

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

207795Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 207,795
Submission Date(s): July 21, 2015; February 29, 2016
Proposed Brand Name Vyzulta
Generic Name Latanoprostene bunod
Reviewer Yongheng Zhang, Ph.D.
Team Leader Philip M. Colangelo, Pharm.D., Ph.D.
OCP Division DCP4
OND Division DTOP
Applicant Bausch & Lomb Inc.
Submission Type; Code NME; 1S
Formulation; Strength(s) Latanoprostene bunod ophthalmic solution, 0.024%
Indication For the reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension
Dosage and Administration One drop in the conjunctival sac of the affected eye(s) once daily in the evening

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1. EXECUTIVE SUMMARY

Latanoprostene bunod (LBN) is a new molecular entity (NME), a novel nitric oxide (NO) donating prostaglandin F2-alpha receptor agonist (PGA) formulated as a topical ophthalmic solution 0.024% for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma (OAG) or ocular hypertension (OHT). It is believed that LBN lowers IOP by a dual mechanism of action, involving increasing both non-conventional (uveoscleral) aqueous outflow (via latanoprost acid) and conventional (trabecular meshwork/Schlemm's canal) aqueous outflow (via NO donation through a relaxing action on the trabecular meshwork tissue).

In support of the NDA, the Applicant submitted nine clinical studies, including two Phase 1 studies, four Phase 2 studies (Studies A9441001 and A9441003 -conducted by Pfizer, Study 659, and Study 803), and three Phase 3 studies (Studies 769, 770, and 811).

The two Phase 1 studies (Study 849 in Japan; Study 809 in the US) are pharmacokinetic studies, conducted in healthy subjects to assess the tolerability and safety of LBN ophthalmic solution 0.024%, as well as the systemic exposure of the parent LBN and its 2 primary active metabolites, latanoprost acid and butanediol mononitrate (**Table 1**).

Table 1: Phase 1 Pharmacokinetic Studies with LBN Ophthalmic Solution 0.024% in Healthy Subjects

Study ID	Number of Centers, Location	Study Design and Type of Control	Study Objectives	Test Product Dose, Route, and Regimen	Number of Subjects by Arm (Randomized)	Diagnosis of Subjects	Duration of Treatment
849 Phase 1	1 Japan	Single-center, single-arm, open-label study control: no	To evaluate clinical efficacy	LBN ophthalmic solution 0.024% QD (PM) bilateral for 14 days	LBN ophthalmic solution 0.024%: 24	Healthy subjects	14 days
809 Phase 1	1 US	Single-center, single-arm, open-label study control: no	To evaluate the systemic PK, safety and tolerability	LBN ophthalmic solution 0.024% QD (AM) bilateral for 28 days	LBN ophthalmic solution 0.024%: 22	Healthy subjects	28 days

In addition, per the Agency's request following the pre-NDA meeting, the sponsor conducted Study 874, "Evaluation of the Percent Methemoglobin-Time Course Profile Following Single and Repeat Instillations of Latanoprostene Bunod (LBN), 0.024%, in Healthy Volunteers - METEOROID Study", to indirectly assess systemic NO exposure by examining the potential change in the percentage of methemoglobin (% MetHb) after a single ocular administration of and after a 7-day once-daily repeated topical bilateral ocular administration. The study report was submitted during the current review cycle.

1.1. Recommendation

The Clinical Pharmacology information provided by the Applicant in the NDA submission is acceptable, and the Clinical Pharmacology review team recommends approval of Vyzulta (Latanoprostene bunod 0.024% ophthalmic solution).

The reviewer's proposed label changes in Appendix 4.1 will be forwarded to the sponsor.

1.2. Phase IV Commitments

None.

1.3. Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

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 (C_{max}) 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 (T_{max}) 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%.

2. QUESTION BASED REVIEW

2.1. General Attributes of the Drug

2.1.1. *What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?*

Latanoprostene bunod is an oil at refrigerated and room temperatures.

Parameter	Results
Physical appearance	Colorless or pale yellow viscous oil
Solubility	Very soluble in acetone, methanol, ethanol, isopropanol, dichloromethane, dimethyl formamide, ethyl acetate, hexane-isopropanol mixture. Practically insoluble in water and hexane.
Specific rotation	(b) (4)

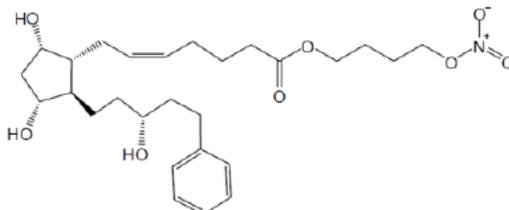
Structural Formula: $C_{27}H_{41}NO_8$

Molecular Weight: 507.62 Dalton

CAS Index Name: 860005-21-6

Chemical Name: 4-nitrooxybutyl (5Z)-7-[(1R,2R,3R,5S)-3,5-dihydroxy-2-[(3R)-3-hydroxy-5-phenyl-pentyl]cyclopentyl]hept-5-enoate

Chemical Structure:



Drug Product:

The Latanoprostene Bunod Ophthalmic Solution, 0.024% (0.24 mg/mL) drug product is a clear, colorless to slightly yellow, sterile, preserved ophthalmic solution formulated for topical delivery to the eye. The qualitative and quantitative compositions for the drug product are provided in **Table 2.1.1-1**.

Table 2.1.1-1: 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)	(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

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

NF = National Formulary

USP = United States Pharmacopeia

2.1.2. What is the proposed mechanism of drug action and therapeutic indication?

Latanoprostene bunod (LBN) is a novel nitric oxide (NO) donating prostaglandin F₂-alpha receptor agonist (PGA) formulated as a topical ophthalmic solution for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma (OAG) or ocular hypertension (OHT).

Following topical ocular administration, LBN is metabolized to 2 active moieties: the prostaglandin F (FP) receptor agonist latanoprost acid (LA), and (b) (4) butanediol mononitrate (BDMN). BDMN is then further hydrolyzed to the active signaling molecule NO and the metabolite 1,4 butanediol. LBN is thought to lower IOP by a dual mechanism of action, mainly involving increasing both non-conventional (uveoscleral) aqueous outflow (via LA) and conventional (trabecular meshwork/Schlemm's canal) aqueous outflow (via NO donation through a relaxing action on the trabecular meshwork tissue).

2.1.3. What are the proposed dosage(s) and route(s) of administration?

One drop in the conjunctival sac of the affected eye(s) once daily in the evening.

2.2. General Clinical Pharmacology

2.2.1. What are the design features of the clinical studies and clinical pharmacology studies used to support dosing or claims?

Two exploratory Phase 2 studies [Study A9441001 (under IND 73435) and Study A9441003 (Japan only, not under IND 73435)] were conducted to evaluate the safety and efficacy of LBN (0.003%, 0.006%, 0.012%, 0.024%, and 0.04%) in adult subjects with OAG. In addition, one Phase 2 Study #659 was conducted to evaluate dose-ranging efficacy of LBN (0.006%, 0.012%, 0.024%, and 0.04%) in patients with OAG or OHT. The dosing regimen of LBN 0.024% QD was

selected for further safety and efficacy assessment in one additional Phase 2 Study #803 and three Phase 3 studies (#769, 770, and 811).

Two Phase 1 pharmacokinetic studies (Study #849, males only in Japan; Study# 809, both males and females in the US) were conducted in healthy subjects to assess the tolerability and safety of LBN ophthalmic solution 0.024%, as well as the systemic exposure of the parent LBN and its 2 primary active metabolites, LA and BDMN.

