PharmaNote

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Latanoprostene Bunod (Vyzulta®): A New Ophthalmic Agent for Open-Angle Glaucoma and Ocular Hypertension

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Glaucoma is a chronic, progressive ocular disease consisting of increased intraocular pressure (IOP), also known as ocular hypertension (OHT), that may lead to damage to the optic nerve and vision loss.[1] Primary open-angle glaucoma (OAG) is the most common form of glaucoma. Glaucoma occurs when there is a slow and gradual blockage inhibiting the outflow of the aqueous humor. The inability of this fluid to drain is what leads to increased IOP and specifically, OAG occurs when there is a wide angle between the iris and cornea. Approximately, open-angle glaucoma accounts for up to 90% of all glaucoma cases and is one of the leading causes of blindness in the United States.[1] Prevalence data from the year 2010 estimates that approximately 2.8 million people in the United States are affected by OAG and this number is expected to increase to 3.4 million by 2020.[2]

It is crucial to decrease IOP to prevent further atrophy to the optic nerve and preserve visual function. Because increased IOP is a major risk factor for development of glaucoma, it is also necessary to reduce IOP in patients with OHT. Medications are the most common initial intervention to lower IOP (compared to laser therapy or incisional glaucoma surgery) and several agents have been approved for the treatment of OAG and OHT.[1] Common medication classes include prostaglandin analogs, beta-adrenergic antagonists, alpha-adrenergic agonists, parasympathomimetic agents, carbonic anhydrase inhibitors and hyperosmotic agents.

Prostaglandin analogs are one of the first-line treatments for OAG because they are highly efficacious at reducing IOP with a typical reduction ranging from 25% to 33%.[1] This class is also well-tolerated and the agents are administered once daily unlike many of the other therapies, which can improve patient adherence. FDA approved prostaglandin analogs for the treatment of glaucoma include latanoprost, bimatoprost, travoprost and tafluprost. Although prostaglandin analogs are efficacious and reducing IOP, many individuals require multiple medications for further reducing IOP in order to prevent further optic damage and preserve visual function. Latanoprostene bunod 0.024% (Vyzulta®), is a novel prostaglandin analog that was FDA approved in November 2017 for the treatment of OAG and OHT.[3] Studies have shown that latanoprostene bunod may be more efficacious at lowering IOP than current commonly used prostaglandin analogs due to a novel mechanism of action that can decrease IOP more than the current therapies by targeting both nonconventional and conventional aqueous outflow pathways. The purpose of this article is to discuss the pharmacology, clinical trials, adverse effects, dosing and administration and precautions of latanoprostene bunod in the treatment of OAG or OHT.

Pharmacology

Mechanism of Action

Latanoprostene bunod (LBN) is a nitric oxide donating prostanoid FP receptor agonist that is rapidly metabolized in the eye to latanoprost acid, an F2α prostaglandin analog, and butanediol mononitrate.[3] Nitric oxide (NO) is released from butanediol mononitrate, which reduces IOP primarily by causing relaxation of the trabecular meshwork and Schlemm's canal. Latanoprost acid decreases IOP through the uveoscleral pathway via remodeling of the extracellular matrices in the ciliary body. Together these two mechanisms increase the outflow of aqueous humor reducing IOP as well as the risk of glaucomatous visual field loss.[3]

Pharmacodynamics/Pharmacokinetics

Reduction of IOP begins approximately 1 to 3 hours following first administration.[3] Maximum effect is reached after 11 to 13 hours in eyes with elevated IOP. Systemic exposure of latanoprostene bunod and its active metabolites, latanoprost acid and butanediol mononitrate, was studied and 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) were detected post dose on day 1 or day 28.[2] The mean maximum 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 minutes post administration on both day 1 and day 28. There were no ocular distribution studies performed in humans.

Following ocular administration, latanoprostene bunod is rapidly metabolized to butanediol mononitrate and latanoprost

IN THIS ISSUE

Table 1 | Pharmacokinetics of Latanoprostene Bunod[3]

Parameter	Value
Absorption	
C_{max} (latanoprost acid)	Day 1: 59.1 pg/mL Day 2: 51.1 pg/mL
T_{max} (latanoprost acid)	~5 minutes
Distribution	N/A*
Metabolism	Rapidly degraded to latanoprost acid and butanediol mononitrate
Elimination	Undetectable 15 minutes after administration

*Not measurable as the drug is rapidly metabolized
C_{max} = maximum concentration; **mL** = milliliters; **pg** = pictograms; **T_{max}** = time to maximum plasma concentration

acid[3]. Once latanoprost acid reaches systemic circulation it is metabolized by the liver via fatty acid β-oxidation to the 1, 2-dinor and 1, 2, 3, 4-tetranor metabolites. Butanediol mononitrate is metabolized to NO and 1, 4-butanediol which is further oxidized to succinic acid and enters the tricarboxylic acid cycle. Latanoprost acid plasma concentration dropped below the LLOQ (30 pg/mL) by 15 minutes following ocular administration in the majority of subjects. See **Table 1** for a summary of pharmacokinetic parameters.

Clinical Trials

There have been five studies evaluating the safety and efficacy of latanoprostene bunod for the treatment of OAG and OHT. The trials include one prospective trial, one phase II trial and three phase III trials. Additionally, change from baseline in IOP was generally the primary outcome of each study, and an IOP reduction of 20-30% from baseline is considered significant for the initial treatment of OAG.[1] Other efficacy measurements are best corrected visual acuity (BCVA), which is considered to be the best vision a patient can achieve with correction as measured by the standard Snellen eye chart[4] BCVA is scored by the Logarithm of the Minimum Angle of Resolution (LogMAR) chart, LogMAR of +0.7 units correlates with a visual acuity of 20/100. BCVA is measured using cup-to-disk ratio, split fixation and decimal visual acuity.[5] Cup-to-disk ratio refers to the diameter of the "cup" portion of the optic disk compared to the total diameter of the optic disk as patients with glaucoma often have more cupping of the optic disk than patients without glaucoma.[6] A normal cup-to-disk ratio is 0.3.[7] Split fixation correlates to visual field loss and is defined as retinal sensitivity of zero in all of the tested locations of the visual field.[8] Decimal visual acuity is similar to BCVA except visual acuity values are represented as a decimal instead of on a logarithmic scale.[5] Below, an overview of the design, patient population, intervention, primary and secondary outcomes as well as results of each study will be discussed. A summary of these trials can be found in **Table 2**.

