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Adherence and Persistence of Bimatoprost in Prior Latanoprost Users

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Primary open-angle glaucoma treatment focuses on reducing intraocular pressure (IOP), the only known modifiable risk factor linked to glaucoma.[1,2] The goal of treatment is preservation of vision by preventing damage (or further damage) to the visual field and function by lowering IOP to within a target range.[1,2] Treatment options include drug therapy (prostaglandin analogs and prostamides [PGAs], alpha-agonists, beta-blockers, carbonic anhydrase inhibitors), laser therapy, and surgery.[1,3] Topical PGAs are a class of newer agents that reduce IOP by increasing aqueous fluid drainage.[2-4] FDA-approved agents in this class include bimatoprost (Lumigan; Allergan plc), latanoprost (Xalatan; Pfizer, Inc), tafluprost (Zioptan; Akorn, Inc), and travoprost (Travatan; Alcon, Inc).

Sustained adherence to (complying with daily treatment) and persistence with (remaining on treatment over time) topical PGAs are important for reducing the risk of visual function loss. Adherence to glaucoma treatment is complex and not completely understood, however.[5] Adverse effects of topical PGAs are thought to contribute to nonadherence.[4,6] Conjunctival hyperemia is the most frequently reported side effect, occurring in approximately 30% of patients, and may result in skipped doses or treatment discontinuation.[3,6] In a physician survey of PGA use and adverse effects, respondents estimated that 18% of their patients had reduced adherence to PGA therapy due to hyperemia.[7] Complexity of the therapeutic regimen also contributes to nonadherence.[4,6,8] Although PGAs provide the most effective topical therapy[4] with once-daily administration, adjunctive therapy may be required, resulting in more complex therapeutic regimens.[4,9] In one study, 28% of patients initiating PGA therapy required adjunctive therapy; however, bimatoprost-treated patients had significantly lower rates of adjunctive therapy use than latanoprost-treated patients (23.2% vs 30.2%; $P<.0001$).[9]

Bimatoprost is the only PGA with 2 formulations. The newer formulation (0.01%) was designed to provide more efficient drug delivery than the original formulation (0.03%), thereby maintaining efficacy while reducing drug exposure and improving tolerability.[10] In a randomized controlled trial, bimatoprost 0.01% had equivalent

ABSTRACT

Objectives: Bimatoprost 0.01%, a newer ophthalmic formulation, was hypothesized to improve adherence and persistence compared with the original bimatoprost 0.03% formulation.

Study Design: A retrospective, observational cohort study was conducted that utilized a pharmacy claims database to examine the adherence to and persistence with prior latanoprost use among patients with glaucoma who were prescribed bimatoprost 0.01% or bimatoprost 0.03% for glaucoma treatment.

Methods: Using pharmacy claims, adherence in 6035 bimatoprost 0.01% patients and 2705 bimatoprost 0.03% patients with prior latanoprost treatment was measured as a proportion of days covered (PDC). Persistence in 7780 bimatoprost 0.01% and 3454 bimatoprost 0.03% latanoprost-experienced patients was measured as the proportion of patients on continuous treatment for up to 12 months.

Results: Adherence to bimatoprost 0.01% was significantly greater than to bimatoprost 0.03% (mean PDC, 0.74 vs 0.68; $P<.001$). Persistence with bimatoprost 0.01% (52%) was significantly greater than with bimatoprost 0.03% (46%). Analyses conducted by age group (aged <65 and ≥65 years) yielded similar results.

Conclusions: In clinical practice, bimatoprost 0.01% demonstrated superior adherence and persistence compared with bimatoprost 0.03% in latanoprost-experienced patients.

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PRACTICAL IMPLICATIONS

Bimatoprost 0.01%, a newer ophthalmic formulation, was hypothesized to improve adherence and persistence compared with the original bimatoprost 0.03% formulation. The objective was to confirm prior findings of superior adherence and persistence for bimatoprost 0.01% versus bimatoprost 0.03% among latanoprost-experienced patients.