Study ID	Number of Centers, Location	Study Design and Type of Control	Study Objectives	Test Product Dose, Route, and Regimen	Number of Subjects by Arm (Randomized)	Diagnosis of Subjects	Duration of Treatment
849 Phase 1	1 Japan	Single-center, single-arm, open-label study control: no	To evaluate clinical efficacy	LBN ophthalmic solution 0.024% QD (PM) bilateral for 14 days	LBN ophthalmic solution 0.024%: 24	Healthy subjects	14 days
809 Phase 1	1 US	Single-center, single-arm, open-label study control: no	To evaluate the systemic PK, safety and tolerability	LBN ophthalmic solution 0.024% QD (AM) bilateral for 28 days	LBN ophthalmic solution 0.024% : 22	Healthy subjects	28 days

Furthermore, per FDA’s request, the sponsor conducted a Phase 1 Study #874 titled “*Evaluation of Systemic Methemoglobin Levels Following Single and Repeat Instillations of BOL-303259-X 0.024% (LBN) Ophthalmic Solution in Healthy Subjects – METEOROID Study*”, to indirectly assess systemic NO exposure by examining any changes in the percentage of methemoglobin (% MethHb) after a single ocular administration of and after a 7-day QD repeated topical bilateral ocular administration of LBN ophthalmic solution 0.024%.

2.2.2. *Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters?*

Yes. Analytical methods were established and validated to quantitate plasma concentrations of the parent latanoprostene bunod and its 2 primary active metabolites, latanoprost acid and BDMN.

2.2.3. *What are the PK characteristics of the drug?*

2.2.3.1 *What are the single dose and multiple dose PK parameters?*

Study # 809 (both males and females healthy subjects in the US; 28 days QD am dosing)

- No detectable latanoprostene bunod (LLOQ of 10 pg/mL) or BDMN (LLOQ of 200 pg/mL, the NO-donor) in all the plasma samples.
- Most subjects had quantifiable latanoprost acid plasma levels on Days 1(n=16 out of 22) and 28 (n=13 out of 22), mostly at early time points (5min and 15 min post dose).
- The latanoprost acid Cmax did not appear to change over time, suggesting little systemic accumulation of latanoprost acid following repeated QD dosing in the study.

Table 2.2.3.1-1: Comparison of Latanoprost Acid C_{max} on Day 1 and Day 28 After Once Daily Bilateral Topical Ocular Instillation of 1 Drop of LBN 0.024% in Study #809

C _{max} of latanoprost acid	(n=20)
Day 1	
n	16
Mean (±SD), pg/mL	59.13 (±16.838)
Median, pg/mL	56.95
Min, max (pg/mL)	38.7, 104.0
Day 28	
n	13
Mean (±SD), pg/mL	51.11 (±25.818)
Median, pg/mL	42.30
Min, max (pg/mL)	30.4, 125.0

Abbreviations: C_{max}= maximum observed plasma concentration; max=maximum; Min=minimum; SD=standard deviation.

Source: [Table 14.2.3](#); 14Mar2015.

Study # 849 (only males healthy subjects in Japan; 14 days QD pm dosing)

- No detectable latanoprostene bunod (LLOQ of 10 pg/mL) in all the plasma samples.
- No detectable BDMN (LLOQ of 200 pg/mL) concentrations in all the plasma sample, except for one subject at one time point (i.e., 307 pg/mL at 6 hour postdose on Day 14)
- All 12 subjects in the PK population had measurable concentrations of latanoprost acid in the plasma samples at Days 1 and 14. The mean T_{max} for latanoprost acid in the plasma samples on Day 1 and Day 14 were 0.097 and 0.14 hrs, respectively. The mean C_{max} for latanoprost acid in the plasma samples on Day 1 and Day 14 were 144 pg/mL and 165 pg/mL, respectively, suggesting little systemic accumulation of latanoprost acid following repeated QD dosing in the study.

In summary, systemic exposure data of latanoprostene bunod, latanoprost acid, and BDMN are consistent in Study #809 and #849. However, for labeling purpose, the reviewer recommends that only data from Study # 809 should be used, because Study #809 has more subjects (22 vs 12), has both male and female (vs. only male in Study #849), and its demographic characteristics are more reflective of the US population than that of Study #849 (i.e., only Japanese male subjects)

2.2.3.2. How does the PK of the drug in healthy volunteers compare to that in patients?

PK following topical ocular administration was only evaluated in healthy subjects.

2.3. Intrinsic Factors

2.3.1. What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

The effect of the commonly known intrinsic factors including race, gender and age on the PK of latanoprostene bunod and major metabolites (latanoprost acid and BDMN) following topical

administration of LBN 0.024 % ophthalmic solution has not been studied. Given the low systemic exposure following topical administration, however, dose adjustment is not warranted in patients based on the commonly known intrinsic factors.

2.4. Extrinsic Factors

2.4.1. *What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?*

Based upon what is known about exposure-response relationships and their variability, what dosage regimen adjustments, if any, do you recommend for each of these factors? If dosage regimen adjustments across factors are not based on the exposure-response relationships, describe the basis for the recommendation.

The impact of the commonly known extrinsic factors on LBN dose-exposure and/or exposure-response has not been evaluated. Because of the systemic exposure is low, the impact, if any, would not be clinically significant. Therefore, no dosage adjustments for extrinsic factors are recommended.

2.4.2. *Drug-drug interactions*

Latanoprostene bunod and its metabolites do not competitively inhibit the CYP enzymes. Latanoprost acid and BDMN are further metabolized by β -oxidation and GST-transferase-mediated denitration, respectively, and these metabolites are also not substrates for CYP; therefore, these compounds would not be expected to competitively inhibit these enzymes.

The interaction of latanoprostene bunod with other medications was not evaluated since no significant systemic exposure of latanoprostene bunod and its metabolites, latanoprost acid and butanediol mononitrate (the nitric oxide-donating moiety), were detected in plasma. Therefore, there is very low potential for latanoprostene bunod, latanoprost acid, and butanediol mononitrate to inhibit or induce drug metabolic enzymes including isozymes of cytochrome P450, and drug transporters.

2.4.2.1. *Is there an in vitro basis to suspect in vivo drug-drug interactions?*

No. Latanoprostene bunod is a prodrug that converts to Latanoprost acid and BDMN, which are further metabolized by β -oxidation and GST-transferase-mediated denitration, respectively.

2.4.2.2. *Is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?*

Latanoprostene bunod and its metabolites do not competitively inhibit the CYP enzymes. Latanoprost acid and BDMN are further metabolized by β -oxidation and GST-transferase-mediated denitration, respectively, and these metabolites are also not substrates for CYP; therefore, these compounds would not be expected to competitively inhibit these enzymes. It is unknown if their metabolism is influenced by genetics or not.

2.4.2.3. *Is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?*

No transporter studies were performed by the sponsor, thus, it is unknown if latanoprostene bunod or its metabolites is an inhibitor and/or substrate of P-glycoprotein transport process.

2.4.2.4. *Are there other metabolic/transporter pathways that may be important?*

No.

2.4.2.5. *Does the label specify co-administration of another drug and, if so, has the interaction potential between these drugs been evaluated?*

No, the label does not specify co-administration of another drug.

2.4.2.7. *What other co-medications are likely to be administered to the target patient population?*

No other co-administered drugs can be specified.

2.4.2.8. *Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?*

No in vivo drug-drug interaction studies have been conducted.

2.4.2.9. *Is there a known mechanistic basis for pharmacodynamic drug-drug interactions, if any?*

There is no known mechanistic basis for PD drug-drug interactions.

