CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207795Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review, Deputy Division Director (DTOP), and Deputy Office Director (OAP) Summary Review of NDA 207795 Class 2 Resubmission

Date	October 31, 2017
From	William M. Boyd, M.D., Wiley A. Chambers, M.D., John Farley, M.D., MPH
Subject	Cross-Discipline Team Leader, Deputy Division Director and Deputy Office Director Summary Review
NDA #	NDA 207795
Applicant	Bausch & Lomb Inc.
Date of Submission	August 17, 2017
PDUFA Goal Date	February 17, 2018
Proprietary Name / Established 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	Approval
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 recommended for approval for the reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

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 clinically significantly 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 eye irritation (5%). The most significant long term adverse events are expected to be related to increases in pigmentation.

Latanoprostene bunod ophthalmic solution 0.024% is 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).	Decreasing intraocular pressure, measured by applanation tonometry 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. It is not uncommon to need more than one class of IOP lowering products to control elevated IOP.	This product, if approved, would add to the choice of prostaglandin analogues which reduce elevated IOP.
Benefit	• Reduction in 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 the active-control, timolol maleate ophthalmic solution, 0.5%.
Risk	• Topical ophthalmic prostaglandin analogues have been used to lower IOP for over twenty years. The risks for using ophthalmic prostaglandin analogues are well established and consistent primarily of actions related directly related to the pharmacologic action of prostaglandins in the eye, including conjunctival hyperemia, increased pigmentation, enhancement of inflammation, and maintenance of eyelashes/hairs in their growth phase.	The safety database contained in this application was consistent with other prostaglandin analogues and 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 an ester linked compound. 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.

This application received a Complete Response letter dated 7/21/2016. See the CDTL review in DARRTS dated 6/17/16. Per the Complete Response letter:

> 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. 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 Agency also had the following comments/recommendations in the 7/21/2016 letter that were not approvability issues:

1. The in-use stability data does not support the label storage statement (b) (4). A scientific justification was not provided to address the observed (b) (4). From the recent inspection of the Bausch and Lomb facility, we are aware of investigations into the (b) (4) issues. A definitive root cause for the (b) (4) (b) (4) stability failures had not been determined.

   In your resubmission, we recommend that you 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. Additionally, please update your submission to include any information

presented in the NDA that is impacted by your actions to address the inspectional issues related to the NDA (e.g. 3.2.R Investigation Report for the (b) (4)

2. The data you have provided concerning pregnancy risk are limited (b) (4) (b) (4) Currently proposed labeling provides exposure margins based on dose multiples (on a mg/m^2 basis, presuming 100% absorption). To further refine the exposure margin estimates, the following could be informative:
    a. Conduct a rabbit embryofetal study by the topical ocular route to more directly address the assessment of risk for the human route of administration.
    b. Provide adequate toxicokinetic data in embryofetal development studies. Measure parent (latanoprostene bunod) and its two active metabolites (latanoprost acid and butanediol mononitrate), as well as release of nitric oxide. Assays should be sufficiently sensitive, and LLOQ adequate to capture the lowest biologically active exposure.
    c. Based on the results of item a. above, conduct a pre-/postnatal study (or peri-/post-natal study) if needed to complete the reproductive and developmental assessments.

A Type A Meeting/Teleconference was held on September 01, 2016. There was discussion of the Complete Response letter and of the Agency's Additional Comments from that letter.

A separate teleconference with the Applicant regarding the proposed labeling received July 8, 2016, was held on September 7, 2016, with particular discussion of Sections 8.1, 12.1 and Section 1.

The Applicant's Class 2 resubmission was received February 24, 2017. The NDA was submitted electronically (available internally via \\CDSESUB1\evsprod\NDA207795\207795.enx).

This application received a second Complete Response letter dated 8/7/2017. See the CDTL review in DARRTS dated 8/1/17. Per the Complete Response letter:

> 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. 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 Applicant's second Class 2 resubmission was received August 17, 2017. The NDA was submitted electronically (available internally via: \\CDSESUB1\evsprod\NDA207795\207795.enx).

A Type A Meeting/Teleconference was held on September 22, 2017. The Applicant and the Agency discussed the actions proposed by the applicant to assure that the facility would be in compliance with current good manufacturing practices.

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.