- The newer bimatoprost formulation (0.01%) was designed to provide more efficient drug delivery than the original formulation (0.03%), thereby maintaining efficacy while reducing overall drug exposure.
- Sustained adherence (complying with daily treatment) and persistence (remaining on treatment over time) to topical prostaglandin analogs and prostamides, such as bimatoprost, are important for reducing the risk of visual function loss in patients with glaucoma.

efficacy to bimatoprost 0.03%.[10] Treatment-related adverse events were less frequent among those receiving 0.01% (38.4% vs 50.8%; $P = .016$), with a significantly lower proportion of bimatoprost 0.01%–treated patients experiencing a moderate to severe increase in hyperemia than those treated with bimatoprost 0.03% (8.6% vs 17.6%; $P = .023$). Adherence has been associated with positive clinical outcomes, and the newer formulation of bimatoprost has the potential to affect adherence by increasing tolerability. Therefore, the current study was designed to confirm prior published results,[11,12] demonstrating improved adherence to and persistence with bimatoprost 0.01% compared with bimatoprost 0.03% among patients previously treated with branded or generic latanoprost, using a different dataset and more recent years of data.

METHODS

This retrospective, observational cohort study utilized data from the Longitudinal Rx (LRx) Database from IMS Health, which includes patient-level prescription claims (without diagnoses) for more than 205 million patients. LRx captures approximately 75% of all prescription claims in the United States, is representative of the US population, and includes a wide range of payers. Patient demographic information (age, gender) is available, but prescription plan enrollment dates are not included in this database.

The study period spanned July 1, 2010, through June 30, 2013, including a 6-month enrollment period from January 1, 2012, through June 30, 2012. Patients were required to have ≥1 prescription fill for bimatoprost 0.01% or bimatoprost 0.03% during the enrollment period. The date of the first fill for either formulation was defined as the index date, and patients were classified into 2 treatment cohorts based on their index formulation. Patient eligibility criteria included: being ≥18 years on the index date; having at least 18 months of continuous pre index pharmacy benefit eligibility, which was proxied by the presence of a pharmacy claim for any medication in each of the 18 months; and having ≥1 prescription fill for latanoprost (branded or generic) within the pre-index period. PGAs may be commonly used as initial eye drops,[1] of which generic latanoprost is likely the most common.[13] All patients who met these selection criteria were included in the postindex persistence analysis. Additionally, 12 months of continuous postindex pharmacy benefit eligibility, proxied by the presence of a pharmacy claim for any medication in each of the 12 months, was required for patients included in the adherence and treatment status analyses.

Outcome Measures

Outcome measures included adherence to and persistence with treatment and monthly treatment status (on or off treatment) in the 12 months following the index prescription. Traditionally, these measures depend on the days' supply reported on pharmacy claims, but these may be inaccurate for nondiscrete drug formulations. Therefore, rather than relying on the pharmacist-recorded days' supply,[14] it was calculated for each prescription fill using a drop count method. This method includes a count of the number of drops per bottle and number of drops per dose for the product dispensed:

Days' supply = [(# of drops)/bottle]/[(# of drops)/dose] x [(# of administrations)/day]

The drop count method was utilized in a prior study,[11] and the number of drops per dose was defined per the labeled indication. Bilateral use was assumed for all patients (ie, twice the number of drops per dose).

Adherence to the index bimatoprost treatment (0.01% or 0.03%) was defined as the proportion of days covered (PDC)[15] during the 12-month postindex period:

PDC = [Total days with index drug available within 365-day measurement period]/365

The numerator of the PDC calculation for each index drug was the number of days within the postindex period covered by ≥1 prescription for that drug, and the denominator was fixed at 365 days. If patients refilled a prescription prior to completion of the previous fill, the start date for the second prescription was adjusted appropriately to avoid double-counting.[16] The mean and median PDCs were calculated by treatment cohort and the proportion of patients with PDC values at different adherence levels: a)

PDC ≤0.20 (low adherence), b) PDC >0.20 to ≤0.80 (moderate adherence), and c) PDC >0.80 (high adherence).

A cross-sectional analysis of patient compliance with the index treatment was also conducted and was defined as the proportion of patients remaining on index therapy at the end of each of the 12 months of follow-up. Patients were categorized monthly as: a) treatment continuers (ie, with a supply of medication in the prior month and either an index refill or a carry-over of supply into the current month), b) treatment discontinuers (no carry-over supply or index prescription fill in the current month), or c) treatment re-starters (a prescription fill in the current month and no supply of index medication in the prior month). Treatment continuers and re-starters in a given month were classified as "on treatment" and discontinuers classified as "off treatment."

