Lower CI	-0.06	-0.59	-0.41	-1.9	-2.05	-1.76	-1.7	-1.87	-1.96	-1.68	-1.93	-2.01
Upper CI	1.11	0.59	0.8	-0.53	-0.69	-0.46	-0.37	-0.62	-0.57	-0.37	-0.61	-0.64
Mean Difference	0.52	0	0.19	-1.21	-1.37	-1.11	-1.03	-1.24	-1.26	-1.02	-1.27	-1.33

Source: Table 14.2.1.1 a

Reviewer's Comment: *The mean IOP of the two treatment groups are comparable. The mean IOP values (latanoprostene 0.024% QD minus timolol 0.5% BID) and the upper confidence intervals are within 1 mmHg at a majority of the time points.*

Figure 6.2.2.-3 Study #769 – PP Population



	Baseline 8AM	Baseline 12PM	Baseline 4PM	Week 2 8AM	Week 2 12PM	Week 2 4PM	Week 6 8AM	Week 6 12PM	Week 6 4PM	Month 3 8AM	Month 3 12PM	Month 3 4PM
Lower CI	-0.29	-0.54	-0.38	-1.87	-2.02	-2.22	-1.81	-2.19	-2.31	-2.06	-2.29	-2.46
Upper CI	1.11	0.87	1.03	-0.26	-0.42	-0.68	-0.25	-0.74	-0.68	-0.55	-0.82	-0.88
Mean Difference	0.41	0.16	0.32	-1.07	-1.22	-1.45	-1.03	-1.47	-1.49	-1.31	-1.56	-1.67

Source: Table 14.2.1.1 a

Reviewer's Comment: *The analysis of the PP population is similar to that of the ITT population.*

Data Quality and Integrity – Reviewers' Assessment

This submission is of sufficient quality to allow for a substantive review. No issues related to data quality or data integrity were identified in this review.

Efficacy Results – Secondary and other relevant endpoints

The key endpoint to evaluate reduction of intraocular pressure is mean IOP. This was performed in the primary efficacy endpoint analyses. The secondary endpoint analyses are exploratory. The Applicant does not plan to make labeling claims based on pre-specified secondary and other endpoints.

Dose/Dose Response

Study #659 was a dose-ranging study that evaluated four doses (0.006%, 0.012%, 0.024%, and 0.040%) of latanoprostene bunod ophthalmic solution compared to latanoprost 0.005% in subjects with open-angle glaucoma or ocular hypertension. The study identified the 0.024% dose as the optimal dose to develop based on a risk-benefit analysis.

Durability of Response

The mean IOP reduction for each of the time points 8AM, 12PM, and 4PM over the three month evaluation period were similar. For more details, see Figure 6.2.2-1.

Persistence of Effect

Latanoprostene bunod ophthalmic solution 0.024% is intended to treat a chronic condition.

Additional Analyses Conducted on the Individual Trial

The key endpoint to evaluate reduction of intraocular pressure is mean IOP. This was performed in the primary efficacy endpoint analyses. Additional analyses are not necessary.

7 Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

7.1.1. Primary Endpoints

Intraocular pressure (IOP) is currently the accepted standard for establishing the efficacy of ocular hypotensive medications. The primary efficacy endpoint for studies #770 and #769 were the same. The primary endpoint was mean IOP measured at multiple time points that are intended to capture the peak and trough of latanoprostene bunod ophthalmic solution 0.024% dosed once daily (QD)in the evening, but did not capture the peak for the active- control, timolol maleate 0.5% dosed twice-daily (BID). Study #770 demonstrated that latanoprostene bunod ophthalmic solution 0.024% was non-inferior to timolol maleate ophthalmic solution 0.5% at the time points measured. The efficacy results were replicated in study #769.

7.1.2. Secondary and Other Endpoints

The key endpoint to evaluate reduction of intraocular pressure is IOP. This was performed in the primary efficacy endpoint analyses. The secondary endpoint analyses are exploratory. The Applicant does not plan to make labeling claims based on pre-specified secondary and other endpoints.

7.1.3. Subpopulations

The difference in mean IOP observed in subjects treated with latanoprostene 0.024% QD versus subjects treated with timolol 0.5% BID in studies #770 and #769 were comparable. The amount of reduction in IOP was consistent across all relevant subpopulations including age, sex, race/ethnicity, and geographic region.

