Intraocular Pressure Reduction in Glaucoma Therapy: An Evolving Effort

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ROUNDTABLE DISCUSSION

BAUSCH + LOMB

VYZULTA™
(latanoprostene bunod ophthalmic solution),0.024%

INDICATION

VYZULTA™ (latanoprostene bunod ophthalmic solution), 0.024% is a prostaglandin F2α analog indicated for the reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

IMPORTANT SAFETY INFORMATION

- Increased pigmentation of the iris and periorbital tissue (eyelid) can occur. Iris pigmentation is likely to be permanent

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Introduction

Glaucoma therapy has undergone many advances since miotics were used as the first ocular hypotensive agents nearly two centuries ago.[1] To this day, though, the principal method for controlling this sight-threatening disease—intraocular pressure (IOP) reduction—has not changed. Of the several identified risk factors for the development and progression of primary open-angle glaucoma (POAG), IOP is the only risk factor that is FDA approved for modification and therefore available as a treatment target.[2] Currently, all approved treatment modalities for glaucoma patients are aimed at lowering IOP to the point where no further optic nerve damage or visual field loss occurs.

In the healthy eye, IOP is regulated by the balance of aqueous humor production at the ciliary body and outflow through two routes—the trabecular (ie, conventional) and uveoscleral (ie, nonconventional) pathways.[3] In patients with POAG or ocular hypertension, chronic cellular contraction and increased extracellular matrix deposition within the trabecular outflow pathway results in reduced aqueous humor outflow, which contributes to IOP elevation.[3-5] It is believed that high IOP levels cause progressive damage of the optic nerve, resulting in vision loss.[3]

A substantial body of evidence has confirmed that IOP reduction can indeed reduce the risk of glaucoma development and progression.[6-11] In the Early Manifest Glaucoma Trial, treated patients had half of the progression risk of those in the untreated control group after a median follow-up of 6 years.[9] In the Advanced Glaucoma Intervention Study, patients whose IOP was lower than 18 mm Hg on all visits over 6 years demonstrated almost no progression in visual field loss; in contrast, patients whose IOP was less than 18 mm Hg on fewer than 50% of visits experienced a significant amount of visual field loss.[6] Furthermore, those with 15 mm Hg IOP showed half the progression of those with 18 mm Hg, and those with 13 mm Hg showed half the progression of 15 mm Hg. When it comes to IOP control in glaucoma, every 1 mm Hg of reduced pressure can make a difference.

We now have a wide variety of topical medications at our disposal for lowering IOP. Prostaglandin analogs (PGAs)—the preferred first-line choice—are effective, have a demonstrated safety profile, and are dosed once daily. Still, effective medical therapy for glaucoma often requires multiple medications. As IOP reduction remains the cornerstone of glaucoma management, there is a continued need for new IOP-lowering therapies. More therapeutic options mean greater flexibility when choosing treatment and the ability to individualize treatment regimens to meet patients' needs.

This supplement documents highlights of a roundtable discussion on medical IOP-lowering therapies among a panel of six glaucoma specialists, myself included. The goal of the program is to provide an informative guide on Vyzulta™ (latanoprostene bunod ophthalmic solution), 0.024%, a novel PGA that is designed to act through two moieties: latanoprost acid, and butanediol mononitrate, which releases nitric oxide (NO). We reviewed the main features of Vyzulta; furthermore, we discussed the ways it can be used to the benefit of our patients and the impact it may have on our practices.

— Andrew Iwach, MD

Setting A Target

ANDREW IWACH, MD **Let's begin with a question that we all ask before initiating treatment: where do we need to set the IOP to minimize the risk of glaucomatous damage? What are your considerations in choosing and modifying a target pressure?**

I. PAUL SINGH, MD Target pressure should vary from patient to patient and from time to time. I usually decide how aggressive I need to be based on disease severity at the time of presentation, historical IOP ranges (medicated and unmedicated), and then make adjustments during the course of treatment depending on rate of progression. In general, I aim for a minimum of 20% to 25% reduction from baseline in early glaucoma and 30% reduction in moderate glaucoma.[2] I want to minimize fluctuation as well, aiming to keep pressures down to my target range but minimize fluctuation through the diurnal and nocturnal time period. Often times, my target is in the middle-to-upper teens around the clock.

IWACH **Do you do diurnal curves in your office?**

SINGH Yes, when I see progression and want to understand why. Some data do support the hypothesis that patients with greater pressure fluctuations tend to have more progression.[12-14] In the Advanced Glaucoma Intervention Study, a 1-mm Hg increase in IOP fluctuation was associated with a 30% increased risk for visual field loss, and long-term IOP fluctuation had a greater impact on progression of visual field loss in patients with low mean IOP than in patients with high mean IOP.[14-15] This suggests that certain patients may be more susceptible to the impact of IOP fluctuation than others.