2.4.2.10. *Are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions, or protein binding?*

There are no unresolved questions related to active metabolites and metabolic drug interactions.

2.4.3. *What issues related to dose, dosing regimens, or administration are unresolved and represent significant omissions?*

No issues related to dose, dosing regimens, or administration remain unresolved.

2.5. General Biopharmaceutics

Not applicable. LBN is formulated as an ophthalmic solution for topical ocular administration.

2.6. Analytical Section

2.6.1. *How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?*

Plasma concentrations for latanoprostene bunod, latanoprost acid, and butanediol mononitrate were determined using validated HPLC/MS/MS methods. The assays were validated with respect to accuracy, precision, and sample stability consistent with the sample collection and storage procedures.

2.6.2. *Which metabolites have been selected for analysis and why?*

Latanoprostene bunod, latanoprost acid, and butanediol mononitrate were selected for analysis because they are the parent drug and two primary metabolites, respectively. LA is further metabolized by the liver to the 1,2-dinor and 1,2,3,4-tetranor metabolites via fatty acid β -oxidation. BDMN is further metabolized to 1,4 butanediol and the active signaling molecule, NO. The metabolite 1,4 butanediol was shown to be further oxidized to succinic acid, which entered the tricarboxylic acid (TCA) cycle and was almost quantitatively excreted in expired air as carbon dioxide (CO₂).

2.6.3. *For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?*

Total latanoprostene bunod, latanoprost acid, and butanediol mononitrate concentrations in the plasma were measured. Free concentrations in the plasma are not considered clinically relevant following ocular topical administration.

2.6.4. *What bioanalytical methods are used to assess concentrations?*

Refer to Section 2.6.1. for further information.

2.6.4.1. *What is the range of the standard curve? How does it relate to the requirements for clinical studies?*

The standard curve in plasma ranges from 10 pg/mL to 10000 pg/mL, 30 pg/mL to 10000 pg/mL, and 0.2 ng/mL to 50 ng/mL for latanoprostene bunod, latanoprost acid, and butanediol mononitrate, respectively. The ranges of standard curve are adequate for purposes of determining plasma concentrations of latanoprostene bunod, latanoprost acid, and butanediol mononitrate in the clinical studies.

2.6.4.2. *What are the lower and upper limits of quantification (LLOQ/ULOQ)?*

The LLOQ and ULOQ for latanoprostene bunod, latanoprost acid, and butanediol mononitrate are 10 pg/mL and 10000 pg/mL, 30 pg/mL and 10000 pg/mL, and 0.2 ng/mL and 50 ng/mL in the undiluted plasma sample, respectively.

2.6.4.3. *What are the accuracy, precision, and selectivity at these limits?*

The assay accuracy and precision were determined from the assay standards and QCs. For latanoprostene bunod, latanoprost acid, and butanediol mononitrate, the accuracy and precision values are satisfactory. Assay selectivity was confirmed by analyzing individual or pooled human plasma samples and none yielded interfering peaks when concentrations were above LLOQ.

2.6.4.4. *What is the sample stability under the conditions used in the study (long-term, freeze-thaw, sample-handling, sample transport, autosampler)?*

For latanoprostene bunod, latanoprost acid, and butanediol mononitrate, sample stability under the conditions used in the study were deemed satisfactory in terms of long-term (-70 °C), freeze-thaw (-20 and -70 °C), and room temperature autosampler stability, et al.

2.6.4.5. *What is the QC sample plan?*

QCs prepared in plasma at concentrations of 90, 520, 3000, and 7500 pg/mL for latanoprost acid, and 30, 300, 3000, and 7500 pg/mL for latanoprostene bunod, respectively, were included in each analysis. For butanediol mononitrate, QCs prepared in plasma at concentrations of 0.6, 3.75, 37.5 ng/mL, were included in each analysis.

3. LABELING RECOMMENDATIONS

See Appendix 4.1. for detail.

4. APPENDICES

4.1. Proposed Package Insert (Original and Annotated) with Clinical Pharmacology edits (noted as underline and ~~striketrough~~)

12.3 Pharmacokinetics

Absorption

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 Vyzulta 0.024% 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. The mean maximal plasma concentrations (C_{max}) of latanoprost acid (LLOQ of 30 pg/mL) were 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.

Distribution

There were no ocular distribution studies performed in humans.

(b) (4)

(b) (4)

Metabolism

After topical dosing, latanoprostene bunod is rapidly metabolized in the eye to latanoprost acid (active moiety) and butanediol mononitrate

(b) (4)

(b) (4)

After latanoprost acid reaches the systemic circulation, it is primarily metabolized by the liver to the 1,2-dinor and 1,2,3,4-tetranor metabolites via fatty acid β -oxidation.

Butanediol mononitrate is metabolized to 1,4-butanediol and (b) (4) (b) (4) nitric oxide. The metabolite 1,4-butanediol is further oxidized to succinic acid and enters the tricarboxylic acid (TCA) cycle.

(b) (4)

Elimination

(b) (4)

The elimination of latanoprost acid from human plasma is rapid as latanoprost acid plasma concentration dropped below the LLOQ (30 pg/mL) in the majority of subjects by 15 min following ocular administration of Vyzulta 0.024% in humans.

4.2. Individual Study Reviews

4.2.1. Pharmacokinetics of Latanoprostene Bunod in healthy subjects: Study #809

Study Number: #809

Evaluation of the Systemic Pharmacokinetics, Safety, and Tolerability of Single and Repeat Instillations of BOL-303259-X 0.024% (Latanoprostene Bunod) Ophthalmic Solution in Healthy Subjects - PLUTO Study

Dates: 23 June, 2014 to 28 July, 2014

Study Director: Jason Vittitow, PhD, Bausch & Lomb Incorporated, Bridgewater, NJ 08807

Analytical sites: (b) (4)

OBJECTIVES:

The objective was to evaluate the systemic pharmacokinetics (PK) and ocular and systemic safety and tolerability of BOL 303259-X 0.024% (latanoprostene bunod) ophthalmic solution in healthy subjects with a normal ophthalmic history.

FORMULATION & ADMINISTRATION

Latanoprostene bunod ophthalmic solution 0.024% 1 drop was instilled topically QD in both eyes each morning. The batch number was PF1480901. The product consists of 0.024% BOL-303259-X (active ingredient), polysorbate 80, glycerin, edetate disodium, and water. The formulation is buffered to pH 5.5 with sodium citrate/citric acid and preserved with (b) (4)% benzalkonium chloride.

STUDY DESIGN:

This was a single-center, single-arm, open-label clinical study in the US. Subjects were assessed and confirmed for eligibility at Visit 1 (Screening, Day -28 to Day -1). Subject enrollment was defined as a signed Institutional Review Board (IRB)-approved Informed Consent Form.

Approximately 20 healthy adult subjects received latanoprostene bunod 0.024% QD in the morning, bilaterally. Subjects instilled 1 drop latanoprostene bunod 0.024% QD in both eyes at approximately 8:00 AM \pm 1 hour for 28 days starting at Visit 2 (Day 1) and ending at Visit 3 (Day 28).

Blood samples for pharmacokinetic analysis of latanoprostene bunod, latanoprost acid, butanediol mononitrate (BDMN), and possibly other metabolite(s) in plasma:

- A predose sample collected prior to administration of the first dose;
- Serial samples collected at 5, 15, and 30 minutes and 1, 2, 4, 6, 8, and 12 hours after study drug instillation on Days 1 and 28;

Demographic characteristics are summarized in **Table 1**.