7.1.4. Dose and Dose-Response

Study #659 was a dose-ranging study that evaluated four doses (0.006%, 0.012%, 0.024%, and 0.040%) of latanoprostene bunod ophthalmic solution compared to latanoprost 0.005% in subjects with open-angle glaucoma or ocular hypertension. The study identified the 0.024% dose as the optimal dose to develop based on a risk-benefit analysis.

7.1.5. Onset, Duration, and Durability of Efficacy Effects

Intraocular pressure was measured at three time points (8AM, 12PM, and 4PM) at Baseline, Week 3, Week 6, and Month 3 in studies #770 and #769. The mean IOP reduction for each of the time points 8AM, 12PM, and 4PM over the three month evaluation period were similar. For more details, see Figures 6.1.2-1 and 6.2.2-1.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

No potential efficacy issues in the postmarket setting have been identified.

7.2.2. Other Relevant Benefits

There are no other relevant benefits for this drug product.

7.3. Integrated Assessment of Effectiveness

The data contained in this submission establishes the efficacy of latanoprostene bunod ophthalmic solution 0.024% dosed once daily in the evening for the treatment of elevated IOP in open-angle glaucoma or ocular hypertension.

Studies #770 and #769 demonstrate that the IOP lowering ability of latanoprostene bunod ophthalmic solution 0.024% does not differ from timolol maleate ophthalmic solution 0.5% by a clinically significant amount. Latanoprostene bunod ophthalmic solution 0.024% lowers IOP by a clinically significant amount.

The benefit of latanoprostene bunod ophthalmic solution 0.024% for the treatment of elevated IOP in open-angle glaucoma or ocular hypertension has been demonstrated in this NDA application. The efficacy of this drug is consistent with the currently marketed prostaglandin analogues.

8 Review of Safety

8.1. Safety Review Approach

The safety database consists of two phase 1 studies (Studies 809 and 849), four phase 2 studies (A9441001 and A9441003 [studies conducted by Pfizer], Study 659, and Study 803), three phase 3 studies (Studies 769, 770, and 811), and one ongoing phase 1 study (Study 874). The total all exposed safety population which includes all subjects exposed to at least one dose of latanoprostene ophthalmic solution 0.024% or higher, including phase 1 studies is 1,335 subjects (0.024% = 1165 and 0.040%=170). The total phase2/3 pooled safety population is 1,289 subjects (0.024% = 1119 and 0.040%=170). The safety data from these studies were reviewed.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

Table 8.2.1-1
Safety Population
(All Exposed Subjects[a])

Study	Latanoprostene Bunod			Latanoprost	Timolol Maleate
	0.024%	0.040%	ALL	0.005%	0.5%
849	24		24		
809	22		22		
A9441001 Stage 1 Stage 2	43	60	103	73	
A9441003	29	29	58	30	
659	83	81	164	82	
803	23		23		23

Study	Latanoprostene Bunod			Latanoprost	Timolol Maleate
769	406		406		135
770	406		406		136
811	130		130		
Total Subjects	**1165**	**170**	**1336**	**185**	**294**

[a] All subjects who received at least 1 dose of latanopostene ophthalmic solution 0.024% or higher.

Table 8.2.1.-2
Summary of Duration of Exposure
(All Exposed Subjects[a])

Study				Latanoprost	Timolol Maleate
	Phase 1 0.024% (N=46)	**0.024% (N=1119)**	**0.040% (N=170)**	**0.005% (N=185)**	**0.5% (N=294)**
Duration of exposure (days)					
N	46	1119	170	185	294
Mean (SD)	19.9 (8.42)	213.2 (131.03)	28.3 (2.55)	27.9 (3.74)	85.6 (23.27)
Median	14.0	189.0	28.0	28.0	92.0
Min, Max	1, 29	1, 385	2, 36	1, 36	3, 117
Subject-year of exposure	2.5	653.7	13.2	14.0	68.9
Duration category (days) (n, %)					
1 to ≤ 28	27 (58.7)	146 (13.0)	103 (60.6)	115 (62.2)	18 (6.1)
29 to ≤ 66	19 (41.3)	73 (6.5)	67 (39.4)	70 (37.8)	21 (7.1)
67 to ≤ 135	0	148 (13.2)	0	0	255 (86.7)
136 to ≤ 225	0	263 (23.5)	0	0	0
226 to ≤ 318	0	119 (10.6)	0	0	0
≥ 319	0	370 (33.1)	0	0	0

[a] All subjects who received at least 1 dose of latanoprostene ophthalmic solution 0.024% or higher.