MARLENE MOSTER, MD When discussing the treatment goal with a first-time patient, I make a point of finding out what his or her untreated pressure is. From there, I typically aim for a 30% drop, albeit more as a range than a single number. Several factors are important to consider in determining the intensity of treatment, including history, prior therapy, and the patient's ability to follow up, as glaucoma requires long-term care to stabilize the disc and visual field. In patients who have a family history of blindness, I would treat them more aggressively to achieve the goal of 30% pressure reduction.

TONY REALINI, MD, MPH I usually take a straightforward "small-medium-large" approach to target pressure: depending on whether the disease is early, moderate, or advanced, I aim for high teens, mid-teens, and low teens, respectively. A target range is not that different from a target number—the top number of the range is a number after all. Nonetheless, it's important to remember that the target pressure is just an educated guess. In the absence of any clinical evidence of progression, committing patients to extra medications merely because they are one or two points higher than the target pressure may not be the best approach. The best we can do is to lower IOP a reasonable amount, follow the patient to watch for progression, and adjust the goal based on the effectiveness of intervention.

BRIAN FLOWERS, MD Just because patients are slightly above target doesn't mean that I will add medication. I take a long-term view when assessing disease status, adjusting therapy according to the patient's lifetime risk for blindness based on rate of progression. Whether I'm adding an additional medication or considering a glaucoma procedure, I make sure the therapeutic benefit outweighs the risk of side effects and additional costs.

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STEVE MANSBERGER, MD, MPH If there's no target pressure, we have no game plan for the patient. However, many referred patients I see are unaware what kind of pressure they should expect to achieve, and their files have no record of an IOP goal. In our practice, we always note the target pressure in a patient's chart—on the premise that some variation is acceptable so long as there is no evident progression. After all, we are not chasing a number but managing a disease. The ultimate goal of IOP-lowering therapy is to preserve vision.

MOSTER Now that more diagnostic tests are available to measure structural and functional changes, we should be able to more reliably track progression and thus better customize the target pressure for the individual patient.

Selecting Treatment

IWACH **What are your thoughts on current IOP-lowering medications? What distinctions between the available options may influence your decision to prescribe one vs. another?**

FLOWERS For any given individual, desirable features of an IOP-lowering agent include maximal IOP reduction at all time points, minimal side effects, and a reasonable cost. The PGAs as the first-line agents are efficacious, have a demonstrated safety profile, and dosed once a day.

MOSTER Often we need more than just a PGA to sufficiently lower IOP. In the Ocular Hypertension Treatment Study, where the goal of treatment was to reduce the pressure by 20% or more, about 60% of patients could be controlled with one medication, but 40% needed two or more.[8] Within that 40%, 9% needed three medications. This suggests that it is unlikely that a target pressure of 18 mm Hg or less can be achieved with just one PGA.

SINGH One size does not fit all. The number and class of drops are dictated by what the target pressure range has to be, and the target range largely depends on disease severity. The lower the target range is, the harder it is to achieve, thus the more medications you may need. In our practice, a major proportion of glaucoma patients are in the later stage of the disease; correspondingly, at least 50% to 60%—if not more—of our patients use more than one medication for adequate IOP reduction.

MOSTER When I have patients with higher pressure in the supine position, I want to make sure the pressure is controlled at nighttime. My first drugs of choice are PGAs and carbonic anhydrase inhibitors (CAIs), which have both been shown to maintain lower pressures at night than the other drug classes.[15-16] Nocturnal IOP effects are especially important to consider in patients with normal tension glaucoma (NTG), who may have nocturnal dips of blood pressure or may even be taking systemic antihypertensives.

MANSBERGER In most of my glaucoma patients, I start therapy with a PGA. My second drug choice is a topical beta blocker, particularly for patients who are not on an oral beta blocker. Beta blockers appear to work primarily during the day,[15-16] but patients can use a once-daily beta blocker in the morning along with a PGA once a day in the evening. For those who are already on an oral beta blocker, I would instead add CAIs, which work at nighttime.[16-17] I usually use alpha agonists as a third-line adjunct.

FLOWERS CAIs have indeed been shown to work best with PGAs, followed by alpha agonists and beta blockers.[18-20] But, when compared with PGA monotherapy, the combinations are all fairly close in terms of the magnitude of IOP reduction.[18] I tend to use a beta blocker once a day as second-line treatment, primarily for its convenient dosing, relative cost, and safety profile.