VOYAGER Study

The VOYAGER study was a phase II, randomized, single-blinded, parallel-group, dose-ranging study that compared the safety and efficacy of four different concentrations of latanoprostene bunod (0.006%, 0.012%, 0.024% or 0.040%) with latanoprost 0.005% ophthalmic solution in subjects with OAG or OHT.[9] The study took place in 23 investigative sites in the United States and European Union. Subjects were included if they were 18 years of age or older, had a diagnosis of OAG or OHT in one or both eyes, had an IOP of 22-32 mmHg with an IOP of ≥24 mmHg for at least two of three measurements at baseline, and had a BCVA of 0.7+ logMAR or better in either eye. Subjects were excluded if they participated in any clinical trial within 30 days prior to screening, had a known hypersensitivity or contraindication to latanoprost, hypersensitivity to any ingredient in the study drugs or known contraindications to NO-donating treatment, were unable to discontinue contact lens use during and for 15 minutes following instillation of study medication, had central corneal thickness >60 μm in either eye, had advanced glaucoma, had any other significant ophthalmic disease or required treatment with ocular or systemic corticosteroids. The primary efficacy endpoint was reduction or change from baseline in mean diurnal IOP at visit 6. The primary safety endpoint was incidence of ocular and systemic AEs including severity of and relation to the study agents.

A total of 598 subjects were randomly assigned in a 1:1:1:1:1 ratio to one of five treatment groups, latanoprostene bunod solution (0.006% (n=82), 0.012% (n=85), 0.024% (n=83) and 0.040% (n=81)) or latanoprost 0.005% solution (n=82).[9] Subjects were to administer one drop of the study solution into the affected eye(s) nightly. Only one eye was studied per patient. If both eyes qualified for the study, the eye with the greater mean IOP on day 0 was studied. Only the investigator was blinded during this study because the active control bottle was visibly different than the latanoprostene bunod bottles and a designee other than the investigator was responsible for distributing bottles. Subjects attended 5 study visits (Day 1, Day 7, Day 14, Day 28 and Day 29) and at each visit, IOP was measured at 8am, 12pm and 4pm. Safety assessments included AEs, BCVA, ocular tolerability, ocular signs and vital signs.

All treatments led to reductions in mean diurnal IOP from baseline ($p < 0.0001$, paired t-test).[9] Magnitude of IOP reductions were dose-dependent in the latanoprostene bunod groups with a plateau effect at doses above latanoprostene bunod 0.024% (latanoprostene bunod 0.006%, mean IOP reduction from baseline = -7.81 mmHg; latanoprostene bunod 0.012%, -8.26 mmHg; latanoprostene bunod 0.024%, -9.00 mmHg; latanoprostene bunod 0.040%, -8.93 mmHg, respectively). The latanoprostene bunod 0.024% and latanoprostene bunod 0.040% groups showed statistically significantly higher reductions in diurnal IOP than the latanoprost group which had a mean reduction in diurnal IOP of -7.77 mmHg ($p=0.005$ and $p=0.009$, respectively). Adverse events are reported in the adverse event section of this manuscript. BCVA, vital signs, ocular signs and tolerability assessments were unremarkable.

JUPITER Study

The JUPITER study was a single-arm, open-label trial that evaluated the long-term safety and efficacy of latanoprostene bunod over one year in Japanese subjects with OAG or OHT.[10] Inclusion criteria were age ≥20 years, diagnosis of OAG or OHT in one or both eyes, mean/median IOP ≥15 mmHg and ≤36 mmHg in at least one eye and IOP ≤36 mmHg in both eyes at baseline, BCVA of ≥0.5 in both eyes and a central corneal thickness ≤600 μm. Subjects were excluded if they participated in another trial within 30 days, had known hypersensitivity or contraindication to any of the ingredients in the study treatments, were

Table 2 | Summary of Clinical Trial Outcomes for Latanoprostene Bunod

Trial	Design	Treatments	Primary Endpoint	Results
VOYAGER[9]	Randomized, investigator-masked, parallel group, dose-ranging study	• LBN 0.006% QPM (n=82) • LBN 0.012% QPM (n=85) • LBN 0.024% QPM (n=83) • LBN 0.040% QPM (n=81) • Latanoprost 0.005% QD (n=82)	Reduction in mean diurnal IOP at Day 28	• LBN 0.006%: IOP reduction = -7.81 mmHg • LBN 0.012%: IOP reduction = -8.26 mmHg • LBN 0.024%: IOP reduction = -9.00 mmHg • LBN 0.040%: IOP reduction = -8.93 mmHg • Latanoprost 0.005%: IOP reduction = -7.77 mmHg LBN 0.024% vs latanoprost (p = 0.005)
JUPITER[10]	Single-arm, multicenter, open-label study	LBN QPM (n=130)	Percent reductions from baseline in IOP at 52 weeks	• 26.3% reduction in study eye • 23.0% reduction in fellow treated eye* • p <0.001 (change from baseline for both eyes)
CONSTELLATION[11]	Prospective, open-label, randomized, crossover study	• LBN QPM (n=21) • Timolol BID (n=21)	Mean change in diurnal and nocturnal IOP from baseline at 4 weeks	**Diurnal IOP** • LBN: 17.6 +/- 2.5 mmHg vs Timolol: 18.9 +/- 2.4 mmHg • Not significant (p-value unreported) **Nocturnal IOP** • LBN: 23.2 +/- 3.4 mmHg vs timolol: 25.6 +/- 3.2 mmHg • P <0.001
APOLLO[12]	Phase 3, randomized, controlled, noninferiority, multicenter, double-masked, parallel group study	• LBN 0.024% QPM (n=283) • Timolol 0.5% BID (n=135)	Mean IOP in the study eye at each of the 9 assessments over 3 months of treatment	• LBN 0.024% : 17.8 to 18.7 mmHg -vs- • Timolol 0.5%: 19.1 to 19.8 mmHg • Noninferiority comparison: p <0.002
LUNAR[13]	Prospective , randomized, double-masked, parallel group, non-inferiority trial	• LBN 0.024% QPM with vehicle QAM (n=278) • Timolol BID (n=136)	Mean IOP reduction at 9 separate daily time points after 3 months of treatment	Mean IOP reduction with LBN was noninferior to timolol at 8 of 9 time points (p ≤ 0.025 for comparison)