8.2.2. Relevant characteristics of the safety population:

The safety population is representative of the population that the drug product is intended to treat. The safety population included primarily subjects with open-angle glaucoma or ocular hypertension. Some healthy volunteers were also included.

8.2.3. Adequacy of the safety database:

The safety database is adequate with respect to size, duration of exposure, duration of treatment, patient demographics, and disease characteristics.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

This submission was of sufficient quality to allow for a substantive review. No issues related to data quality or data integrity were identified in this review.

8.3.2. Categorization of Adverse Events

The Integrated Summary of Safety (ISS) analyzes the reported treatment-emergent adverse events (TEAEs). These were defined as adverse events (AEs) known to start or worsen following the administration of first dose of the study drug but on or before 30 days after the last administration of study drug.

Adverse events were coded according to the Medical Dictionary for Regulatory Activities (MedDRA®). All calculations were performed using the preferred term (PT) by system organ class (SOC). The most recent version of MedDRA (MedDRA version 17.1) was used to generate all the AE tables for the ISS.

8.3.3. Routine Clinical Tests

The routine clinical testing to evaluate safety concerns for latanoprostene bunod ophthalmic solution 0.024% was adequately addressed in the design and conduct of the clinical trials.

8.4. Safety Results

8.4.1. Deaths

One death was reported during study #770 (subject 7701307181748). One subject who was treated with latanoprostene in study #769 died of sepsis after exiting from the study (subject 7691307851321).

Table 8.4.1.-1
Deaths in the Safety Population

Study #	Patient #	Age (yrs)	Treatment	Time on treatment	Cause of death/Event
770	7701307181748	68	latanoprostene	4 months	Myocardial ischemia

8.4.2. Serious Adverse Events

Table 8.4.2.-1
Ocular Serious Adverse Events

(Phase 2/3 Pooled)

Adverse Event	Latanoprostene Bunod 0.024% (N=1073) n (%)	Latanoprost 0.005% (N=162) n (%)	Timolol Maleate 0.5% (N=292) n (%)
OCULAR			
General disorders and administration site conditions	**1 (0.1)**	**0**	**0**
Device dislocation	1 (0.1)	0	0

Source: ISS Table 10-25

Table 8.4.2.-2
Non-Ocular Serious Adverse Events
(Phase 2/3 Pooled)

Adverse Event	Latanoprostene Bunod 0.024% (N=1119) n (%)	Latanoprost 0.005% (N=185) n (%)	Timolol Maleate 0.5% (N=294) n (%)
NONOCULAR			
Cardiac Disorders	**1 (0.1)**	**1 (0.5)**	**0**
Acute myocardial infarction	0	1 (0.5)	0
Coronary artery disease	1 (0.1)	0	0
Gastrointestinal Disorders	**0**	**1 (0.5)**	**0**
Gastric ulcer	0	0	0
Gastric ulcer hemorrhage	0	1(0.5)	0
Gastrointestinal hemorrhage	0	0	0
General Disorders and Administration Site Conditions	**2 (0.2)**	**0**	**0**
Chest pain	2 (0.2)	0	0
Hepatobiliary Disorders	**1 (0.1)**	**0**	**0**
Cholelithiasis	1 (0.1)	0	0
Immune System Disorder	**1 (0.1)**	**0**	**0**
Food allergy	1 (0.1)	0	0
Infections and Infestations	**2 (0.2)**	**0**	**0**
Pneumonia	1 (0.1)	0	0
Vestibular neuronitis	1 (0.1)	0	0
Injury, Poisoning and Procedural Complications	**14 (1.3)**	**0**	**1 (0.3)**
Ankle fracture	1 (0.1)	0	0
Arthropod bite	0	0	1 (0.3)
Fall	3 (0.3)	0	0
Femoral neck fracture	1 (0.1)	0	0
Fibula fracture	1 (0.1)	0	0
Head injury	1 (0.1)	0	0
Joint dislocation	2 (0.2)	0	0
Road traffic accident	1 (0.1)	0	0