SINGH PGAs are a first-line option for lowering IOP for not only their efficacy and tolerability but also for their once-daily dosing. Mechanism of action (MOA) is also important to consider, especially with adjunct medications, because having different mechanisms in play can achieve synergistic effects. My second-line agent is typically a CAI or an alpha agonist.

IWACH **Dr. Realini, does prior laser therapy influence how you choose adjunct medications?**

REALINI It does not. There are reports that laser therapy and PGAs may reduce each other's effectiveness, but some studies have shown otherwise.[21-24] My standard stepped approach to medical therapy is PGA first and CAI second. That said, I use fixed combinations as adjunct to PGAs more often than anything else. We can get an extra 2 or 3 points of IOP lowering no matter what we add as a single agent to a PGA,[19,20,25,26] but that's just not enough if the patient is 4 or 5 points away from the target pressure. Meanwhile, it has been shown that adding a fixed-combination to a PGA can lower pressure 5 or 6 points.[27-29] In an era where we have good pharmacologic options and thus an ability to tailor therapies to patients' individual needs, the "start low and go slow" approach may not apply as much anymore. After nearly two decades of experience with modern fixed-combinations, I think we can use them as a first adjunct without worrying that we're adding too much too quickly.

SINGH Our target pressures have become lower over time. About 10 years ago, when I started out of fellowship, an 18 mm Hg IOP was considered satisfactory for most patients. Now there is a tendency to aim for pressures lower than 15 mm Hg. Bringing the IOP down to the low-teens range is difficult. That's where combination drops can be a great help. I know if I need an extra 30% reduction from the PGA-treated baseline, I'll add a combination drop.

Current Therapies

IWACH **What are some of the current IOP-lowering therapies, and what unmet needs exist for glaucoma patients?**

REALINI The PGAs have set a high bar in terms of efficacy, tolerability, and once-daily dosing. A new therapy would have to surpass the efficacy and safety profile seen with the PGAs to create a paradigm shift in glaucoma pharmacotherapy.

FLOWERS One thing I would add is an MOA that targets the trabecular meshwork (TM). While some PGAs do target the TM, currently available therapies do not primarily impact aqueous outflow through the TM, which accounts for 60% to 80% of total outflow in healthy human eyes.[30] PGAs, the first-line IOP-lowering agents in the current pharmacotherapy of glaucoma, are believed to work primarily within the uveoscleral pathway by upregulating matrix metalloproteinase activity. This increases the interstitial spaces between the ciliary muscle bundles to allow for greater aqueous humor outflow.[3,31]

SINGH Plenty of data support that prolonged diversion of aqueous outflow can lead to collapse of Schlemm's canal.[32] I agree it will be beneficial to promote outflow through the TM at the same time as we enhance outflow through the uveoscleral pathway.

FLOWERS I believe the trabecular outflow mechanism is important for IOP regulation.

MOSTER In my practice, about 80% of our patients can be controlled with drops and laser treatment, and 20% will eventually need surgical intervention. For the 80%, I want an agent that is dosed once-daily. If this drug also combines more than one mechanisms to lower IOP, it would be a first-line option for me.

Dual-action Therapy

IWACH **Vyzulta™ (latanoprostene bunod ophthalmic solution), 0.024% is is metabolized into two moieties: latanoprost acid, a prostaglandin alpha-2 agonist, which acts on the uveoscleral outflow pathway, and butanediol mononitrate, a nitric oxide (NO)-releasing moiety. NO acts primarily on the TM and Schlemm's canal.[33,34] One other treatment modality that is clearly directed at the TM is laser trabeculoplasty. The procedure can produce IOP reduction comparable to that of a PGA.[35,36] What do we know about NO's effects in the eye and possible roles in glaucoma management?**

MANSBERGER NO is an endogenous signaling molecule generated by a family of enzymes called the NO synthases (NOS).[34] NO has been shown to regulate diverse physiologic functions throughout the body, including regulation of blood flow through vascular smooth muscle relaxation (such as in certain structures of the eye).[37] There is also growing evidence to suggest that NO plays a role in regulating IOP by increasing aqueous humor outflow through the trabecular pathway.[34,37]

REALINI The importance of NO in human physiology and pathology has long been recognized. In 1992, NO was picked by Science as the "Molecule of the Year."[38] In 1998, the Nobel Prize in Medicine was awarded to three scientists for their work on NO's function in the cardiovascular system. It is logical to presume that NO also plays a role in the physiology and pathophysiology of the human eye. Some evidence suggests that levels of L-arginine—the precursor to NO—may be higher in the aqueous humor of patients with POAG; NO levels, on the contrary, are low in these patients.[39-41] Additionally, genetic studies have associated endothelial NO synthase