LBN = latanoprostene bunod 0.024% solution; **IOP** = intraocular pressure; **QAM** = once daily in the morning; **QPM** = once daily in the evening; **BID** = twice daily
*Treated fellow eyes were eyes that were not considered to be the study eye but still received treatment

unable to discontinue contact lens use during and 15 minutes after instillation of the study drug, had a history of significant ophthalmic disease or required the use of systemic or ocular steroids. Eligible subjects administered one drop of latanoprostene bunod 0.024% into the study eye once daily in the evening for 52 weeks and were evaluated every 4 weeks. Treated fellow eyes were considered to be eyes that underwent the conventional treatment although they were not considered to be the study eye. The primary efficacy endpoints were absolute IOP values and reduction from baseline IOP. Safety endpoints were AEs, vital signs, corrected decimal visual acuity, slit-lamp examination, ophthalmoscopy, photographs, visual field assessment, gonioscopy and pachymetry.

The results at week 52 for the primary outcomes of absolute IOP values and reduction from baseline IOP revealed that IOP percent reductions of 26.3% were seen in the study eye.[10] In both study eyes and treated fellow eyes, there was a statistically significant reduction in IOP from baseline (26.3% and 23.0%, respectively) [p<0.001] at every study visit. MDVA did not significantly differ over the course of treatment. Other than increased number of abnormal iris findings, no other ocular assessments were remarkable. Analysis of iris photographs showed that at week 52, 10.0% (13/130) of study eyes and 8.8% of (11/125) of treated fellow eyes were judged as having a clear iris pigmentation increase from baseline; and an additional 14.6% (19/130) of study eyes and 13.6% (17/ 125) of treated fellow eyes were judged as having a possible iris pigmentation increase from baseline. There were no notable results from visual field assessments, gonioscopy or pachymetry. Complete details of reported adverse events are covered in the adverse events section of this manuscript.

CONSTELLATION Study

The CONSTELLATION study was a prospective, open-label, randomized crossover trial that compared the diurnal and nocturnal IOP lowering effects of latanoprostene bunod 0.024% to that of timolol maleate 0.5% solution in patients with OAG or OHT.[11] Inclusion criteria were age between 40-90 years with untreated IOP ≥22 mmHg in one eye and ≤36 mmHg in both eyes. Subjects were excluded if they had previous glaucoma surgery, had past ocular trauma, had a sleep disorder, ocular inflammation, narrow iridocorneal angle, severe cardiovascular or diabetic condition or used a medication that could interfere with the safety and efficacy of the study agent. Vitals were obtained at baseline and IOPs were taken at baseline in a sleep laboratory every 2 hours during a 16-hour diurnal period and during an 8 hour sleep period. Subjects were randomized to receive either latanoprostene bunod 0.024% once daily or timolol 5% BID. IOP values were recorded again after 4 weeks followed by a crossover period of 4 weeks with subsequent vital and IOP recordings.

The main objective was to compare the change in mean IOP from baseline over the diurnal period and sleep period, between the latanoprostene bunod and timolol groups.[11] Mean arterial pressure, mean ocular perfusion pressure and mean heart rate were also calculated over the diurnal period and the sleep period; values were compared between groups. A total of 25 subjects were enrolled in this study. Diurnal IOP levels were significantly lower than baseline values in both the latanoprostene bunod and timolol groups (in the range of 2.3 to 3.9 mmHg; p<0.001). The IOP difference between the two groups (1.1 to 1.2 mmHg) was not statistically significant. In the latanoprostene bunod 0.024% group, sleep period IOP values were significantly lower than baseline (2.5 ± 3.1 mmHg lower, p=0.002) and the timolol group (2.3 ± 3.0 mmHg lower, p=0.004). Diurnal IOP reduction was larger than nocturnal IOP reduction in the latanoprostene bunod 0.024% group (difference 1.5 ± 3.0 mmHg, p=0.039, paired t-test). There were no significant changes in mean arterial pressure during treatment. Diurnal ocular perfusion pressure was significantly greater in the latanoprostene bunod 0.024% group compared to baseline (p<0.001). Heart rate was significantly lower than baseline in the timolol group (p<0.001). Reported adverse events in this study can be found in **Table 3**.

APOLLO Study

The APOLLO study was phase 3, randomized, multicenter, double masked, parallel group clinical trial that compared the diurnal IOP-lowering effect of latanoprostene bunod 0.024% ophthalmic solution once nightly to timolol maleate ophthalmic solution twice daily (BID) in subjects with OAG or OHT.[12] The APOLLO study was conducted in two phases, an active-controlled 3-month efficacy phase to establish non-inferiority, followed by an open-label 9-month safety extension phase to compare the safety of latanoprostene bunod 0.024% to timolol maleate. The primary outcome in the study was mean IOP reduction of latanoprostene bunod 0.024% compared to timolol maleate. The key secondary endpoints were proportion of subjects with IOP ≤18 mmHg and proportion of subjects with IOP reduction ≥25%, both at all 9 time points (measured at 8am, 12pm and 4pm at week 2, week 6 and month 3 follow-up visits) in the first 3 months. Safety endpoints for each study included BCVA, conjunctival hyperemia assessment and incidence of ocular and systemic AEs. The study was conducted at 45 investigational sites in the United States and Europe.