3. Product Quality

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

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		
Sodium citrate		Buffer
Citric acid,		Buffer
Glycerin		(b) (4)
Water		

Source: Module 3.2.P.1

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]
[e]

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 Product Quality review dated 10/23/17 for this Class 2 resubmission:

INSPECTIONS

Drug Substance Manufacturers

Establishment Name and Address	FEI Number	Responsibilities and profile codes	Initial Assessment	Final Recommendation
(b) (4)		DS manufacturing, release testing and stability testing, CSN	• Low risk	• **Acceptable based on the inspection history and the manufacturing capability**

Reviewer's Assessment: Adequate

Facility Name	FEI	Profile Code	Responsibilities	Facility Sub-Score	Process Sub-Score	Product Sub-Score	Overall Initial Facility Risk Assessment
(b) (4)							

Drug Product Manufacturers

Establishment Name and Address	FEI Number	Responsibilities and profile codes	Initial Assessment	Final Recommendation
Bausch & Lomb	1000113778	DP manufacturing, testing and packaging, SLQ	• OAI, initial WH based on findings	• **Approve based on RAI response and tcon with sponsor/manufacturing facility**
Bausch & Lomb	1313525	Alternate facility for analytical and microbiological release an stability testing for DP, CTL	Low Risk	**Acceptable based on the inspection history and the manufacturing capability**
(b) (4)		Alternate analytical facility for compendial testing of incoming API, and excipients, CTL	Low Risk	**Acceptable based on the inspection history and the manufacturing capability**
		Alternate analytical facility for compendial testing of incoming API, and excipients, CTL	Low Risk	**Acceptable based on the inspection history and the manufacturing capability**

Review Recommendation: Approval with post-approval inspection

Review Summary:
Drug substance is proposed to be manufactured at (b) (4) (b) (4) The initial acceptable assessment of this facility remains unchanged.

Drug product is proposed to be manufactured at Bausch & Lomb (FEI 1000113778). A pre-approval inspection was conducted in May 2017 to evaluate the correction of deficiencies from last cycle. The PAI found the firm continues to have deficiency in its (b) (4) The submission was put on WH due to the initial pOAI inspection outcomes. The firm provided the response on 6/19/2017 and 8/16/2017. After carefully reviewed the response, and a face-to-face meeting with the firm on 9/22/2017, it is agreed that the pOAI is down-graded to VAI. The facility is acceptable. However, a post-approval inspection is recommended to verify the corrective actions on the deficiencies found during the inspection in May 2017.

List Submissions being reviewed (table):

Type of submission	Submission date	Supporting document number	Ectd Sequence number
Resubmission of NDA	2/24/2017	30	0029
Resubmission of NDA	8/15/2017	35	0035

Highlight Key Outstanding Issues from Last Cycle:
Bausch & Lomb (FEI 1000113778) was recommended for withhold due to an OAI inspection.

Concise Description Outstanding Issues Remaining:
None.

QUALITY ASSESSEMENT SUMMARY RECOMMENDATIONS

Satisfactory information and responses have been submitted to support the quality of biopharmaceutics aspect; refer to IQA#1 dated 3/25/2016. Quality micro reviewer has recommended approval of this NDA as documented in Addendum #1 to Review #1 dated 4/14/2016. The original NDA was issued a complete response due to the GMP non-compliance of the drug product manufacturing facility (Tampa, Florida).

Drug product, drug substance and process reviewers have recommended approval of this NDA in the resubmission IQA#2, however, the NDA upheld the complete response because the drug product manufacturing facility (Tampa, Florida) had once again resulted in the Office of Process and Facilities recommending Withhold.

As documented in this resubmission, the Office of Process and Facilities has issued an overall recommendation for all facilities on 10/13/2017. Therefore, NDA 207795 is recommended for approval from Product Quality perspective.

4. Nonclinical Pharmacology/Toxicology

There are no new nonclinical or clinical data provided in this resubmission.

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.

In the Pharmacology/Toxicology review (dated 8/1/17) of the label provided in the February 24, 2017, resubmission, labeling revisions are provided. Additional revisions to the labeling were made in internal labeling team meetings. The Agency's Additional Comments from the Complete Response letter, item #2, are resolved with the revised labeling.

See labeling attached at the end of this CDTL review.

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

See the original Medical Officer review dated 4/21/16 in DARRTS for detailed efficacy information. There are no new nonclinical or clinical data provided in this resubmission.

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 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. No clinical data has been submitted that demonstrates a contribution of nitric oxide (NO), to either the safety or efficacy of the product (either positively or negatively).

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

8. Safety

See the original Medical Officer review dated 4/21/16 in DARRTS for detailed efficacy information. There are no new nonclinical or clinical data provided in this resubmission.

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).

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%). Consistent with other prostaglandin analogues, the most significant long term adverse events are expected to be related to increases in pigmentation.

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, and on 8/1/17 in this review cycle.

In the original 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).

In the second review cycle, DRISK deferred comment on the need for a REMS.