(eNOS) gene polymorphisms with risk of POAG.[42-43] Given the evidence suggesting that NO synthesis may be impaired in glaucoma and that higher dietary nitrate intake may be associated with a lower POAG risk,[39-41,44] it's entirely plausible that the NO pathway would make a good therapeutic target for glaucoma. In fact, preclinical studies support that NO increases outflow through the trabecular pathway.[45-49] To increase trabecular outflow, NO induces cell relaxation in the TM by activating the NO-soluble guanylate cyclase–cyclic guanosine-3',5'-monophosphate (NO-sGC-cGMP) signaling pathway. This leads to a widening of intercellular spaces in the TM, thus increasing aqueous humor outflow.[34-37,45,46] Because the majority of aqueous humor outflow occurs through the conventional pathway, this process plays an increasingly recognized role in regulating IOP.[3-4] Studies have found reduced levels of NO markers in the anterior chambers of the eyes of patients with POAG, providing further evidence for the potential therapeutic value of NO-releasing molecules for patients with this disease.[40,41,51]

SINGH As a novel IOP-lowering molecule, Vyzulta™ (latanoprostene bunod ophthalmic solution), 0.024% is metabolized into two moieties: latanoprost acid, a prostaglandin alpha-2 agonist, and butanediol mononitrate, an NO-releasing moiety (Figure 1). It's a single agent but acts on the trabecular and uveoscleral outflow pathways (Figure 2).

MOSTER PGAs work primarily by increasing uveoscleral outflow: they relax the ciliary muscle and alter the extracellular matrix (ECM) of the ciliary body to make it more responsive to aqueous outflow.[30,51] In a preclinical study, Vyzulta™ was shown to relax the TM to increase the outflow facility through the TM, the juxtacanalicular tissue, and the inner wall of Schlemm's canal, (Figure 3) which together provides the bulk of aqueous humor outflow resistance; and this is thought to be the contribution of NO.[52-54] What Vyzulta offers is increased uveoscleral outflow plus relaxation of the TM to improve trabecular outflow, all in one package.

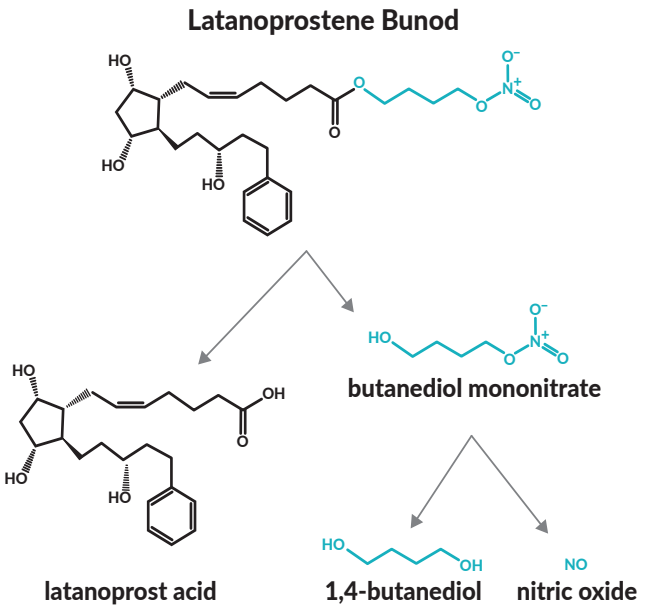

FIGURE 1 Vyzulta™ molecular structure and metabolism.

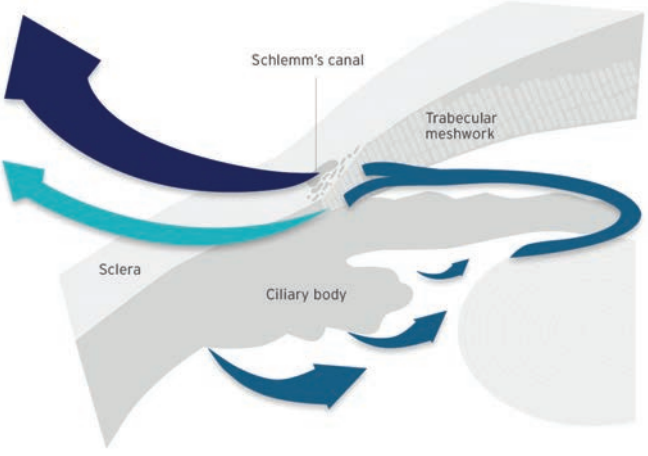

FIGURE 2 LBN acts on both outflow pathways.