Inclusion criteria were ≥18 years of age, diagnosis of OAG or OHT in one or both eyes, baseline IOP ≥26 mmHg at a minimum of 1 time point, IOP of 24 mmHg or greater a 1 time point in the same eye, or IOP of 36 mmHg or below at all 3 measurement time points in both eyes, and a best-corrected visual acuity (BCVA) of +0.7 (logMAR) units or better in either eye.[12] Subjects were excluded if they had participated in any clinical trial within 30 days before screening for subjects requiring a washout period or 30 days before baseline for subjects not requiring a washout period, known hypersensitivity or contraindications to latanoprost, NO-donating medications, timolol maleate, other beta-adrenergic receptor antagonists or sensitivity to any ingredients in study drugs, central corneal thickness >600 μm in either eye, any condition that prevented reliable applanation tonometry, concurrent treatment with ocular corticosteroids, systemic corticosteroids or other agents that may affect IOP, advanced glaucoma (cup -to-disk ratio >0.8 or split fixation) or other significant ophthalmic disease.

Once baseline IOP measurements were obtained, eligible subjects were randomized in a 2:1 fashion to receive either latanoprostene bunod 0.024% once daily in the evening (QPM) and placebo once daily in the morning (QAM) or timolol 0.5% BID for three months.[12] Only one eye was studied per patient. If both eyes qualified for the study, the eye with the greater mean IOP on day 0 was studied. After randomization, subjects were to complete study visits at week 2, week 6 and month 3. At each visit, IOP was measured at 8am, 12pm and 4pm using the Goldmann applanation tonometer. Safety was assessed by adverse events (AE), vital signs, BCVA, conjunctival hyperemia assessment, slit-lamp examination findings, ophthalmoscopy findings and specular microscopy. The primary efficacy analysis was performed with an analysis of covariance (ANCOVA) in the intention-to-treat (ITT) popula-

tion. The ITT population consisted of all randomized subjects who instilled at least 1 dose of study drug and had a least 1 post-baseline IOP assessment.

In the APOLLO Study, of 679 subjects screened, 420 were randomized to receive either latanoprostene bunod 0.024% (n= 264) or timolol 0.5% (n=123) and a total of 387 subjects completed the study and were analyzed.[12] For the primary outcome, mean IOP was significantly lower in the latanoprostene bunod 0.024% group (range 17.8 to 18.7 mmHg) than the timolol 0.5% group (range 19.1 to 19.8 mmHg) at all efficacy time points and established noninferiority between the two treatments ($p \leq 0.002$ at all time points). Likewise, secondary analysis of the ANCOVA results demonstrated the superiority of latanoprostene bunod 0.024% to timolol 0.5% in the ITT population as the upper limit of the 95% CIs for the difference between treatments was 0 mmHg at all 9 time points. For the other secondary outcomes, a higher percentage of subjects in the latanoprostene bunod 0.024% group (22.9%) had an IOP <18 mmHg at all efficacy time points in comparison to the timolol 0.5% group (11.3%) (Difference = 11.6%; 95% CI, 4.3% to 18.9%). Also, a higher percentage of subjects in the latanoprostene bunod 0.024% group (34.9%) had an IOP reduction >25% at all efficacy time points in comparison to the timolol 0.5% group (19.5%) (Difference = 15.3%; 95% CI, 6.6% to 24.0%). Mean logMAR BCVA values did not significantly differ between groups over the course of this study.

LUNAR Study

The LUNAR study was conducted with the same design as the APOLLO study and was also conducted in two phases, an active-controlled 3-month efficacy phase followed by an open-label 3-month safety extension.[13] In addition to design, the LUNAR study also shared the same inclusion and exclusion criteria as well as primary, secondary and safety endpoints, interventions, measurements and statistical analysis as the APOLLO study.

In the LUNAR study, 420 participants were randomized to latanoprostene bunod 0.024% (n=283) or timolol 0.5% (n=137) with a total of 387 subjects that completed the study and were analyzed.[13] For the primary endpoint, mean IOP was significantly lower in the latanoprostene bunod 0.024% group than the timolol 0.5% group in the majority of measured time points (12pm, 4pm at week 2, 8am, 12pm, 4pm at week 6 and month 3) with a p value of <0.025 for each time point measuement. Noninferiority of latanoprostene bunod 0.024% to timolol 0.5% was demonstrated based on ANCOVA results (upper limit of the 95% CIs did not exceed 1.0 mmHg at any of the 9 time points). Latanoprostene bunod 0.024% also met the criteria for statistical superiority over timolol 0.5% at all time points except the 8 AM time point at week 2 (upper limit of the 95% CI exceeded 0 mm Hg at this single assessment point). Similarly, to the APOLLO study secondary outcomes, a higher percentage of subjects in the latanoprostene bunod 0.024% group (31.0%) had an IOP reduction >25% at all efficacy time points in comparison to the timolol group (18.5%) (Difference = 12.5%; 95% CI, 4.0% to 21.1%). For the percentage of subjects with mean IOP ≤18 mmHg at all 9 time points, there was not a significant difference between the latanoprostene bunod 0.024% (17.7%) and timolol (11.1%) groups (difference of proportions, 6.6%; 95% CI: -0.4% to 13.5%). Mean logMAR BCVA values did not significantly differ between groups over the course of this study. Reported adverse events for each trial are included in the adverse event section along with a **Table 3**.

Adverse Effects and Precautions

In the VOYAGER study, at day 28, a higher incidence of ocular AEs were reported in the latanoprostene bunod groups in comparison to the latanoprost group and events were most commonly reported as instillation site pain.[9] Ocular hyperemia was more frequently reported in the latanoprost group (8.5%) than in the latanoprostene bunod groups (1.2%, 6.0%, 2.4%, and 4.9%). All ocular AEs were considered to be mild or moderate in severity. The only non-ocular event considered to be potentially treatment related was headache (1 subject in each of the latanoprostene bunod 0.012%, latanoprostene bunod 0.024% and latanoprost groups).