DMEPA
In the second 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 6/14/17. 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.

DMEPA completed a review dated 5/25/17 of the labeling submitted by Bausch & Lomb, Inc. on February 24, 2017. DMEPA recommended reduction of the size of the graphic image with the letter "V" on the principal display panel, stating competes in size and prominence with the most important information on the carton labeling such as proprietary name, established name, and strength. DTOP did not agree with this recommendation; the proprietary name, established name, and strength are clearly legible on the proposed cartons. The container labels do not contain a graphic.

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

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 labeling submitted on August 17, 2017, is acceptable and is attached at the end of 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

None.

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

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

/s/

WILLIAM M BOYD
11/01/2017

WILEY A CHAMBERS
11/01/2017

JOHN J FARLEY
11/02/2017

Cross-Discipline Team Leader Review and Deputy Division Director Summary Review of NDA 207795 Class 2 Resubmission

Date	August 1, 2017
From	William M. Boyd, M.D., Wiley A. Chambers, M.D.
Subject	Cross-Discipline Team Leader Review
NDA #	NDA 207795
Applicant	Bausch & Lomb Inc.
Date of Submission	February 24, 2017
PDUFA Goal Date	August 24, 2017
Proprietary Name / Established 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). See Section 2, Background, of this review for additional information.

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 clinically significantly 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 eye irritation (5%). The most significant long term adverse events are expected to be related to increases in pigmentation.

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. It is not uncommon to need more than one class of IOP lowering products to control elevated IOP.	This product, if approved, would add to the choice of prostaglandin analogues which reduce elevated IOP.
Benefit	• Reduction in 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 the active-control, timolol maleate ophthalmic solution 0.5%.
Risk	• Topical ophthalmic prostaglandin analogues have been used to lower IOP for over twenty years. The risks for using ophthalmic prostaglandin analogues are well established.	The safety database contained in this application was consistent with other prostaglandin analogues and 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 an ester linked compound. 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.

This application received a Complete Response letter dated 7/21/2016. Per the letter:

> 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. 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 Agency had the following comments/recommendations in the 7/21/2016 letter that were not approvability issues:

1. The in-use stability data does not support the label storage statement (b) (4) A scientific justification was not provided to address the observed (b) (4). From the recent inspection of the Bausch and Lomb facility, we are aware of investigations into the (b) (4) issues. A definitive root cause for the (b) (4) (b) (4) stability failures had not been determined.

   In your resubmission, we recommend that you 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. Additionally, please update your submission to include any information presented in the NDA that is impacted by your actions to address the inspectional issues related to the NDA (e.g. 3.2.R Investigation Report for the (b) (4)

2. The data you have provided concerning pregnancy risk are limited [redacted] Currently proposed labeling provides exposure margins based on dose multiples (on a mg/m^2 basis, presuming 100% absorption). To further refine the exposure margin estimates, the following could be informative:
    a. Conduct a rabbit embryofetal study by the topical ocular route to more directly address the assessment of risk for the human route of administration.
    b. Provide adequate toxicokinetic data in embryofetal development studies. Measure parent (latanoprostene bunod) and its two active metabolites (latanoprost acid and butanediol mononitrate), as well as release of nitric oxide. Assays should be sufficiently sensitive, and LLOQ adequate to capture the lowest biologically active exposure.
    c. Based on the results of item a. above, conduct a pre-/postnatal study (or peri-/post-natal study) if needed to complete the reproductive and developmental assessments.

A Type A Meeting/Teleconference was held on September 01, 2016. There was discussion of the Complete Response letter and of the Agency's Additional Comments from that letter.

A separate teleconference with the Applicant regarding the proposed labeling received July 8, 2016, was held on September 7, 2016, with particular discussion of Sections 8.1, 12.1 and Section 1.

The Applicant's Class 2 resubmission was received February 24, 2017. The NDA was submitted electronically (available internally via \\CDSESUB1\evsprod\NDA207795\207795.enx).

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	[redacted] preservative
Polysorbate 80	[redacted]	[redacted]
Edetate disodium		
Sodium citrate		Buffer
Citric acid,		Buffer
Glycerin		[redacted]
Water		

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)		(b) (4) NMT %
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]
[e]

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 Quality Assessment review dated 7/31/17:

REGARDING AGENCY'S ADDITIONAL COMMENTS FROM 7/21/16 LETTER

Per the Agency's recommendation, the applicant performed additional in-use study on two registration batches 186772 and 186782 in this resubmission, both batches were 7.5 mL bottles and were stored for 30 months at long term storage condition. The results of (b) (4) at intermediate time points including 42, 49, 56 and 61 days at 20-25°C show that they met the specification and comply with USP <789> Table 2. All the other quality attributes are within the specification.