Adverse Event	Latanoprostene Bunod 0.024% (N=1119) n (%)	Latanoprost 0.005% (N=185) n (%)	Timolol Maleate 0.5% (N=294) n (%)
Scapula fracture	1 (0.1)	0	0
Subdural hemorrhage	1 (0.1)	0	0
Tibia fracture	1 (0.1)	0	0
Ulna fracture	1 (0.1)	0	0
Musculoskeletal and Connective Tissue Disorders	**1 (0.1)**	**0**	**1 (0.3)**
Arthralgia	1 (0.1)	0	0
Rotator cuff syndrome	0	0	1 (0.3)
Neoplasms Benign, Malignant and Unspecified (including cysts and polyps)	**5 (0.4)**	**0**	**0**
Breast cancer recurrent	1 (0.1)	0	0
Gastric cancer	1 (0.1)	0	0
Lung adenocarcinoma	1 (0.1)	0	0
Lung neoplasm malignant	2 (0.2)	0	0
Nervous System Disorders	**5 (0.4)**	**0**	**0**
Aphasia	1 (0.1)	0	0
Convulsion	1 (0.1)	0	0
Coordination abnormal	1 (0.1)	0	0
Dizziness	1 (0.1)	0	0
Subarachnoid hemorrhage	1 (0.1)	0	0
Renal and Urinary Disorders	**1 (0.1)**	**0**	**0**
Hydronephrosis	1 (0.1)	0	0
Skin and Medical Procedures	**1 (0.1)**	**0**	**0**
Angioedema	1 (0.1)	0	0
Vascular Disorders	**1 (0.1)**	**0**	**0**
Hypertension	1 (0.1)	0	0

Source: ISS Table 10-24

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

Table 8.4.3.-1
Discontinuations Due to Adverse Events
(Phase 2/3 Pooled)

Adverse Event	Treatment	Patient Number	Study Number
Exacerbation of asthma	Latanoprostene 0.006%	6591601511348	659
Pain and burning sensation after drug application	Latanoprostene 0.040%	6592301471311	659
Headache, dyspnea, tachycardia	Latanoprost 0.005%	6592301471555	659
Ocular burning post dose	Latanoprostene 0.012%	6594426651165	659
Ophthalmic migraine	Latanoprostene 0.006%	6595739421365	659
Allergic reaction hyperemia and swelling	Latanoprostene 0.024%	6598592951195	659

Adverse Event	Treatment	Patient Number	Study Number
after instillation			
Pain in left eye	Latanoprostene 0.040%	6599152401197	659
Acute myocardial infarction	Latanoprost 0.005%	6599212341233	659
Allergic conjunctivitis	Latanoprostene 0.024%	7691400691388	769
Dizziness	Latanoprostene 0.024%	7692307911193	769
Chemosis, conjunctival irritation	Latanoprostene 0.024%	7692307911558	769
Increased IOP	Timolol 0.5%	7692308291462	769
Erythema and swelling of eyelid	Timolol 0.5%	7692401621331	769
Elevated IOP	Timolol 0.5%	7695046071032	769
Burning upon instillation	Timolol 0.5%	7695915451272	769
Fatigue	Latanoprostene 0.024%	7695915451559	769
Elevated IOP	Latanoprostene 0.024%	7697344071516	769
Worsening of ocular allergies	Timolol 0.5%	7697344071538	769
Elevated IOP	Timolol 0.5%	7697563881144	769
Scleritis	Latanoprostene 0.024%	7697563881164	769
Allergic conjunctivitis	Timolol 0.5%	7697843611474	769
Right upper lobe lung cancer	Timolol 0.5%/ Latanoprostene 0.024%	7699621931066	769
Dislocated intraocular lens implant	Timolol 0.5%/ Latanoprostene 0.024%	7699781771464	769
Increased insomnia, chest tightness, increased inhaler use for breathing due to asthma	Latanoprostene 0.024%	7701207821417	770
Blurriness intermittent, burning sensation after drug instillation and intermittent during the day, eye pain intermittent, headache	Latanoprostene 0.024%	7701500361254	770
Dizziness, drowsiness, frontal headache	Timolol 0.5%	7701607771179	770
Allergy to study eyedrops	Timolol 0.5%/ Latanoprostene 0.024%	7702304151305	770
Patient reported ocular redness	Latanoprostene 0.024%	7703300421096	770
Ocular redness	Timolol 0.5%/ Latanoprostene 0.024%	7703300421211	770
Periocular rash	Latanoprostene 0.024%	7703300421294	770
Superficial punctate keratitis	Timolol 0.5%/ Latanoprostene 0.024%	7703601311007	770
Nausea, sweating	Latanoprostene 0.024%	803-290280-1014	803
Stomach cancer	Latanoprostene 0.024%	8111807621466	811
Lung cancer	Latanoprostene 0.024%	8112307441408	811
Lung adnocarcinoma	Latanoprostene 0.024%	8112307481304	811
Cataract progressive	Latanoprostene 0.024%	8112407411214	811
Bulbar conjunctiva hyperemia	Latanoprostene 0.024%	A944100310021011	A9441003