In the JUPITER study, at 52 weeks, ocular AEs were reported in 48% of study eyes and were most frequently reported as conjunctival hyperemia (17.7%), growth of eyelashes (16.2%), eye irritation (11.5%) and eye pain (10.0%).[10] Ocular AEs were considered to be mild to moderate in severity. No non-ocular AEs were considered to be related to the study drug. Frequencies of commonly reported study adverse events are provided in **Table 3**.

The most commonly reported adverse events at month 3 in the APOLLO and LUNAR trials were conjunctival hyperemia (6%), eye irritation (4%), eye pain (3%) and instillation site pain (2%).[12,13] Other adverse reactions occurring in <1% of subjects for latanoprostene bunod 0.024% include increased pigmentation, eyelash changes, intraocular inflammation, macular edema and bacterial keratitis. Approximately 0.6% of combined study subjects discontinued treatment in the latanoprostene bunod 0.024% arms of the APOLLO and LUNAR trials due to ocular hyperemia, conjunctival irritation, eye irritation, eye pain, conjunctival edema, blurred vision, punctate keratitis or foreign body sensation.

Latanoprostene bunod may cause changes to pigmented tissues, particularly of the iris and periorbital tissue (eyelid), due to increased melanin content in the melanocytes.[3] This is the most frequently reported change with prostaglandin analogs and is expected to increase as long as latanoprostene bunod is administered. After discontinuation of latanoprostene bunod, pigmentation changes of periorbital tissue are likely to be reversible while pigmentation changes of the iris are usually permanent. Typically, the brown pigmentation around the pupil spreads towards the periphery and parts of the iris or the entire iris become more brown which may not be noticeable for several months to years. Latanoprostene bunod may also cause increased length, thickness and number of eyelashes but these changes are usually reversible upon discontinuation of treatment.

Latanoprostene bunod may exacerbate intraocular inflammation and should be used with caution in patients with a history of intraocular inflammation (iritis/uveitis).[3] It should also be used with caution in aphakic patients, in pseudophakic patients with a torn posterior lens capsule or patients with risk factors for macular edema as macular edema has been reported during treatment with prostaglandin analogs. Use of multiple-dose containers of topical ophthalmic agents have resulted in bacterial keratitis usually due to containers that have been contaminated by patients who had corneal disease or disruption of the ocular epithelial surface. Avoid use of latanoprostene bunod with contacts in place because this product contains benzalkonium chloride (may insert contacts 15 minutes after administration). There are no known drug interactions with latanoprostene bunod.

Table 3 | Reported Adverse Events from Clinical Trials

Adverse Effect	VOYAGER[9] (LBN[a] vs Lat)	JUPITER[10] (LBN)	CONSTELLATION[11] (LBN vs Tim)	APOLLO[12] (LBN vs Tim)	LUNAR[13] (LBN vs Tim)
Conjunctival hyperemia	4.8% vs 0.0%	17.7%	0.0% vs 0.0%	2.8% vs 1.5%	9.0% vs 0.7%
Eye irritation	3.6% vs 0.0%	11.5%	0.0% vs 0.0%	3.9% vs 2.2%	7.2% vs 4.4%
Eye pain	0.0% vs 0.0%	10.0%	0.0% vs 0.0%	1.4% vs 0.7%	5.8% vs 3.7%
Instillation site pain	12% vs 6.1%	0.0%	0.0% vs 4.3%	1.1% vs 1.5%	1.4% vs 0.0%

Data represents adverse event incidence with percent of study population
a: 0.024% concentration of latanoprostene bunod
LBN = latanoprostene bunod 0.024% solution; **Tim** = timolol maleate 0.5% solution; **Lat** = latanoprost 0.005% solution

Dosing and Administration

Latanoprostene bunod is a 0.24 mg/mL topical ophthalmic solution that should be administered as one drop into the conjunctival sac of the affected eye(s) once daily in the evening.[3] Administration more frequently than once daily may decrease the IOP lowering effect. If administering latanoprostene bunod with other ophthalmic agents, separate administration of each product at least five minutes apart.

This agent is supplied as a 7.5 mL bottle with a fill volume of 5 mL.[3] During shipment, bottles may be stored for up to 14 days at a temperature of up to 40°C (104°F). Unopened bottles should be refrigerated at 2° to 8°C (36° to 46°F). Once opened, a bottle should be store at 2° to 25°C (36° to 77°F) for up to 8 weeks.

There are no available human data for the use of latanoprostene bunod during pregnancy. The lack of effects of latanoprostene bunodon the breastfed infant or the effects on milk production is likely due to the low systemic absorption at the FDA approved dose.[3] There are no clinical differences in safety or efficacy in the elderly population. Latanoprostene bunod is not recommended in pediatric patients 16 years or younger due to potential safety concerns related to pigmentation following long-term use. There are no necessary dose adjustments for patients with hepatic or renal dysfunction.

Conclusions

With the serious progressive nature of OAG and OHT it is important to initiate therapy to decrease IOP to prevent optic nerve damage and vision loss. Vyzulta® (latanoprostene bunod 0.024% ophthalmic solution) is the newest FDA approved agent in the prostaglandin class, which reduces IOP in patients with OAG or OHT with once daily dosing. Multiple phase 3 clinical trials have demonstrated the safety and efficacy of Vyzulta® in comparison to current common IOP lowering therapies. These trials have also demonstrated that Vyzulta® has superior IOP lowering effects than some of the current therapies (timolol maleate 0.5% and latanoprost 0.005%). The most commonly reported adverse events were considered mild or moderate in severity and included conjunctival hyperemia, eye irritation, eye pain and instillation site pain. Overall, Vyzulta® may be an appropriate therapy choice in patients with OAG or OHT.