Table 1: Demographic and Baseline Characteristics

Demographic/Baseline Characteristic	(n=22)
Sex, n (%)	
Male	15 (68%)
Female	7 (32%)
Race, n (%)	
White	10 (45%)
Black	10 (45%)
Asian	2 (9%)
Ethnicity, n (%)	
Hispanic	10 (45%)
Not Hispanic	12 (55%)
Age, years	
Mean (±SD)	34.5 (±15.95)
Median	27.0
Min, max	18, 59
Height, inches	
Mean (±SD)	68.0 (±2.70)
Median	68.0
Min, max	63, 72
Weight, lbs	
Mean (±SD)	210.2 (±44.51)
Median	199.0
Min, max	148, 309

Abbreviation: max=maximum; Min=minimum; SD=standard deviation.

ASSAY METHODOLOGY:

Latanoprost acid and Latanoprostene bunod

Human plasma was collected in BD P800 tubes with a proprietary cocktail (b) (4)

. Latanoprost free acid and BOL-303259-X were extracted from study samples using a multi-stage extraction procedure and subsequently analyzed on separate instruments. The data were collected using (b) (4) LC/MS/MS SRM (b) (4)

(b) (4) were used as internal standards.

This assay was calibrated using a standard curve generated from eight latanoprost acid standards (30, 60, 200, 500, 1500, 4000, 8000, 10000 pg/mL) and ten BOL-303259-X standards (10, 20, 30, 60, 200, 500, 1500, 4000, 8000, 10000 pg/mL). In addition, QCs prepared in plasma at

concentrations of 90, 520, 3000, and 7500 pg/mL for latanoprost acid, and 30, 300, 3000, and 7500 pg/mL for latanoprostene bunod, respectively, were included in each analysis.

Butanediol Mononitrate (BDMN)

The analyte, BDMN, and internal standard, (b) (4), were extracted from 250 µL of human plasma by a liquid-liquid extraction procedure. The compounds were detected and quantified by tandem mass spectrometry (b) (4) on a Finnigan TSQ mass spectrometer.

This assay was calibrated using a standard curve generated from eight BDMN standards (0.2, 0.4, 1.0, 2.0, 4.0, 20.0, 40.0, and 50.0 ng/mL). In addition, QCs prepared in plasma at concentrations of 0.6, 3.75, 37.5 ng/mL, were included in each analysis.

Criterion	Latanoprostene bunod	Latanoprost acid	Butanediol mononitrate	Comments
Conc. range,	10-10000 pg/mL (0.2 mL sample)	30 -10000 pg/mL (0.2 mL sample)	0.2 -50 ng/mL (0.25 mL sample)	satisfactory
LLOQ,	10 pg/mL	30 pg/mL	0.2 ng/mL	satisfactory
Linearity, r ²	>0.99	>0.99	>0.99	satisfactory
Accuracy, % RE	-4.7% – 3.0% ^a -4.3% – 1.7% ^b	-0.8% – 1.5% ^a -7.2% – 0.4% ^b	Satisfactory	Satisfactory
Precision, % CV	≤ 5.7% ^a ≤ 6.3% ^b	≤ 5.0% ^a ≤ 5.5% ^b	Satisfactory	Satisfactory
Selectivity	Satisfactory			
Incurred sample reanalysis	Satisfactory	Satisfactory	Not evaluated	Satisfactory
Stability	Benchtop (ice bath): 7 hours Freeze/thaw (-20 and -70 °C): 5 cycles Freezer (-70 °C): 297 days Rejection reproducibility (RT): 70 hours Processed samples (RT): 28 hours		Satisfactory	Satisfactory

^a, based on standards; ^b, based on QCs;

From Document 130432VSMB_BRN, 140753ASMB_BRN, and 8527.083014

DATA ANALYSIS

Descriptive statistics were used to summarize the systemic pharmacokinetic parameters including C_{max}, T_{max}, AUC_{0-t}, and AUC_{0-inf}.

PK RESULTS:

No detectable concentrations of latanoprostene bunod (parent compound; LLOQ of 10 pg/mL) or BDMN (inactive metabolite providing nitric oxide, the active signaling moiety; LLOQ of 200 pg/mL) in plasma samples.

Latanoprost acid plasma concentration:

- Detectable at 5 min (n=16) and 15 min (n=7) after administration on Day 1; ranging from 15 pg/mL to 104 pg/mL.
- Detectable at 5 min (n=13), 15 min (n=4), 30 min (n=2), 1 hour (n=1), and 2 hours (n=1) after administration; ranging from 15 pg/mL to 125 pg/mL.
- On Day 1, the mean ± SD C_{max} of latanoprost acid was 59.13 ± 16.84 pg/mL, and on

Day 28, it was 51.11 ± 25.82 pg/mL - **Table 2**.

Table 2: C_{max} of Latanoprost Acid (PK Population)

C _{max} of latanoprost acid	(n=20)
Day 1	
n	16
Mean (±SD), pg/mL	59.13 (±16.838)
Median, pg/mL	56.95
Min, max (pg/mL)	38.7, 104.0
Day 28	
n	13
Mean (±SD), pg/mL	51.11 (±25.818)
Median, pg/mL	42.30
Min, max (pg/mL)	30.4, 125.0

Abbreviations: C_{max}= maximum observed plasma concentration; max=maximum; Min=minimum; SD=standard deviation.

Source: [Table 14.2.3](#); 14Mar2015.

- The mean T_{max} of latanoprost acid was approximately 5 min post administration on Day 1 and 28.

SAFETY RESULTS:

AEs and safety assessments showed that latanoprostene bunod instilled QD each morning in both eyes of healthy volunteers for 28 days was not associated with any potential or identified safety risks. Only 2 TEAEs (blood glucose increased) were reported, and both were mild, not serious, and judged as unlikely to be related to treatment. Furthermore, vital signs and laboratory parameters from blood and urine demonstrated primarily modest changes, with none of the mean changes representing a clinically meaningful difference from baseline.

SPONSORS CONCLUSIONS:

This study of 22 healthy volunteers demonstrated that instillation of 1 drop latanoprostene bunod QD each morning in both eyes was tolerable, and it identified no safety signals. No ocular AEs were reported and changes in vital signs and laboratory parameters were modest.

Efficacy was not assessed in this study but PK analyses showed detectable latanoprost acid concentrations ranging from 15 pg/mL to 104 pg/mL in 16 blood samples at 5 minutes and 15 minutes on Day 1 and from 15 pg/mL to 125 pg/mL in 13 blood samples from 5 minutes through 2 hours on Day 28. Little change in latanoprost acid concentrations were observed over time, although the number of patients with paired data (n=11) was too small to make firm conclusions. Neither latanoprostene bunod (LLOQ of 10.0 pg/mL) nor BDMN (LLOQ of 200 pg/mL) was

detected in the blood samples collected in this study, which is consistent with negligible systemic exposure of these compounds after bilateral QD dosing of the study drug.

REVIEWER'S ASSESSMENT & RECOMMENDATION:

Results from Study #809 adequately assessed the systemic exposures of latanoprostene bunod, latanoprost acid, butanediol mononitrate (BDMN), following repeated topical ocular administrations of latanoprostene bunod 0.024% ophthalmic solution.