Source: ISS Listing 12

8.4.4. **Significant Adverse Events**

Refer to Section 8.3.2

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

Table 8.4.5.-1
Treatment-Emergent Adverse Events
Occurring in ≥ 2% of Subjects in Any Treatment Group
(Phase2/3 Pooled)

Adverse Event	Latanoprostene Bunod 0.024% N=1119 n (%)	Latanoprost 0.005% N=185 n (%)	Timolol Maleate 0.005% N=294 n (%)
OCULAR			
Eye Disorders	**278 (24.8)**	**28 (15.1)**	**35 (11.9)**
Conjunctival hyperemia	87 (7.8)	5 (2.7)	4 (1.4)
Eye irritation	51 (4.6)	4 (2.2)	7 (2.4)
Eye pain	33 (2.9)	1 (0.5)	6 (2.0)
Ocular hyperemia	20 (1.8)	9 (4.9)	2 (0.7)
Punctate keratitis	17 (1.5)	3 (1.6)	4 (1.4)
General Disorders and Administration Site Conditions	**60 (5.4)**	**5 (2.7)**	**8 (2.7)**
Instillation site pain	42 (3.8)	5 (2.7)	6 (2.0)
NONOCULAR			
Infections and Infestations	**122 (10.9)**	**5 (2.7)**	**18 (6.1)**
Nasopharyngitis	53 (4.7)	2 (1.1)	4 (1.4)

Source: ISS Tables 10-1

Reviewer's Comments:
The most common ocular adverse events (pooled) were conjunctival/ocular hyperemia (10%) and eye irritation (5%). The most common nonocular adverse event was nasopharyngitis (5%).

8.4.6. Laboratory Findings

Clinical laboratory assessments were not conducted in Studies 849, 659, 803, 811, 769 or 770. Studies A9441001, A9441003, and 809 did include clinical laboratory assessments. No clinically significant differences from baseline were observed in the data that was collected.

8.4.7. Vital Signs

The median values for systolic blood pressure, diastolic blood pressure, and heart rate values for subjects in the latanoprostene bunod ophthalmic solution 0.024% group at Baseline were

130.0 and 78.0, and 70.0, respectively. No clinically significant changes in vital signs were observed in any of the treatment groups.

8.4.8. Electrocardiograms (ECGs)

EKGs were not collected in any of the studies conducted in the clinical development program.

8.4.9. QT

QT studies were not performed.

8.4.10. Immunogenicity

There is no known potential to cause immunogenicity.

8.5. Analysis of Submission-Specific Safety Issues

No specific safety issues were identified for the submission.

8.6. Specific Safety Studies/Clinical Trials

No special safety studies were performed during the clinical development program.

8.7. Additional Safety Explorations

8.7.1. Human Carcinogenicity or Tumor Development

There is no data to suggest that latanoprostene bunod has any tumorigenic potential.

8.7.2. Human Reproduction and Pregnancy

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.

8.7.3. Pediatrics and Assessment of Effects on Growth

Effects on growth were not evaluated.

8.7.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

There is no evidence for the potential for overdose or potential abuse with latanoprostene bunod ophthalmic solution.

8.8. Safety in the Postmarket Setting

8.8.1. Safety Concerns Identified Through Postmarket Experience

Latanoprostene bunod ophthalmic solution 0.024% is not a marketed product; there is no post-marketing experience with this product.

8.8.2. Expectations on Safety in the Postmarket Setting

Latanoprostene bunod is a prostaglandin analogue, F2-alpha receptor agonist. 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 recommended labeling.

8.9. Additional Safety Issues From Other Disciplines

There are no specific safety concerns from other disciplines.

8.10. Integrated Assessment of Safety

The safety database contained in this submission establishes the safety of latanoprostene bunod ophthalmic solution 0.024% dosed once daily in the evening for the treatment of elevated IOP in open-angle glaucoma or ocular hypertension.

The safety profile of latanoprostene bunod ophthalmic solution 0.024% is similar to other marketed topical prostaglandin analogues. The risk for using this drug is consistent with the currently marketed prostaglandin analogues. The most common ocular adverse events were conjunctival/ocular hyperemia (10%) and eye irritation (5%)

9 Advisory Committee Meeting and Other External Consultations

No Advisory Committee Meeting was required or convened for this NDA. There are multiple drug products in this drug class, prostaglandin analogues marketed in the United States.