Therefore, the proposed label storage statement of 25ºC for 8 weeks is supported by the in-use stability data.

INSPECTIONS

Drug Substance Manufacturers

Establishment Name and Address	FEI Number	Responsibilities and profile codes	Initial Assessment	Final Recommendation
(b) (4)		DS manufacturing, release testing and stability testing, CSN	• Low risk	• **Acceptable based on the inspection history and the manufacturing capability**

Reviewer's Assessment: Adequate

Facility Name	FEI	Profile Code	Responsibilities	Facility Sub-Score	Process Sub-Score	Product Sub-Score	Overall Initial Facility Risk Assessment
							(b) (4)

Drug Product Manufacturers

Establishment Name and Address	FEI Number	Responsibilities and profile codes	Initial Assessment	Final Recommendation
Bausch & Lomb	1000113778	DP manufacturing, testing and packaging, SLQ	• OAI	• **Withhold based on PAI findings**
Bausch & Lomb	1313525	Alternate facility for analytical and microbiological release an stability testing for DP, CTL	Low Risk	**Acceptable based on the inspection history and the manufacturing capability**
(b) (4)		Alternate analytical facility for compendial testing of incoming API, and excipients, CTL	Low Risk	**Acceptable based on the inspection history and the manufacturing capability**
		Alternate analytical facility for compendial testing of incoming API, and excipients, CTL	Low Risk	**Acceptable based on the inspection history and the manufacturing capability**

Reviewer's Assessment: Inadequate

Facility Name	FEI	Profile Code	Responsibilities	Facility Sub-Score	Process Sub-Score	Product Sub-Score	Overall Initial Facility Risk Assessment
Bausch & Lomb	1000113778	SLQ	DP manufacturing, tesitng and packaging	High	Medium	Low	High
Bausch & Lomb	1313525	CTL	Alternate facility for analytical and microbiological release an stability testing for DP	Medium	Low	Low	Medium

(b) (4)

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 Quality Assessment review dated 7/31/17:

Satisfactory information and responses have been submitted to support the quality of biopharmaceutics aspect; refer to IQA#1 dated 3/25/2016. Quality micro reviewer has recommended approval of this NDA as documented in Addendum #1 to Review #1 dated 4/14/2016. The original NDA was issued a complete response due to the GMP non-compliance of the drug product manufacturing facility (Tampa, Florida). As documented in this resubmission, all drug product issues have been satisfactorily resolved; drug substance and process Review #1 recommended Approval and Review #2 upholds the approval recommendations after evaluating this resubmission.

However, the outcome of the most recent inspection of the drug product manufacturing facility (Tampa, Florida) has once again resulted in the Office of Process and Facilities recommending Withhold. Therefore, NDA 207795 is recommended for Complete Response from Product Quality perspective.

The following statement about the unacceptable manufacturing facility (Tampa, Florida) should be included in the CR letter:

> *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.*

4. Nonclinical Pharmacology/Toxicology

There are no new nonclinical or clinical data provided in this resubmission.

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.

In the Pharmacology/Toxicology review (dated 8/1/17) of the label provided in the February 24, 2017, resubmission, labeling revisions are provided. Additional revisions to the labeling were made in internal labeling team meetings. The Agency's Additional Comments from the Complete Response letter, item #2, are resolved with the revised labeling.

See labeling attached at the end of this CDTL review.

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

See the original Medical Officer review dated 4/21/16 in DARRTS for detailed efficacy information. There are no new nonclinical or clinical data provided in this resubmission.

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 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

See the original Medical Officer review dated 4/21/16 in DARRTS for detailed efficacy information. There are no new nonclinical or clinical data provided in this resubmission.

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).

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%). Consistent with other prostaglandin analogues, the most significant long term adverse events are expected to be related to increases in pigmentation.

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, and on 8/1/17 in this review cycle.

In the original 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).

In this review cycle, DRISK has deferred comment on the need for a REMS at this time.

DMEPA
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 6/14/17. 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.

DMEPA completed a review dated 5/25/17 of the labeling submitted by Bausch & Lomb, Inc. on February 24, 2017. DMEPA recommended reduction of the size of the graphic image with the letter "V" on the principal display panel, stating competes in size and prominence with the most important information on the carton labeling such as proprietary name, established name, and strength. DTOP does not agree with this recommendation; the proprietary name, established name, and strength are clearly legible on the proposed cartons. The container labels do not contain a graphic.

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

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 revisions to the 7/24/17 labeling are 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.

11 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
08/01/2017

WILEY A CHAMBERS
08/01/2017