The reviewer's conclusions are similar to the sponsor's as follows:

- Neither latanoprostene bunod nor BDMN was detected in the blood samples collected on Day 1 and Day 28 following daily topical ocular administration of latanoprostene bunod 0.024% ophthalmic solution.
- Latanoprost acid concentrations were quantifiable in the majority of subjects, especially in the early time point (i.e. 5 min post dose). The elimination of latanoprost acid from human plasma is rapid as latanoprost acid plasma concentration dropped below the LLOQ in the majority of subjects by 15 min post dose.
- The latanoprost acid C_{max} did not appear to change over time, suggesting little systemic accumulation of latanoprost acid following repeated QD dosing in the study.

Systemic exposure data of latanoprostene bunod, latanoprost acid, and BDMN in Study #809 are consistent with that in Study #849 (Appendix 4.2.2). However, for labeling purpose, the reviewer recommends that only data from Study # 809 should be used, because Study #809 has more subjects (22 vs 12), has both male and female (vs. only male in Study #849), and its demographic characteristics are more reflective of the US population than that of Study #849 (i.e., only Japanese male subjects).

4.2.2. Pharmacokinetics of Latanoprostene Bunod in healthy subjects: Study #849

Study Number: #849

A Single-Center, Open-Label Study Evaluating the Efficacy of Latanoprostene Bunod Ophthalmic Solution, 0.024% in Lowering Intraocular Pressure Over a 24-Hour Period in Japanese Healthy Male Volunteers – KRONUS Study

Dates: 04 July, 2013 to 04 Aug, 2013

Study Director: Quintus Ngumah, PhD, Bausch & Lomb Incorporated, Bridgewater, NJ 08807

Pharmacokinetics Report: (b) (4)

Analytical site: (b) (4)

OBJECTIVES:

The primary objective was to evaluate the effect of latanoprostene bunod (BOL-303259-X) 0.024% dosed once daily (QD) in reducing intraocular pressure (IOP) measured over a 24-hour period in healthy subjects.

The secondary objective was to evaluate the systemic pharmacokinetics (PK) of latanoprostene bunod, latanoprost acid, butanediol mononitrate (BDMN), and possibly other metabolite(s) following a single dose and QD dosing of latanoprostene bunod 0.024% for 14 days (2 weeks).

FORMULATION & ADMINISTRATION

Topical latanoprostene bunod ophthalmic solution 0.024%, contained the active ingredient latanoprostene bunod, 0.024%. Other ingredients include polysorbate 80, glycerin, edetate disodium (EDTA), and water. The formulation was buffered to pH 5.5 with citric acid/sodium citrate and preserved with (b) (4)% benzalkonium chloride. The lot number used in this study: 168031; Batch number: PF1384901.

STUDY DESIGN:

This was a single-arm, single-center, open-label, clinical study. The study was initiated at a single center in Japan. Subjects were examined and evaluated according to the following schedule: Visit 1 (Day -28 to -1), Visit 2 (Day 0-2), and Visit 3 (Day 14-15). A total of 24 healthy male volunteers were enrolled, who instilled latanoprostene bunod 0.024% QD in both eyes.

Approximately 24 healthy male volunteers were enrolled to provide at least 20 evaluable subjects. Of the 24 subjects, a subset of 12 subjects (to provide at least 10 evaluable subjects) provided blood samples during the study for PK analysis. All subjects were treated for approximately 14 days (2 weeks), starting on Day 1 and ending the evening of Day 14 or the morning of Day 15

Blood samples were obtained from a subset of 12 subjects during the study for PK analysis. All subjects were treated for 14 days (2 weeks), starting on Day 1 and ending the evening of Day 14.

Blood samples for pharmacokinetic analysis of latanoprostene bunod, latanoprost acid, butanediol mononitrate (BDMN), and possibly other metabolite(s) in plasma:

- A predose sample collected prior to administration of the first dose (8 pm);

- Serial samples collected at 5, 15, and 30 minutes and 1, 2, 4, 6, 8, and 12 hours after study drug instillation on Days 1 and 14;

ASSAY METHODOLOGY:

The same assays for latanoprost acid, latanoprostene bunod, and butanediol mononitrate (BDMN) used in the Study # 809 were used in the current study.

Latanoprost acid and Latanoprostene bunod

Human plasma was collected in BD P800 tubes with a proprietary cocktail of (b) (4). Latanoprost free acid and BOL-303259-X were extracted from study samples using a multi-stage extraction procedure and subsequently analyzed on separate instruments. The data were collected using (b) (4) LC/MS/MS SRM (b) (4).

(b) (4) were used as internal standards.

This assay was calibrated using a standard curve generated from eight latanoprost acid standards (30, 60, 200, 500, 1500, 4000, 8000, 10000 pg/mL) and ten BOL-303259-X standards (10, 20, 30, 60, 200, 500, 1500, 4000, 8000, 10000 pg/mL). In addition, QCs prepared in plasma at concentrations of 90, 520, 3000, and 7500 pg/mL for latanoprost acid, and 30, 300, 3000, and 7500 pg/mL for latanoprostene bunod, respectively, were included in each analysis.

Butanediol Mononitrate (BDMN)

The analyte, BDMN, and internal standard, (b) (4), were extracted from 250 µL of human plasma by a liquid-liquid extraction procedure. The compounds were detected and quantified by tandem mass spectrometry (b) (4) on a Finnigan TSQ mass spectrometer.

This assay was calibrated using a standard curve generated from eight BDMN standards (0.2, 0.4, 1.0, 2.0, 4.0, 20.0, 40.0, and 50.0 ng/mL). In addition, QCs prepared in plasma at concentrations of 0.6, 3.75, 37.5 ng/mL, were included in each analysis.

Criterion	Latanoprostene bunod	Latanoprost acid	Butanediol mononitrate	Comments
Conc. range,	10-10000 pg/mL (0.2 mL sample)	30 -10000 pg/mL (0.2 mL sample)	0.2 -50 ng/mL (0.25 mL sample)	satisfactory
LLOQ,	10 pg/mL	30 pg/mL	0.2 ng/mL	satisfactory
Linearity, r ²	>0.99	>0.99	>0.99	satisfactory
Accuracy, % RE	-1.0% – 2.0% ^a -2.0% – 0.0 % ^b	-2.3 % – 4.2 % ^a 0.8 % – 2.1 % ^b	Satisfactory	Satisfactory
Precision, % CV	≤ 5.3 % ^a ≤ 5.0 % ^b	≤ 6.3 % ^a ≤ 7.3 % ^b	Satisfactory	Satisfactory
Selectivity	Satisfactory			
Incurred sample reanalysis	Satisfactory	Satisfactory	Not evaluated	Satisfactory
Stability	Benchtop (ice bath): 7 hours Freeze/thaw (-20 and -70 °C): 5 cycles Freezer (-70 °C): 234 days Rejection reproducibility (RT): 70 hours Processed samples (RT): 28 hours		Satisfactory	Satisfactory

^a, based on standards; ^b, based on QCs;

From Documents 130990ASMB_BRN, 130432VSMB_BRN, and 8405.093014

DATA ANALYSIS

Descriptive statistics were used to summarize the systemic pharmacokinetic parameters including C_{max} , T_{max} , AUC_{0-t} , and AUC_{0-inf} .

PK RESULTS:

Plasma samples were collected from all subjects in the PK population (12/12). There were no detectable levels of latanoprostene bunod (LLOQ of 10.0 pg/mL) in any of the plasma samples from subjects in the PK population. One subject had a measureable concentration of BDMN at Visit 3, i.e., Day 14/15 (C_{max} = 307 pg/mL at the 6.0 hour time point). All 12 subjects in the PK population had measurable concentrations of latanoprost acid in the plasma samples at Days 1 and 14. The mean T_{max} for latanoprost acid in the plasma samples on Day 1 and Day 14 were 0.097 and 0.14 hrs, respectively. The mean C_{max} for latanoprost acid in the plasma samples on Day 1 and Day 14 were 144 pg/mL and 165 pg/mL, respectively. The mean AUC_{last} values for latanoprost acid were 35.7 pg hr/mL and 55.9 pg hr/mL on Day 1 and Day 14, respectively.