Persistence with the index bimatoprost (0.01% or 0.03%) treatment was assessed over a period of up to 12 months following the index date. Patients were considered persistent with index treatment as long as they continued to refill their prescription ≤30 days after exhausting their existing days' supply and nonpersistent (ie, discontinued) if they did not refill within 30 days. The treatment discontinuation date was set at 30 days after the exhaustion of the days' supply of the last continuous prescription fill because a prior study reported similar persistence results when comparing 15-, 30-, and 60-day allowable refill gaps.[17]

Statistical Analyses

Baseline demographic characteristics, including age at index, gender, and payer type (commercial, Medicare, Medicaid, cash) were used to describe the treatment cohorts (bimatoprost 0.01% and bimatoprost 0.03%). Statistical differences in baseline demographics were evaluated with χ^2 tests for proportions and Student's *t* tests for means. Within each cohort, patients were stratified into 2 age groups (aged <65 and ≥65 years) at index. Mean and median PDCs were calculated by treatment cohort (overall and stratified by age). Student's *t* tests were used to assess the statistical significance of differences in mean PDC, and Wilcoxon signed rank tests were used to assess differences in median PDC between cohorts.

Mean PDC (adjusted) in the bimatoprost 0.01% cohort was evaluated with a general linear model, with bimatoprost 0.03% used as the reference cohort and patient age, gender, insurance type, and pre-period latanoprost adherence used as covariates. Diagnostic tests of suitability of the linear model (minimum and maximum predicted PDC) to predict the bounded mean value were performed. Comparisons of the proportions of patients with low, moderate, and high adherence and of patients on treatment (continuers plus re-starters) were conducted using χ^2 tests. Adjusted analyses of adherence level (low and high categories) and treatment status (on or off treatment) were performed using logistic regression adjusted with the same covariates as the linear model. Time to nonpersistence of the index agent was evaluated by Kaplan-Meier survival analysis, including the log-rank test of homogeneity and survival plots. A Cox proportional hazards model was used to compare the covariate-adjusted hazards of nonpersistence between cohorts, with results reported as hazard ratios (HRs) with their 95% confidence intervals (CIs) and associated *P* values. A *P* value of ≤.05 was considered statistically significant.

RESULTS

A total of 11,234 patients met the criteria for the persistence analysis; 69.3% of patients had bimatoprost 0.01% as their index agent and 30.7% had bimatoprost 0.03%. A majority of patients (77.8%; n = 8740) met the eligibility requirements for the adherence and treatment status analyses, and the proportions of bimatoprost 0.01% and bimatoprost 0.03% users were nearly identical to those of the persistence analysis (69.1% and 30.9%). A comparison of baseline demographic and clinical characteristics yielded few significant differences between treatment cohorts in both the adherence and persistence populations (**Table 1**). There were slightly more females in the bimatoprost 0.01% cohort (*P* = .0362) in the persistence population.

There were no substantial differences between insurance types and pre-index brand/generic latanoprost use, although the differences present were statistically significant. Higher proportions of commercial and lower proportions of Medicare enrollees in the bimatoprost 0.01% cohort were observed. In the bimatoprost 0.01% cohort, 34% used brand and generic, 15% used only generic, and 51% used only branded latanoprost, while in the bimatoprost 0.03% cohort, 21% used brand and generic, 19% used only generic, and 60% used only branded latanoprost (*P* <.001). In the 18-month pre-index period, adherence to latanoprost (branded and generic combined) was significantly higher in the bimatoprost 0.01% cohort than in bimatoprost 0.03% users (mean latanoprost PDC: 0.49 vs 0.43; *P* <.0001).