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Secnidazole (Solosec®): A New Single-Dose Treatment for Bacterial Vaginosis

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Bacterial Vaginosis (BV) affects over 21 million women in the United States and is the most common vaginal infection in reproductive-age women aged 14 to 49 years, affecting an estimated 29% of women.[1] It occurs when the normally dormant Lactobacillus spp, which produce hydrogen peroxide in the healthy vagina, is disturbed leading to an increased vaginal pH and a shift in microbiota.[2-3] The most common pathogens involved in BV are *Garderella vaginalis*, *Prevotella*, *Peptostreptococcus*, and *Bacteroides spp.*[4] Aside from distressing symptoms, BV is also associated with an increased risk of serious health complications including an approximate two-fold increased risk of acquiring Sexually Transmitted Infections (STIs) including HIV, and herpes simplex type 2 infection.[5] The dangers of BV extend beyond the directly affected women, it also raises the risk of transmitting HIV to male partners by more than three-fold as well as increasing the risk of miscarriage by six-fold.[6-7] Diagnosis is made using the "Amsel criteria" which includes a vaginal pH of >4.5; a fishy odor when vaginal discharge is mixed with 10% potassium hydroxide; and the presence of clue cells (epithelial cells coated with bacteria).[7] The Nugent assay, which relies on more objective observation of gram-stained vaginal secretions, may also be used as a diagnostic tool. This assay uses a scale from 0-10 where a score of 7-10 is consistent with bacterial vaginosis and a score of 0-4 is indicative of a normal *Lactobacillus* flora.[2]

The current first-line treatment options recommended by the U.S. Center for Disease Control (CDC) include; oral metronidazole, topical metronidazole, or topical clindamycin.[5] Additional second-line therapies include oral tinidazole or oral clindamycin.[5,9] Despite the availability of multiple treatment modalities, a high recurrence rate of 30% has been observed at 60 days post-treatment.[10] It is also worth noting that difficulties with swallowing pills may also represent an underrecognized problem for select populations.[11] Secnidazole (Solosec®) is a single dose treatment that has recently been approved by the FDA for the treatment of BV. Secnidazole has been available in Europe for several years as an alternative to metronidazole therapy. The purpose of this article is to review the safety and efficacy data of secndiazole for the treatement of BV.

Clinical Pharmacology

Secnidazole is a 5-nitroimidazole antibiotic which carries out its anti-bacterial activity by entering bacterial cells. Within the cells, it is reduced to radical ions which interfere with DNA synthesis therefore stopping bacterial replication. The nitro group is selectively reduced by bacterial enzymes thus human cells are not harmed. Other members of this class include metronidazole and tinidazole. Currently there are two other agents within this class of drugs, metronidazole and tinidazole, both used for the same indication with only the duration differing. Antibiotics in this class share a common spectrum of activity against anaerobic microorganisms commonly found to cause BV (*Garderella vaginalis*, *Prevotella*, *Peptostreptococcus*, and *Bacteroides spp)* while having limited activity against vaginal Lactobacillus species.[13] Additionally 5-nitroimidazoles also appear particularly effective in the treatment of amoebiasis, giardiasis, and trichomoniasis.[14]

The median time to peak concentration (Tmax) was 4 hours following administration of secnidazole 2 g. The half-life range in healthy adults is 17-39 hours which allows secnidazole to be taken as a single dose. For comparison, the average half-life of metronidazole is 8 hours. Secnidazole is mostly metabolized in the liver by CYP450 enzymes and approximately 15% is excreted in the urine unchanged.[15] In vitro studies have shown that even though Secnidazole is extensively metabolized by over 30 different CYP 450 enzymes, there is minimal potential for interactions with CYP 450 substrates, inhibitor, or inducers.[16] See **Table 1** for information on Secnidazole pharmacology.

Clinical Trials

Secnidazole had previously been available in overseas markets for several years before the agent gained interest in the United States. Several clinical trials were conducted for FDA mandated safety and efficacy results before approval in the United States. These trials included two phase I, a phase II, and a pair of phase III trials. Additionally, a phase III international trial was referenced extensively since it was the only head-to-head trial comparing secnidazole directly to metronidazole. The following section discusses the clinical trials with results summarized in **Table 2**.

Phase I Trials

Conducted by Pentikis and Adetoro, the two phase I trials were published together as one article.[17] These single-center, single-dose, randomized crossover studies were performed to determine the pharmacokinetics of secnidazole 2 g under various dosing conditions. The population studied in both trials included overall healthy reproductive-age women. In the first of the two studies (study 102) the primary objective was to determine if the pharmacokinetics of secnidazole were affected by fasting and non-fasting state. Participants in both treatment groups received a single-dose of secnidazole 2 g administered in granules sprinkled over applesauce. The subjects were asked to fast overnight for >10 hours then randomized into two groups, fasting vs non-

Table 1 | Secnidazole Pharmacokinetics[13-16]

Parameter	Value*
Absorption	
C_{MAX}	45.4 mcg/mL
T_{MAX}	4 hours
Distribution	
V_d	42 L
Metabolism	
Pathway	>30 CYP450 enzymes
Elimination	
Excretion	~15% unchanged renally
Clearance	25 mL/min
$T_{1/2}$	17-39 hours

*: Values are reported as averages
C_{MAX} = maximum concentration; **CYP450** = cytochrome P450; **mcg** = microgram; **min** = minute; **mL** = milliliter; **$T_{1/2}$** = half-life; **T_{MAX}** = time to maximum concentration; **Vd** = volume of distribution

fasting. The fasting group was given medication with just 4 oz of applesauce. In the non-fasting group, administration of secnidazole was preceded by a high-fat, high-calorie breakfast served to the subjects 30-minutes before dosing. Each group was given 240 mL of water, with no additional food allowed for 4 hours following administration. Blood samples were collected for determination of secnidazole plasma concentrations at various intervals starting at 15 minutes and up to 96 hours following administration. Similar secnidazole plasma concentrations were evident when administered under both conditions. The mean half-life observed was 17.53 hours (+/- 2.8 hours) for the fasting group and 16.9 hours (+/- 2.5 hours) for the non-fasting group. No difference was found between the groups for any of the measured parameters. The secondary objective of study 102 was to examine the safety of secnidazole. The most common adverse drug effects (ADEs) reported by participants included headaches (41.7%), nausea (12.5%), and dysgeusia (distortion of the sense of taste, 20.8%); however, no placebo values were reported.