SAFETY RESULTS:

The 24 subjects in the ITT population had a mean duration of exposure of 14 days. A total of 59 ocular TEAEs associated with 22 subjects were reported during the course of the study (30 and 29 ocular TEAEs associated with the study eye and fellow eye, respectively). Eye disorders were the most common TEAEs, with punctate keratitis (13/24 subjects; 54.2%) and conjunctival hyperemia (14/24 subjects; 58.3%) being the most commonly reported events. The majority of TEAEs (29/30 and 28/29 ocular TEAEs for the study eye and fellow eye, respectively) were judged to be at least possibly or probably related to the study drug. All TEAEs reported during the course of the study were mild in severity.

SPONSORS CONCLUSIONS:

A total of 45 subjects were screened, resulting in the enrollment of 24 subjects in the clinical investigation. All 24 subjects completed the study and were included in the ITT, PP and Safety populations. A statistically significant reduction in IOP (p value < 0.001) was observed in the study population (ITT and PP) at all measured time points over the 24 hour monitoring period after 14 days (2 weeks) of treatment.

There were no detectable levels of latanoprostene bunod in any of the plasma samples from subjects in the PK population, and only one subject had a measureable concentration of the metabolite BDMN at a single time point. The metabolite latanoprost acid was detected in the plasma samples of subjects on Day 1 after a single instillation of latanoprostene bunod 0.024%, and after 14 days of QD dosing. All 12 subjects in the PK population had evidence of systemic exposure to latanoprost acid on Day 1 and Day 14. When comparing the mean C_{max} and mean AUC_{last} values for latanoprost acid between Day 1 and Day 14 within individual subjects, 7 and 8 subjects had Day 14 values that were greater than the Day 1 values, respectively. However, based on the actual mean C_{max} and mean AUC_{last} values, the systemic levels and exposure of latanoprost acid were low.

REVIEWER'S ASSESSMENT & RECOMMENDATION:

Results from Study #849 adequately assessed the systemic exposures of latanoprostene bunod, latanoprost acid, butanediol mononitrate (BDMN), following repeated topical ocular administrations of latanoprostene bunod 0.024% ophthalmic solution.

Systemic exposure data of latanoprostene bunod, latanoprost acid, and BDMN in Study #849 are consistent with that in Study #809(Appendix 4.2.1). However, for labeling purpose, the reviewer recommends that only data from Study # 809 should be used, because Study #809 has more subjects (22 vs 12), has both male and female (vs. only male in Study #849), and its demographic characteristics are more reflective of the US population than that of Study #849 (i.e., only Japanese male subjects).

4.2.3. Evaluation of the Methemoglobin-Time Course Profile: Study #874

Study Number: #874

Dates: 02 September 2015 to 24 September 2015

Study Director: Jason Vittitow PhD, Bausch & Lomb Incorporated, Bridgewater, New Jersey 08807

Title: Evaluation of the Percent Methemoglobin-Time Course Profile Following Single and Repeat Ocular Instillations of latanoprostene bunod, 0.024%, in Normal Healthy Volunteers - METEOROID Study

Objectives:

To determine the effect of BOL-303259-X 0.024% (latanoprostene bunod) ophthalmic solution on percent methemoglobin (MetHb) levels using Masimo Rad-57 pulse oximetry in healthy subjects with a normal ophthalmic history.

Formulation & Administration

Latanoprostene bunod 0.024% topical ophthalmic solution containing the active ingredient, 0.024% BOL-303259-X (lot number 189421) and Vehicle (identical to the investigational product but does not contain the active ingredient, BOL-303259-X; lot number 168041).

During the study, subjects performed instillations of the assigned test product to both eyes once per day at approximately the same time of day in the morning. Instillations were performed in the clinic at Visit 2 (Day 1) and Visit 3 (Day 7 ± 1), and at home between the study visits.

Methods:

This was a single-center, randomized, double-masked clinical study conducted in the US. There were 2 treatments: Latanoprostene bunod 0.024% topical ophthalmic solution containing the active ingredient, 0.024% BOL-303259-X and Vehicle.

Screening to determine eligibility occurred between Days -28 and Day -1. Subjects instilled the assigned test material (0.024% BOL-303259-X or Vehicle) bilaterally in both eyes once per day starting at Visit 2 (Day 1) at approximately 8 AM ± 1 hour. Treatment duration was approximately 7 days.

Methemoglobin (MetHb) concentration, in percent (0.1% resolution), were determined using a Masimo Rad-57 Handheld Pulse CO-Oximeter with a rainbow[®] SET[®] Technology finger clip sensor (accuracy ± 1%) within 1 hour prior to study drug instillation and at 5, 15, and 30 minutes and 1, 2, 4, 6, 8, and 12 hours after study drug instillation at Visit 2 (Day 1) and Visit 3 (Day 7). Subjects were closely monitored for AEs throughout the study.

MetHb Concentration (%) and change from baseline were summarized using continuous summary statistics, with the addition of two-sided 95% confidence intervals, by time (Pre-Instillation, 5 minutes, 15 minutes...12 hours) within visits (Visit 2, Visit 3) by treatment group. Additionally, the Hodges-Lehmann median difference (BOL-303259-X 0.024% minus Vehicle) and its exact, two-sided 95% confidence interval were provided for each instillation time for both the MetHb (%) concentration and its change from baseline.

A total of 18 subjects were screened and 16 subjects were randomized.

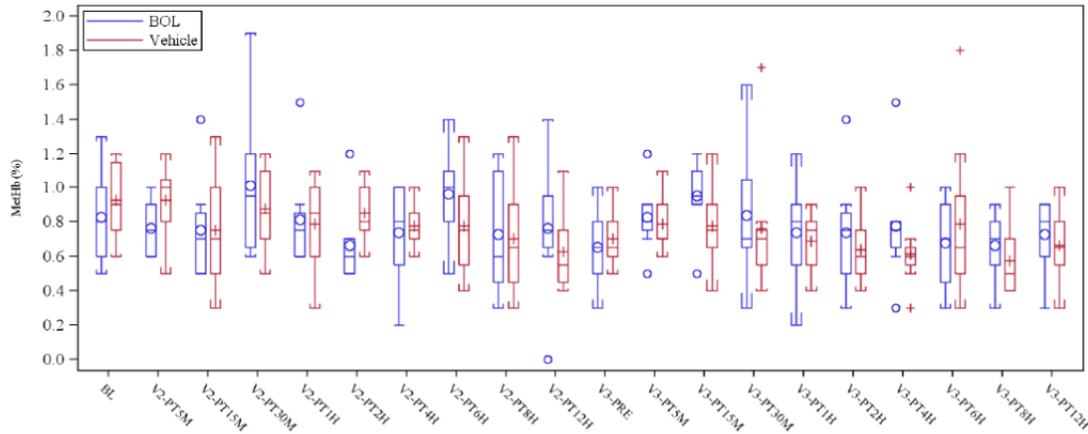
Table 1: Subject Demographic and Baseline Characteristics