Adherence

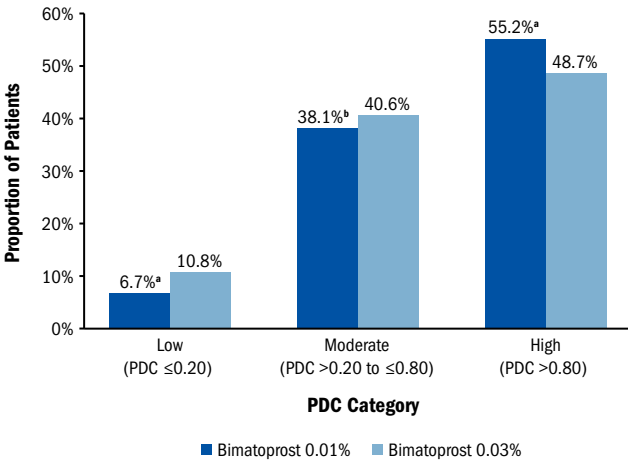
In this study of latanoprost-experienced patients, adherence to bimatoprost treatment was significantly greater among bimatoprost 0.01% users than among bimatoprost 0.03% users, overall (mean PDC, 0.74 vs 0.68; adjusted *P* <.0001; median PDC, 0.88 vs 0.75; *P* <.0001). Over the 12-month postindex period, the bimatoprost 0.01% cohort had a significantly higher proportion of patients with

Table 1. Patient Demographics

		Bimatoprost 0.01%	Bimatoprost 0.03%	*P*
Adherence		N = 6035	N = 2705	
Age	Age in years, mean (SD)	72.5 (10.7)	72.3 (11.1)	NS
	≥65 years (%)	78.8%	77.9%	NS
Gender	Female (%)	64.4%	62.4%	NS
Insurance type (%)	Cash	2.3%	2.8%	<.0001
	Commercial	14.1%	11.3%	
	Medicaid	2.2%	2.6%	
	Medicare	81.4%	83.3%	
Pre-index latanoprost use (%)	Brand	50.9%	60.4%	<.0001
	Generic	14.6%	18.8%	
	Brand and generic	34.5%	20.9%	
Persistence		N = 7780	N = 3454	
Age	Age in years, mean (SD)	72.6 (10.7)	72.7 (11.0)	NS
	≥65 years (%)	78.8%	78.9%	NS
Gender	Female (%)	64.9%	62.9%	.0362
Insurance type (%)	Cash	2.6%	2.6%	<.0001
	Commercial	14.3%	11.0%	
	Medicaid	2.1%	2.7%	
	Medicare	81.0%	83.8%	
Pre-index latanoprost use (%)	Brand	50.8%	60.4%	<.0001
	Generic	14.9%	18.9%	
	Brand and generic	34.4%	20.8%	

NS indicates not significant; SD, standard deviation.

Figure 1. High, Moderate, and Low Adherence to Study Medication Throughout 12 Months



PDC indicates proportion of days covered.
[a]*P* <.0001.
[b]*P* <.05.

high adherence and a significantly lower proportion of patients with low adherence compared with the bimatoprost 0.03% cohort (high: 55.2% vs 48.7%, respectively; *P* <.0001; low: 6.7% vs 10.8%; *P* <.0001) (Figure 1). Adherence results were similar when stratified by age groups (<65 and ≥65 years) (not shown). In adjusted analyses (Table 2), patients treated with bimatoprost 0.01% had a 23% higher likelihood of being a high adherer (odds ratio [OR], 1.233; 95% CI, 1.125-1.353; adjusted *P* <.0001) and a 40% lower likelihood of being a low adherer (OR, 0.602; 95% CI, 0.513-0.707; adjusted *P* <.0001) compared with patients treated with bimatoprost 0.03%.

Treatment Status

The results of the monthly treatment analysis demonstrated that the proportion of patients remaining on index therapy were greater in the bimatoprost 0.01% cohort than in the bimatoprost 0.03% cohort starting at month 3, with 80.4% of bimatoprost 0.03% patients and 83.7% of bimatoprost 0.01% patients remaining on treatment (Figure 2) (adjusted *P* = .0062). In each subsequent month, while smaller proportions of patients in each cohort were on treatment, larger reductions were observed in bimatoprost 0.03% patients compared with bimatoprost 0.01% patients. By month 12, 72.5% of bimatoprost 0.01% patients were on treatment compared with 53.6% of bimatoprost 0.03% patients (adjusted *P* <.0001) (Table 2).