The second phase I trial (study 103) had a similar study population and methods. The primary objective was determination of pharmacokinetic changes when secnidazole was administered with different foods.[17] Participants were randomized into three groups each receiving secnidazole 2 g administered by sprinkled granules in applesauce (n = 24), yogurt (n = 24), or pudding (n = 23). The foods in this study were selected based on variations in properties such as water content and pH to provide a range of conditions to account for individual patient preferences for drug consumption. Secnidazole plasma concentrations were obtained at intervals starting at 15 minutes following administration and up to 96 hours after administration. Mean secnidazole plasma concentration-time profiles for all three food administrations were not statistically different. The secondary objective of study 102 was to examine the safety of secnidazole. The most common ADEs with secnidazole were headaches (50%), constipation (41.7%), somnolence (33.3%), and nausea (16.7%); however, no placebo values were reported. No severe ADEs leading to discontinuation occurred. Additionally, no clinically significant changes in laboratory, physical examination, and vital sign findings were observed in the studies.

Phase II Trials

Hillier et al. conducted a randomized, double-blind, dose-ranging, placebo-controlled, multi-center phase II study to evaluate the efficacy of Secnidazole 1 g and 2 g dosing for the treatment of BV.[18] Patients were randomized in a 1:1:1 ratio to receive either secnidazole 1 g orally once (n= 71), secnidazole 2 g orally once (n=72) or matching placebo (n=72). The primary endpoint measured was clinical cure, described as normalization of vaginal discharge, odor, and number of clue cells (<20% of total epithelial cells), 21-30 days following treatment. Secondary endpoints included microbiologic cure, defined as a Nugent score of 0-3, and a therapeutic cure, defined as meeting the criteria for both clinical and microbiologic cure. Patients included were adult females diagnosed with recurrent BV based on a Nugent score of greater than 4. Exclusion criteria were were pregnancy, STIs present at baseline, Nugent Score <4, or antimicrobial therapy in the previous 14 days.

The primary outcome, clinical cure rate, occurred in 51.6% of the secnidazole 1 g group, 67.7% of the secnidazole 2 g group, and 17.7% of the placebo group ($p<0.001$ for both secnidazole doses compared to placebo). The secondary endpoint, microbiologic cure, occurred in 23.4% of the secnidazole 1 g group, 40.3% of the secnidazole 2 g group, and 6.5% of the placebo group ($p<0.001$ secndiazole 2 g compared to placebo; $p<0.007$ secndidzole 1 g compared to placebo). A similar trend was observed for therapeutic cure with an occurrence of 21.9% in the secnidazole 1 g group, 40.3% in the secnidazole 2 g group, and 6.5% in placebo. The results demonstrated that both 1 g and 2 g doses were superior to placebo, and that 2 g dosing was superior to 1 g supporting the development of secnidazole 2 g for treating BV. As with the previous Phase I studies, all treatment-emergent adverse events were mild to moderate with no severe ADE were reported. The most common ADEs reported were nausea, dysgeusia, and yeast infection which were similar in frequency across both groups which received secnidazole.

Phase III Trials

Published in France in 2010, a phase III double-blind, double-dummy, non-inferiority trial compared the efficacy of secnidazole for treatment of bacterial vaginosis to metronidazole.[12] Patients were randomly allocated in a 1:1 ratio to receive either a single-dose of secnidazole 2 g orally (n = 290) or metronidazole 500 mg orally twice daily for 7 days (n = 287). The primary outcome measured was therapeutic cure defined as a composite of clinical cure (normalization of the three Amsel criteria; vaginal discharge, a negative KOH whiff test, vaginal pH <4.5) and bacteriological cure (Nugent score <4) measured after 28 days of treatment. Participants were selected following inclusion criteria requiring subjects to be non-pregnant women aged 18-65 years (mean 36 years) with clinical signs of Bacterial Vaginosis and diagnosis established based on the Amsel criteria. Patients were excluded if they had previously received antibiotic or antifungal medications within the past 14 days. The primary outcome, therapeutic cure rate at 28 days after start of intervention, as measured by the intention-to-treat (ITT) population occurred in 58.3% of the secnidazole group and in 57.8% of the metronidazole group (secnidazole-metronidazole difference 95% CI = -7.6% to 8.5%) with an average time to resolution of BV symptoms of 7.12 days and 6.83 days in the metronidazole and secnidazole group, respectively. The secondary outcome, clinical cure rate, occurred in 77% of the secnidazole group and 79.3% of the metronidazole group (secnidazole-metronidazole difference = -2.3%; 95% CI = -9.8% to 5.2%) after 28 days from the initial treatment further demonstrating that secnidazole was non-inferior to metronidazole. A similar proportion of ADEs were reported between groups, 38% of metronidazole group reported at least one ADE and 39% in the secnidazole group reported at least one ADE. No differences were observed in the frequencies of ADE classified by organ system with the exception of headaches more frequently reported in the secnidazole group (n = 10 versus n = 4 in the metronidazole group).

Published in 2017, a phase III, prospective, double-blind, placebo controlled study examined the efficacy of a single dose of secnidazole 2 g for the treatment of BV.[19] Enrollment criteria included women with a clinical diagnosis of bacterial vaginosis (defined as meeting the Amsel criteria for BV). In total 164 women, age 18-54, were enrolled and randomized assigned in a 2:1 ratio to receive a single dose of secnidazole 2 g (n = 107) or matched placebo (n = 57). Participants were excluded if they had a Nugent score <4 or if they had a separate STI present during randomization. The primary endpoint was the proportion of clinical responders, defined as normalization of the three Amsel criteria measured between 21 and 30 days after medication administration. The participants were followed for 21 to 30 days after the

administration of a single oral dose of secnidazole 2 g sprinkled over 4 oz of applesauce regardless of fed status. The clinical outcome responders rate at the end of the study visit was 53.3% (n = 57) for the secnidazole 2 g group vs 19.3% (n = 11) for the placebo group (P < 0.001) demonstrating that secnidazole was superior to placebo. The overall rate of ADEs was reported as 34.4% (n=37) and 21.9% (n=13) for the secnidazole and placebo group, respectively. Most ADEs were mild or moderate intensity and none led to study discontinuation. The most common adverse events reported in the secnidazole group included; vulvovaginal candidiasis/mycotic infection (13.6%), nausea (4.8%), and headache (4.8%). The results reported support secnidazole as an effective and well-tolerated treatment for BV.