Demographic Variable	BOL-303259- X 0.024% N = 8	Vehicle N = 8	Total N = 16
Age (years)			
Mean (SD)	29.9 (9.82)	32.4 (13.67)	31.1 (11.57)
Median (min, max)	28.0 (21, 43)	28.5 (20, 63)	28.5 (20, 63)
Age group, n (%)			
< 65 years	8 (100)	8 (100)	16 (100)
≥ 65 to <75 years	0	0	0
≥ 75 years	0	0	0
Sex, n (%)			
Male	4 (50.0)	3 (37.5)	7 (43.8)
Female	4 (50.0)	5 (62.5)	9 (56.3)
Race, n (%)			
American Indian/Alaskan Native	0	0	0
Asian	0	0	0
Black/African American	2 (25.0)	3 (37.5)	5 (31.3)
Native Hawaiian/Pacific Islander	0	0	0
White	6 (75.0)	5 (62.5)	11 (68.8)
Ethnicity, n (%)			
Hispanic or Latino	6 (75.0)	5 (62.5)	11 (68.8)
Not Hispanic and not Latino	2 (25.0)	3 (37.5)	5 (31.3)
Height – screening (cm)			
Mean (SD)	166.37 (11.440)	167.32 (8.948)	166.85 (9.934)
Median (min, max)	165.10 (152.4, 182.9)	165.10 (154.9, 180.3)	165.10 (152.4, 182.9)
Weight – screening (kg)			
Mean (SD)	90.69 (22.727)	90.86 (23.033)	90.77 (22.105)
Median (min, max)	91.48 (59.0, 124.9)	87.40 (60.8, 131.7)	87.62 (59.0, 131.7)

Source: [Table 14.1.2.1](#)**Results:***MetHb (%)*

The MetHb (%) values by analysis visit (time point and actual treatment group) for the mITT population are presented in Figure 1.

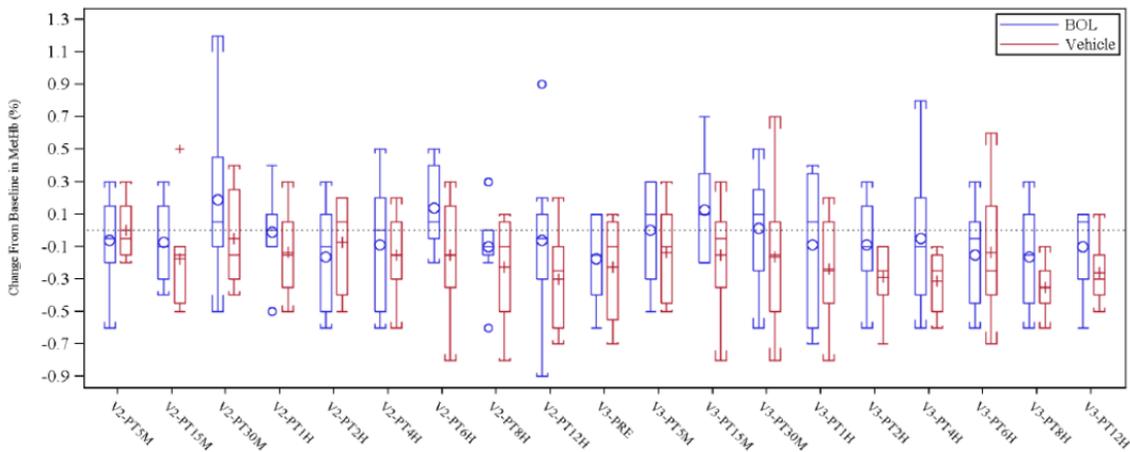
The MetHb (%) values were similar for each treatment group. The Hodges-Lehmann median difference (BOL – Vehicle) for MetHb (%) ranged from -0.30 to 0.20. All 95% confidence intervals about these Hodges-Lehmann median differences included zero.



Source: Figure 14.2.1.1

Figure 1: MetHb (%) by Analysis Visit – Time Point and Actual Treatment Group

The MetHb (%) change from baseline values was similar for each treatment group (Figure 2). The Hodges-Lehmann median difference (BOL – Vehicle) for MetHb (%) change from baseline values ranged from -0.10 to 0.25. All 95% confidence intervals about these Hodges-Lehmann median differences included zero.



Source: Figure 14.2.2.1

Figure 2: Change from Baseline in MetHb (%) by Analysis Visit – Time Point and Actual Treatment Group

Reviewer’s comments: The sponsor’s methods are valid. The data indicates that both MetHb (%) values and MetHb (%) change from baseline were similar for each treatment group, suggesting limited NO systemic exposure following single and repeats (7 days) once daily dosing of latanoprostene bunod ophthalmic solution 0.024% in healthy subjects.

Safety

During the study, one ocular TEAE was observed for 1 subject in the BOL-303259-X 0.024% treatment group (12.5% of treatment group subjects; 6.3% of all subjects). The AE (conjunctival hyperemia) was mild and determined to be possibly related to the study drug. No non-ocular TEAEs were observed or reported by subjects during the course of the study. There were no serious AEs or AEs leading to study discontinuation or death during the study.

Sponsor's Conclusions

The MetHb (%) after a single bilateral ocular administration and 7 days of QD repeated topical bilateral ocular administration of BOL-303259-X 0.024% (latanoprostene bunod) ophthalmic solution was evaluated. There were no significant changes from baseline in the MetHb (%) for both vehicle- and BOL treated subjects on Day 1 and Day 7. Also, there was no difference in the changes in the MetHb (%) between the two treatment groups when directly compared. The overall results of safety assessments (ocular signs, vital signs measurement) support the safety of BOL-303249-X 0.024% in an adult population after 7 ± 1 consecutive daily instillations.

Reviewer's Assessment and Recommendations:

The conduct and submission of the Study # 874 was as the result of the Agency's recommendations following the pre-NDA meeting dated 02/09/2015 for NDA #207795. In the Advice Letter to the sponsor (dated in DARRTS 03/26/2015), the Agency stated the following:

"... .. we recommend that you conduct a separate study to obtain 12-hour % methemoglobin-time course profiles following single and repeat (e.g., 7 days) once daily dosing of latanoprostene bunod ophthalmic solution 0.024% in 8 to 12 healthy subjects. Since this study is not a requirement for initial submission of an NDA, it is acceptable to submit the clinical study report during the NDA review cycle.

Note that we asked that you consider determining the effect of the proposed product on methemoglobin concentrations in humans for the following reasons:

- 1. Latanoprostene bunod or BOL-303259-X is a New Molecular Entity. In vivo, it is converted to metabolites including latanoprost acid and butanediol mononitrate (BDMN). You proposed that BDMN (the NO-donating moiety) may have an additive effect to latanoprost acid. Thus, we consider BDMN to be an active moiety, in addition to latanoprost acid; however the metabolic instability of BDMN precluded you from quantifying it in human plasma samples in PK Study #809.*
- 2. Rather than attempting to quantify NO and other secondary metabolites in plasma (which may require that you expend time in developing PK assays), the change from baseline % methemoglobin will be used as an indirect clinical measure of NO exposure.*
- 3. There are several commercially available assays routinely used for quantifying methemoglobinemia.*
- 4. The lack of a significant change from baseline % methemoglobin in healthy subjects, along with the absence of clinically significant systemic adverse events in healthy subjects and patients, would support the systemic safety of the proposed to-be-marketed latanoprostene bunod ophthalmic product.*

Following the original NDA#207795 submission on 07/21/2015, the sponsor submitted the protocol for Study #874 (as requested by the Agency) on 08/28/2015. The proposed study protocol was deemed acceptable from the clinical pharmacology perspective. Refer to the Clinical Pharmacology review dated 09/14/2015 in DARRTS for IND 73435.