IMPORTANT SAFETY INFORMATION

- There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products that were inadvertently contaminated by patients
- Contact lenses should be removed prior to the administration of VYZULTA and may be reinserted 15 minutes after administration

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Vyzulta™: Key Features

IOP-LOWERING EFFICACY AND RESPONDER RATE

IWACH **What results from the clinical studies of Vyzulta™ struck you as most important in terms of efficacy and responder rates?**

REALINI In APOLLO (N = 418) and LUNAR (N = 415), two phase 3 studies, Vyzulta™ produced an IOP reduction of 7.5 to 9.1 mm Hg from baseline between week 2 and month 3 in patients with OAG or ocular hypertension (Table I).[55,56] IOP reduction with Vyzulta dosed once daily at night was non-inferior to that with timolol 0.5% dosed twice daily. Vyzulta™ demonstrated superiority over timolol at month 3 in both studies, with an additional 1.2 mm Hg reduction in mean diurnal IOP. In VOYAGER (N = 413), a phase 2, dose-ranging study in patients with OAG or ocular hypertension, Vyzulta lowered IOP by 9.0 mm Hg from baseline after 4 weeks of treatment, a statistically significant, additional 1.2 mm Hg over latanoprost 0.005% ($P = 0.005$).[57] In JUPITER (N = 130), another phase 3 study, Vyzulta treatment led to significant IOP reduction sustained through week 52 in a group of patients with OAG or ocular hypertension (Figure 4).[58] These subjects had a notably low baseline IOP (19.6 mm Hg on average for the study eye, and 18.7 mm Hg for the treated fellow eye). By week 4, the mean IOP dropped about 20% from baseline (to 15.3 mm Hg in the study eye, and to 15.0 mm Hg in the treated fellow eye); by week 52, the degree of IOP reduction was about 25% (to 14.4 mm Hg in the study eye, and to 14.4 mm Hg in the treated fellow eye).

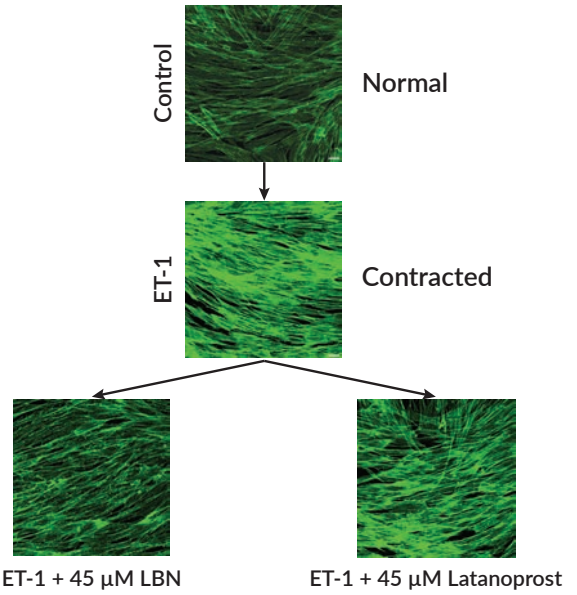

FIGURE 3 **In vitro data in cultured human trabecular meshwork cells (HTMCs) shows that NO released from LBN relaxed endothelin-1 contracted HTMCs.**

SINGH Responder rates are also important. Topical PGAs are effective IOP-lowering agents, but, since patients respond differently to a drug, the percentage of patients achieving their target pressure may differ between different agents within the class.[59] For someone who has a response to latanoprost, switching to another PGA is unlikely to make a big difference. But those who don't respond well

TABLE I **Change from baseline in mean IOP in APOLLO and LUNAR study**

	Week 2			Week 6			Month 3		
	8 am	12 pm	4 pm	8 am	12 pm	4 pm	8 am	12 pm	4 pm
APOLLO									
LBN mean CFB (mm Hg)	−9.0	−8.5	−7.7	**−9.1**	−7.9	−9.0	−8.7	−7.9	
Timolol mean CFB (mm Hg)	−7.8	−7.2	−6.6	−8.0	−7.4	−6.7	−7.9	−7.4	−6.6
Treatment difference	**−1.21**	**−1.37**	**−1.11**	**−1.03**	**−1.24**	**−1.26**	**−1.02**	**−1.27**	**−1.33**
P value	<0.001	<0.001	<0.001	<0.002	<0.001	<0.001	<0.002	<0.001	<0.001
LUNAR									
LBN mean CFB (mm Hg)	−8.3	−8.1	**−7.5**	−8.8	−8.5	−7.8	−8.8	−8.6	−7.9
Timolol mean CFB (mm Hg)	−7.9	−7.3	−6.9	−7.9	−7.7	−6.8	−7.9	−7.4	−6.6
Treatment difference	**−0.44**	**−0.76**	**−0.69**	**−0.92**	**−0.84**	**−0.98**	**−0.88**	**−1.29**	**−1.34**
P value	0.216	0.022	0.025	0.005	0.007	0.003	0.006	<0.001	<0.001

NI: Claimed if upper CI <1.5 mm Hg at all time points and <1.0 mm Hg for at least 5 of 9 time points. Superiority: Claimed if upper CI <0.0 mm HG at all time points. References 55 and 56.