10 Labeling Recommendations

10.1. Prescribing Information

See labeling recommendations under Section 13.3.

10.2. Patient Labeling

No Medication Guide, patient package insert, or instructions for use is recommended.

10.3. Nonprescription Labeling

Not applicable. This is a prescription NDA.

11 Risk Evaluation and Mitigation Strategies (REMS)

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

11.1. Safety Issue(s) that Warrant Consideration of a REMS

Not applicable.

11.2. Conditions of Use to Address Safety Issue(s)

Not applicable.

11.3. Recommendations on REMS

Not applicable.

12 Postmarketing Requirements and Commitments

There are no recommended Postmarketing Requirements or Phase 4 Commitments.

13 Appendices

13.1. References

An independent literature review was not conducted for this application.

13.2. Financial Disclosure

Clinical Investigator Financial Disclosure
Review Template

Application Number: NDA 207795

Submission Date(s): July 21, 2015

Applicant: Bausch & Lomb Inc.

Product: Latanoprostene bunod Ophthalmic Solution 0.024%

Reviewer: Lucious Lim, MD, MPH, Medical Officer

Date of Review: April 14, 2016

Covered Clinical Study (Name and/or Number):

- Study #769
- Study #770

Covered Clinical Study (Name and/or Number): Study #769

Was a list of clinical investigators provided:	Yes X	No ☐ (Request list from Applicant)
Total number of investigators identified: 48		
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 3455): 2		
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)): 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: 2 Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial	Yes X	No ☐ (Request details from Applicant)

interests/arrangements:		
Is a description of the steps taken to minimize potential bias provided:	Yes X	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 2		
Is an attachment provided with the reason:	Yes X	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): Study #770

Was a list of clinical investigators provided:	Yes X	No ☐ (Request list from Applicant)
Total number of investigators identified: 44		
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 3455): 1		
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)): 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: 1 Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes X	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes X	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 1		
Is an attachment provided with the reason:	Yes X	No ☐ (Request explanation from Applicant)

13.3. Labeling

NDA 207795 is recommended for approval with the labeling revisions found in this review.

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/

LUCIOUS LIM
04/21/2016

WILLIAM M BOYD
04/21/2016

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 207795 **Applicant:** Bausch & Lomb Inc. **Stamp Date:** July 21, 2015

Drug Name: Vesneo (latanoprostene bunod ophthalmic solution) 0.024% **NDA/BLA Type:** NDA

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

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.				eCTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2).				505(b)(1)
505(b)(2) Applications					
13.	If appropriate, what is the reference drug?				
14.	Did the applicant provide a scientific bridge demonstrating the relationship between the proposed product and the referenced product(s)/published literature?				
15.	Describe the scientific bridge (e.g., BA/BE studies)				
DOSE					
16.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: #659 Study Title: A Randomized, Multicenter, Single-Masked, Parallel-Group Dose Finding Study Comparing the Safety and Efficacy of BOL-303259-X (0.006%, 0.012%, 0.024% and 0.040%) to Latanoprost 0.005% in Subjects	X			

	Content Parameter	Yes	No	NA	Comment
	With Open Angle Glaucoma or Ocular Hypertension Sample Size: 413 Arms: 5 Location in submission: Section 5.3.5.1				
EFFICACY					
17.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 #769 Indication: reduction of IOP in patients with open angle glaucoma or ocular hypertension Pivotal Study #2 #770 Indication: reduction of IOP in patients with open angle glaucoma or ocular hypertension	X			
18.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
19.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
20.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	
SAFETY					
21.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
22.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			X	
23.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
24.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?	X			
25.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
26.	Has the applicant submitted the coding dictionary[2] used for		X		

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	mapping investigator verbatim terms to preferred terms?				
27.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
28.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
29.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			X	
30.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
31.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			
ABUSE LIABILITY					
32.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
33.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS					
34.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
35.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
36.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
37.	Are all datasets to support the critical safety analyses available and complete?	X			
38.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			X	
CASE REPORT FORMS					
39.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
40.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	
FINANCIAL DISCLOSURE					
41.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
42.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

(verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ___ Yes_____

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

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

None.

Lucious Lim, MD, MPH	9/14/2015
Reviewing Medical Officer	Date
William M. Boyd, MD	9/14/2015
Clinical Team Leader	Date

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

/s/

LUCIOUS LIM
09/14/2015

WILLIAM M BOYD
09/14/2015