The clinical study report of Study #874 was submitted on 02/29/2016, during the current review cycle for NDA #207795.

In the current study, methemoglobin levels were determined using a Masimo Rad-57 oximeter equipped with rainbow[®] technology and rainbow[®] fingertip sensor, which is a commercial instrument designed to accurately measure clinical parameters including total hemoglobin, oxygen content, and methemoglobin.

The reviewer agrees with the sponsor's conclusion that there is lack of significant change (Figure 1 and Figure 2) from baseline % methemoglobin in healthy subjects, following single and repeated (7 days) once daily dosing of latanoprostene bunod ophthalmic solution 0.024% in healthy subjects.

The results from the study reassured the notion that the NO systemic exposure is likely to be limited following repeated once daily dosing of Vyzulta. Incorporating this information into the proposed label is not warranted at present.

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

/s/

YONGHENG ZHANG
04/07/2016

PHILIP M COLANGELO
04/07/2016

CLINICAL PHARMACOLOGY FILING FORM

Application Information

NDA/BLA Number	207795	SDN	001
Applicant	Bausch & Lomb Inc.	Submission Date	07/21/2015
Generic Name	Latanoprostene bunod	Brand Name	VESNEO (proposed)
Drug Class	Nitric oxide donating prostaglandin F2 α receptor agonist		
Indication	For the reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension		
Dosage Regimen	One drop in the conjunctival sac of the affected eye(s) once daily in the evening.		
Dosage Form	Ophthalmic eye drop solution	Route of Administration	Topical ocular
OCP Division	IV	OND Division	DTOP
OCP Review Team	Primary Reviewer(s)	Secondary Reviewer/ Team Leader	
Division	Yongheng Zhang, Ph.D.	Philip Colangelo Pharm. D., Ph.D.	
Pharmacometrics	-		
Genomics	-		
Review Classification	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Expedited		
Filing Date	9/19/2015	74-Day Letter Date	10/3/2015
Review Due Date	3/16/2016	PDUFA Goal Date	7/21/2016

Application Fileability

Is the Clinical Pharmacology section of the application fileable?

- Yes
 No

If no list reason(s)

Are there any potential review issues/ comments to be forwarded to the Applicant in the 74-day letter?

- Yes
 No

If yes list comment(s)

Is there a need for clinical trial(s) inspection?

- Yes
 No

If yes explain

Clinical Pharmacology Package

Tabular Listing of All Human Studies	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No	Clinical Pharmacology Summary	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Bioanalytical and Analytical Methods	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No	Labeling	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No

Clinical Pharmacology Studies

Study Type	Count	Comment(s)
In Vitro Studies		
<input type="checkbox"/> Metabolism Characterization		
<input type="checkbox"/> Transporter Characterization		
<input type="checkbox"/> Distribution		

<input type="checkbox"/> Drug-Drug Interaction			
In Vivo Studies			
Biopharmaceutics			
<input type="checkbox"/> Absolute Bioavailability			
<input type="checkbox"/> Relative Bioavailability			
<input type="checkbox"/> Bioequivalence			
<input type="checkbox"/> Food Effect			
<input type="checkbox"/> Other			
Human Pharmacokinetics			
Healthy Subjects	<input type="checkbox"/> Single Dose		
	<input checked="" type="checkbox"/> Multiple Dose		Study# 809 and Study# 849 (See Note below)
Patients	<input type="checkbox"/> Single Dose		
	<input type="checkbox"/> Multiple Dose		
<input type="checkbox"/> Mass Balance Study			
<input type="checkbox"/> Other (e.g. dose proportionality)			
Intrinsic Factors			
<input type="checkbox"/> Race			
<input type="checkbox"/> Sex			
<input type="checkbox"/> Geriatrics			
<input type="checkbox"/> Pediatrics			
<input type="checkbox"/> Hepatic Impairment			
<input type="checkbox"/> Renal Impairment			
<input type="checkbox"/> Genetics			
Extrinsic Factors			
<input type="checkbox"/> Effects on Primary Drug			
<input type="checkbox"/> Effects of Primary Drug			
Pharmacodynamics			
<input type="checkbox"/> Healthy Subjects			
<input type="checkbox"/> Patients			
Pharmacokinetics/Pharmacodynamics			
<input type="checkbox"/> Healthy Subjects			
<input type="checkbox"/> Patients			
<input type="checkbox"/> QT			
Pharmacometrics			
<input type="checkbox"/> Population Pharmacokinetics			
<input type="checkbox"/> Exposure-Efficacy			
<input type="checkbox"/> Exposure-Safety			
Total Number of Studies		In Vitro	In Vivo
Total Number of Studies to be Reviewed			
			2
			2

Criteria for Refusal to File (RTF)		
RTF Parameter	Assessment	Comments
1. Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	
2. Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	
3. Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	Study# 809 & Study#849 (completed); Study #874 (proposed). Refer to Table 1 and Note below.
4. Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	
5. Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	#130432VSMB_BRN – method for latanoprost acid and latanoprostene bunod (i.e., LBN; the prodrug); #8268.033014 – method for the active metabolite, butanediol mononitrate (BDMN)
6. Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
7. Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	
8. Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
9. Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
Complete Application 10. Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or justification for not conducting studies, as agreed to at the pre-	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	

NDA or pre-BLA meeting? If the answer is 'No', has the sponsor submitted a justification that was previously agreed to before the NDA submission?		
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality) Checklist		
Data		
1. Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
2. If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	
Studies and Analysis		
3. Is the appropriate pharmacokinetic information submitted?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
4. Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	
5. Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	Dose-finding studies: A9441001 and 659.
6. Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	
7. Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	
General		
8. Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
9. Was the translation (of study reports or other study information) from another language needed and provided in this submission?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	

Table 1: Tabular Listing of Clinical Pharmacology Studies

Study ID	Number of Centers, Location	Study Design and Type of Control	Study Objectives	Test Product Dose, Route, and Regimen	Number of Subjects by Arm (Randomized)	Diagnosis of Subjects	Duration of Treatment
849 Phase 1	1 Japan	Single-center, single-arm, open-label study control: no	To evaluate clinical efficacy	LBN ophthalmic solution 0.024% QD (PM) bilateral for 14 days	LBN ophthalmic solution 0.024%: 24	Healthy subjects	14 days
809 Phase 1	1 US	Single-center, single-arm, open-label study control: no	To evaluate the systemic PK, safety and tolerability	LBN ophthalmic solution 0.024% QD (AM) bilateral for 28 days	LBN ophthalmic solution 0.024% : 22	Healthy subjects	28 days

Note:

The protocol of study #874, “*Evaluation of the Percent Methemoglobin-Time Course Profile Following Single and Repeat Instillations of Latanoprostene Bunod (LBN), 0.024%, in Healthy Volunteers - METEOROID Study*”, was submitted under IND 73435 on 08/28/2015. B&L anticipates submitting the clinical study report (CSR) during the review of the NDA. FDA agreed on 03/26/2015 that the sponsor may submit the CSR during the NDA review cycle.

The proposed study will be a single-center (in US), randomized, vehicle-controlled study of LBN 0.024% ophthalmic solution in approximately 12 healthy subjects (6 treated with LBN & 6 treated with vehicle). Systemic NO exposure will be evaluated by examining any changes in the percentage of methemoglobin (% MetHb) after a single ocular administration of and after a 7-day QD repeated topical bilateral ocular administration (i.e., on both Days 1 and 7).

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

/s/

YONGHENG ZHANG
09/11/2015

PHILIP M COLANGELO
09/14/2015