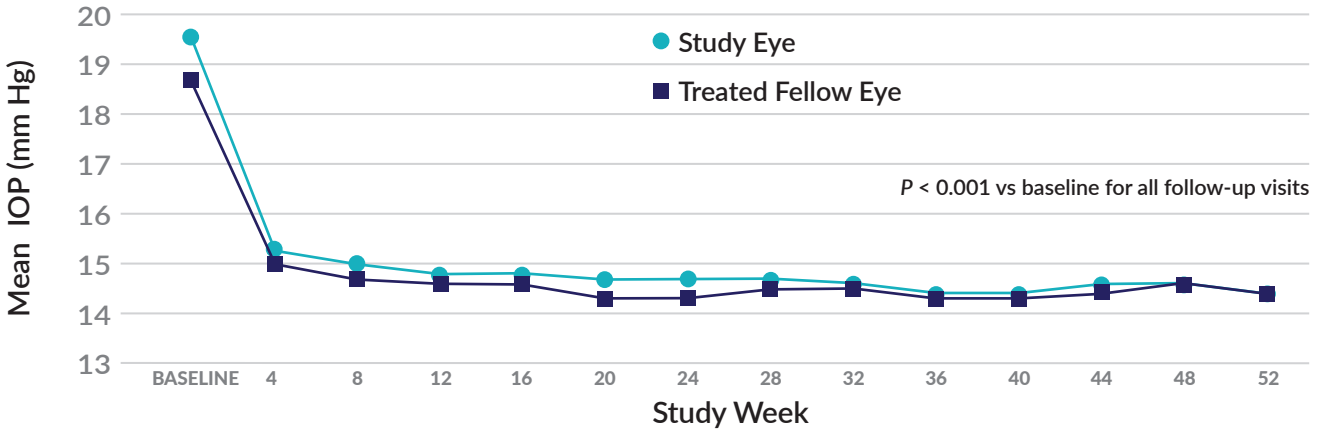

FIGURE 4 JUPITER efficacy results.

to latanoprost may respond with a different PGA.[60] A retrospective analysis of a group of patients who switched over from latanoprost to bimatoprost found that those who had more than 30% IOP reduction with latanoprost did not achieve more pressure lowering with bimatoprost, whereas patients who had an initial response of less than 20% reduction had a greater than 15% additional reduction after switching to bimatoprost.[61] I'm curious to see what responder rates with Vyzulta will be in clinical practice, especially in patients thought to be PGA nonresponders.

TOLERABILITY AND SAFETY

IWACH **What about tolerability and safety? What are the important findings of the Vyzulta™ clinical studies?**

MANSBERGER Vyzulta™ has a side effect profile comparable to other PGAs.[55-58] The most common ocular adverse reaction (AE) observed in the clinical studies is conjunctival hyperemia (6%), a well-recognized side effect of topical PGAs.[62]

MOSTER One side effect I discuss with patients prior to starting topical PGA therapy is iris hyperpigmentation.

REALINI Having a discussion with patients beforehand about the potential side effects of PGA therapy can help reduce their negative reactions. Every time I hand out a prescription for a PGA, I say "This will make your eyes red for the first few weeks, but for many of my patients, that fades with time."

MOSTER Patients do much better when they understand both the upsides and the downsides of any medicine we prescribe. With topical PGAs, I would make sure patients—especially younger women—understand the possible cosmetic consequences: hyperemia, lash growth, dark circles, and change in eye color. I tell them that it's likely they'll get red eyes, but that usually dissipates within a month.

SINGH The bottom line is the clinical study experience supports the safety profile of Vyzulta™—the NO-releasing moiety seems to bring no additional safety concerns to the table along with its IOP-lowering efficacy.

Vyzulta™ in Practice

IWACH **How do you foresee the use of Vyzulta™ in your practice? Where do you see this drug fitting into the tiers of treatment options for glaucoma patients?**

REALINI I see more than one way to use Vyzulta™: as a starting agent, or as a replacement/switch, or as adjunctive therapy, depending on the patient's target IOP. All things being equal, Vyzulta would be my first choice for treatment-naive patients.