A more recent phase III, prospective, single-arm, open-label study evaluated the safety of secnidazole 2 g for the treatment of BV.[20] Enrollment criteria included non-pregnant females over the age of 12 with a clinical diagnosis of BV, defined by the Amsel criteria. Exclusion criteria were pregnancy, vaginal bleeding, confirmed alternative causes of vaginal symptoms, or concomitant anti-microbial/fungal therapies. Treatment was provided as a single-dose of secnidazole 2 g orally administered with 4 oz of applesauce (unsweetened), followed by 8 oz of water regardless of additional meals. Patients were provided treatment on day 1 and contacted by telephone once between days 8 and 10 with a final end-of-study visit conducted on days 21-30. The purpose of these phone calls was to gather data regarding the ADEs experienced by participants. The primary objective of this study was to assess safety outcomes including TEAEs, and serious adverse events (SAEs, defined as severe if they were incapacitating and resulted in an inability to perform normal activities). A total of 283 patients completed the study. The overall number of reported treatment emergent adverse events (TEAEs) was 29.6% (n = 95). The most frequently reported TAEs reported by participants were vulvovaginal mycotic infections at 5.3% (n=15), nausea 4.4% (n=12), and dysgeusia 3.1% (n=9). Two SEAEs were reported; one unrelated to treatment (foot burn) and one loss of consciousness. These findings indicate that secnidazole 2 g is well tolerated and a safe treatment option for the treatment of BV.

Dosing and Administration

Secnidazole is administered by sprinkling a 2 g packet of Secnidazole granules on foods such as applesauce, yogurt, or pudding. Solosec® was studied using only the previously mentioned food vehicles for administration but others are unlikely to affect pharmacokinetic parameters.[17] Administration with water alone was not studied although a glass of water may be taken after the administration of Secnidazole to aid in swallowing. No known major drug-drug or drug-food interactions were observed during initial drug trials but interactions known to occur with other members of the 5-nitroimidazole class may later be documented. Unlike Metronidazole which requires 10 days of alcohol abstinence (7 days of treatment plus 3 days after treatment) due to a significant risk for disulfiram-like reaction.[21] Secnidazole only requires 3 days of abstinence. Limited date is available for use during pregnancy.[18] No dosing adjustment is required in patients with reduced renal clearance or hepatic dysfunction.[15] There is currently no available data to determine the maximum frequency of secnidazole use.

Cost

At the time of this manuscript writing, Solosec® is not covered under Medicare or Medicaid. The average cash price for a

Table 2 | Summary of Efficacy Clinical Trials for Secnidazole

Trial	Interventions	Primary Endpoint	Results
Hillier et al.[18] Phase II Trial	• Secnidazole 1 g once (n=64) • Secndiazole 2 g once (n=62) • Placebo once (n=62)	Clinical cure† rate evaluated between days 21-30 after treatment	• Secnidazole 1 g: 51.6% (95% CI: 38.7% to 64.2%) • Secndiazole 2 g: 67.7% (95% CI: 54.7% to 79.1%) • Placebo: 17.7% (95% CI: 9.2% to 29.5%) • Both secnidazole doses were superior to placebo (p<0.001 for both comparisons)
Bohbot et al.[12] Phase III trial	• Secnidazole 2 g once (n=290) • Metronidazole 500 mg BID x7 days (n=287)	Therapeutic success at day 28‡	Secnidazole vs Metronidazole = 58.3% vs 57.8% Secnidazole-Metronidazole Difference = 0.5% (95% CI = -7.6% to 8.5%)
Schwebke et al.[19] Phase III	• Secnidazole 2 g once (n=107) • Placebo once (n=57)	Clinical cure† rate evaluated between days 21-30 after treatment	• Secndiazole 2 g: 53.3% (95% CI: 43.4% to 63.0%) • Placebo: 19.3% (95% CI: 10.0% to 31.9%) • Secnidazole superior to placebo (p<0.001)

†: Clinical cure was defined as a patient who had all three of the following at days 21–30 (Amsel criteria): normal vaginal discharge, negative potassium hydroxide whiff test, and clue cells less than 20%.

‡: Defined as a a composite of clinical and bacteriological cure. Clinical cure was defined as the normalisation of the three Amsel[b] criteria and bacteriological cure was defined as a Nugent score ≤3. The Nugent assay uses a scale from 0-10 where a score of 7-10 is consistent with bacterial vaginosis and a score of 0-4 is indicative of a normal Lactobacillus flora.

95% CI = 95% confidence interval; **BID** = twice daily **g** = gram; **mg** = milligram

single dose of secnidazole is expected to cost over $100 for those who lack prescription insurance. Currently the manufacturer (Lupin Pharmaceuticals Inc.) offers an assistance program that can reduce patient co-pays when billed through a commercial insurance that covers secnidazole. The alternative 7-day regimen of oral metronidazole is available for a cash price of ~$10 and is covered under Medicare and most insurance plans as a tier 1 product.[22] Clindamycin vaginal cream is also covered under Medicare and as a tier 1 product covered under most insurance with a cash price of ~$40 for the uninsured.[22]

Summary

Administered as a single dose, secnidazole 2 g has the potential for improved patient adherence, and lower number of treatment failures due to incomplete antibiotic course as compared to the alternative treatment courses. It is currently unknown whether secnidazole would be an effective alternative in patients that already failed metronidazole or tinidazole therapy. However, clinical studies have demonstrated that secnidazole is just as effective and safe as metronidazole for the treatment of BV. A single oral dose regimen with secnidazole 2 g is an appropriate therapeutic option for the treatment of BV.

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