FLOWERS A PGA is the first-line choice for most physicians. I would certainly use Vyzulta™ as initial therapy. The most common combination regimen in my practice is

IMPORTANT SAFETY INFORMATION

- Most common ocular adverse reactions with incidence ≥2% are conjunctival hyperemia (6%), eye irritation (4%), eye pain (3%), and instillation site pain (2%)

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a PGA plus a beta blocker. As someone who always try to keep patients on as little medicine as possible, I would feel compelled to see if the patients under this regimen could instead get by with Vyzulta alone.

SINGH I see no reason to not use Vyzulta™ as a first-line agent, although access will be important. With its dual MOA, LBN has the potential to provide a viable alternative for patients who are previous PGA nonresponders. In patients considering surgery, I would try Vyzulta before opting for surgery—they might respond differently and achieve their target IOP. The vast majority of glaucoma patients are already on a PGA, but many of them will require adjunct medications to effectively control IOP. In these patients, switching to Vyzulta could help achieve the pressure goal and may reduce the need for adjunct medications.

MOSTER It makes sense to me to use Vyzulta™ as first-line therapy, provided it's affordable and performs well in a real world setting.

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BRIEF SUMMARY OF PRESCRIBING INFORMATION

This Brief Summary does not include all the information needed to use VYZULTA safely and effectively. See full Prescribing Information for VYZULTA.

VYZULTA™ (latanoprostene bunod ophthalmic solution), 0.024%, for topical ophthalmic use.

Initial U.S. Approval: 2017

1 INDICATIONS AND USAGE

VYZULTA™ (latanoprostene bunod ophthalmic solution) 0.024% is indicated for the reduction of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Pigmentation

VYZULTA™ (latanoprostene bunod ophthalmic solution), 0.024% may cause changes to pigmented tissues. The most frequently reported changes with prostaglandin analogs have been increased pigmentation of the iris and periorbital tissue (eyelid).

Pigmentation is expected to increase as long as latanoprostene bunod ophthalmic solution is administered. The pigmentation change is due to increased melanin content in the melanocytes rather than to an increase in the number of melanocytes. After discontinuation of VYZULTA, pigmentation of the iris is likely to be permanent, while pigmentation of the periorbital tissue and eyelash changes are likely to be reversible in most patients. Patients who receive prostaglandin analogs, including VYZULTA, should be informed of the possibility of increased pigmentation, including permanent changes. The long-term effects of increased pigmentation are not known.

Iris color change may not be noticeable for several months to years. Typically, the brown pigmentation around the pupil spreads concentrically towards the periphery of the iris and the entire iris or parts of the iris become more brownish. Neither nevi nor freckles of the iris appear to be affected by treatment. While treatment with VYZULTA™ (latanoprostene bunod ophthalmic solution), 0.024% can be continued in patients who develop noticeably increased iris pigmentation, these patients should be examined regularly *[see Patient Counseling Information (17) in full Prescribing Information]*.

5.2 Eyelash Changes

VYZULTA may gradually change eyelashes and vellus hair in the treated eye. These changes include increased length, thickness, and the number of lashes or hairs. Eyelash changes are usually reversible upon discontinuation of treatment.

5.3 Intraocular Inflammation

VYZULTA should be used with caution in patients with a history of intraocular inflammation (iritis/uveitis) and should generally not be used in patients with active intraocular inflammation as it may exacerbate this condition.

5.4 Macular Edema

Macular edema, including cystoid macular edema, has been reported during treatment with prostaglandin analogs. VYZULTA should be used with caution in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema.

5.5 Bacterial Keratitis

There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products. These containers had been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithelial surface.

5.6 Use with Contact Lens

Contact lenses should be removed prior to the administration of VYZULTA because this product contains benzalkonium chloride. Lenses may be reinserted 15 minutes after administration.

6 ADVERSE REACTIONS

The following adverse reactions are described in the Warnings and Precautions section: pigmentation (5.1), eyelash changes (5.2), intraocular inflammation (5.3), macular edema (5.4), bacterial keratitis (5.5), use with contact lens (5.6).

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

VYZULTA was evaluated in 811 patients in 2 controlled clinical trials of up to 12 months duration. The most common ocular adverse reactions observed in patients treated with latanoprostene bunod were: conjunctival hyperemia (6%), eye irritation (4%), eye pain (3%), and instillation site pain (2%). Approximately 0.6% of patients discontinued therapy due to ocular adverse reactions including ocular hyperemia, conjunctival irritation, eye irritation, eye pain, conjunctival edema, vision blurred, punctate keratitis and foreign body sensation.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available human data for the use of VYZULTA during pregnancy to inform any drug associated risks.

Latanoprostene bunod has caused miscarriages, abortion, and fetal harm in rabbits. Latanoprostene bunod was shown to be abortifacient and teratogenic when administered intravenously (IV) to pregnant rabbits at exposures ≥ 0.28 times the clinical dose. Doses ≥ 20 µg/kg/day (23 times the clinical dose) produced 100% embryofetal lethality. Structural abnormalities observed in rabbit fetuses included anomalies of the great vessels and aortic arch vessels, domed head, sternebral and vertebral skeletal anomalies, limb hyperextension and malrotation, abdominal distension and edema. Latanoprostene bunod was not teratogenic in the rat when administered IV at 150 mcg/kg/day (87 times the clinical dose) *[see Data]*.

The background risk of major birth defects and miscarriage for the indicated population is unknown. However, the background risk in the U.S. general population of major birth defects is 2 to 4%, and of miscarriage is 15 to 20%, of clinically recognized pregnancies.

Data

Animal Data

Embryofetal studies were conducted in pregnant rabbits administered latanoprostene bunod daily by intravenous injection on gestation days 7 through 19, to target the period of organogenesis. The doses administered ranged from 0.24 to 80 mcg/kg/day. Abortion occurred at doses ≥ 0.24 mcg/kg/day latanoprostene bunod (0.28 times the clinical dose, on a body surface area basis, assuming 100% absorption). Embryofetal lethality (resorption) was increased in latanoprostene bunod treatment groups, as evidenced by increases in early resorptions at doses ≥ 0.24 mcg/kg/day and late resorptions at doses ≥ 6 mcg/kg/day (approximately 7 times the clinical dose). No fetuses survived in any rabbit pregnancy at doses of 20 mcg/kg/day (23 times the clinical dose) or greater. Latanoprostene bunod produced structural abnormalities at doses ≥ 0.24 mcg/kg/day (0.28 times the clinical dose). Malformations included anomalies of sternum, coarctation of the aorta with pulmonary trunk dilation, retroesophageal subclavian artery with absent brachiocephalic artery, domed head, forepaw hyperextension and hindlimb malrotation, abdominal distention/edema, and missing/fused caudal vertebrae.

An embryofetal study was conducted in pregnant rats administered latanoprostene bunod daily by intravenous injection on gestation days 7 through 17, to target the period of organogenesis. The doses administered ranged from 150 to 1500 mcg/kg/day. Maternal toxicity was produced at 1500 mcg/kg/day (870 times the clinical dose, on a body surface area basis, assuming 100% absorption), as evidenced by reduced maternal weight gain. Embryofetal lethality (resorption and fetal death) and structural anomalies were produced at doses ≥ 300 mcg/kg/day (174 times the clinical dose). Malformations included anomalies of the sternum, domed head, forepaw hyperextension and hindlimb malrotation, vertebral anomalies and delayed ossification of distal limb bones. A no observed adverse effect level (NOAEL) was established at 150 mcg/kg/day (87 times the clinical dose) in this study.

8.2 Lactation

Risk Summary

There are no data on the presence of VYZULTA in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered, along with the mother's clinical need for VYZULTA, and any potential adverse effects on the breastfed infant from VYZULTA.

8.4 Pediatric Use

Use in pediatric patients aged 16 years and younger is not recommended because of potential safety concerns related to increased pigmentation following long-term chronic use.

8.5 Geriatric Use

No overall clinical differences in safety or effectiveness have been observed between elderly and other adult patients.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Latanoprostene bunod was not mutagenic in bacteria and did not induce micronuclei formation in the *in vivo* rat bone marrow micronucleus assay. Chromosomal aberrations were observed *in vitro* with human lymphocytes in the absence of metabolic activation.

Latanoprostene bunod has not been tested for carcinogenic activity in long-term animal studies. Latanoprost acid is a main metabolite of latanoprostene bunod. Exposure of rats and mice to latanoprost acid, resulting from oral dosing with latanoprost in lifetime rodent bioassays, was not carcinogenic.

Fertility studies have not been conducted with latanoprostene bunod. The potential to impact fertility can be partially characterized by exposure to latanoprost acid, a common metabolite of both latanoprostene bunod and latanoprost. Latanoprost acid has not been found to have any effect on male or female fertility in animal studies.

13.2 Animal Toxicology and/or Pharmacology

A 9-month toxicology study administered topical ocular doses of latanoprostene bunod to one eye of cynomolgus monkeys: control (vehicle only), one drop of 0.024% bid, one drop of 0.04% bid and two drops of 0.04% per dose, bid. The systemic exposures are equivalent to 4.2-fold, 7.9-fold, and 13.5-fold the clinical dose, respectively, on a body surface area basis (assuming 100% absorption). Microscopic evaluation of the lungs after 9 months observed pleural/subpleural chronic fibrosis/inflammation in the 0.04% dose male groups, with increasing incidence and severity compared to controls. Lung toxicity was not observed at the 0.024% dose.

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