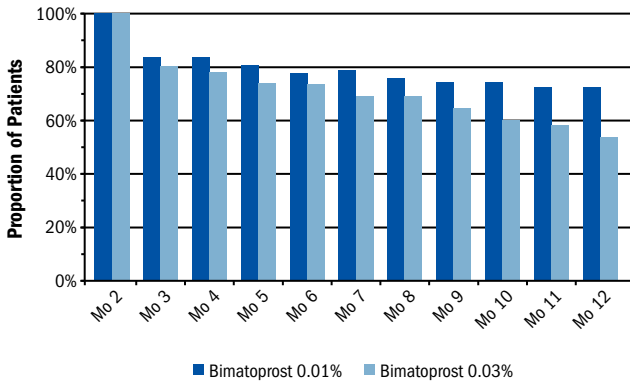
Persistence

Results from the analysis of persistence indicated that significantly higher proportions of bimatoprost 0.01% patients were persistent with their index therapy, both overall (52.2% vs 45.5%; *P* <.0001) and within each age group (aged ≥65 years, 52.7% vs 46.2%; *P* <.0001; aged <65 years, 50.5% vs 43.1%; *P* = .0009) compared with bimatoprost 0.03% patients. At any point in time, the bimatoprost 0.01% cohort had a 10% lower probability of nonpersistence compared with the bimatoprost 0.03% cohort, based on the covariate-adjusted analysis (HR, 0.896; 95% CI, 0.848-0.948; adjusted *P* = .0001) (Table 2). Kaplan-Meier curves depicting greater persistence for bimatoprost 0.01% compared with bimatoprost 0.03% were statistically significant (log-rank; *P* <.001) for all ages (Figure 3) and by age group (<65 and ≥65 years) (not shown). The median survival time (ie, time to discontinuation) was 10.9 months for the bimatoprost 0.01% cohort and 9.1 months for the bimatoprost 0.03% cohort.

DISCUSSION

In this retrospective cohort study utilizing a large pharmacy claims database, there was significantly better

Figure 2. Proportion of Patients on Treatment Each Month[a]



Mo indicates month.
[a]Note that the analysis of treatment status was conducted with the adherence sample (N = 8740).

Table 2. Covariate-adjusted Results (bimatoprost 0.01% vs bimatoprost 0.03%)

		95% LCL	95% UCL	Adjusted *P*
	Odds ratio[a]			
High adherence (PDC >0.80) logistic model	1.233	1.125	1.353	<.0001
	Odds ratio[a]			
Low adherence (PDC ≤0.20) logistic model	0.602	0.513	0.707	<.0001
	Odds ratio[a]			
Treatment status at month 12 logistic model	2.240	2.037	2.464	<.0001
	Hazard ratio[a]			
Persistence Cox proportional hazards model	0.896	0.848	0.948	.0001

LCL indicates lower confidence limit; PDC, proportion of days covered; UCL, upper confidence limit.
[a]Reference: bimatoprost 0.03%.

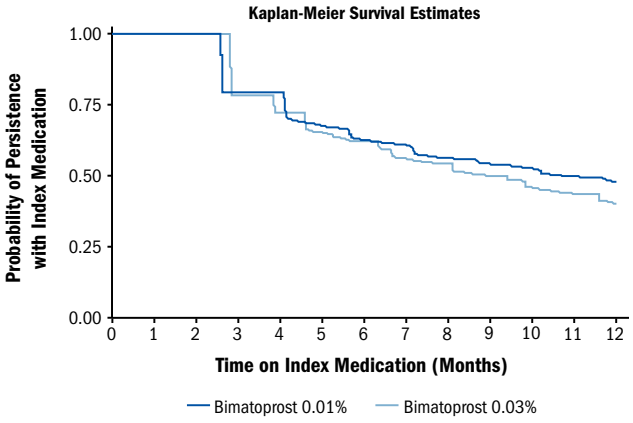
adherence to therapy for latanoprost-experienced patients using the topical IOP-lowering therapy bimatoprost 0.01% compared with bimatoprost 0.03% over the course of their first year of bimatoprost treatment. High adherence (PDC ≥0.80) was significantly more prevalent in the bimatoprost 0.01% cohort compared with the bimatoprost 0.03% cohort overall and when stratified by those <65 and ≥65 years. The present analysis also provided evidence for better persistence with bimatoprost 0.01% therapy over 1 year of treatment. In addition, a comparison of treatment status at the end of 1 year showed a higher proportion of bimatoprost 0.01% users on index treatment compared with bimatoprost 0.03% users.

The adherence findings are consistent with a previously published study of PGA treatment-naïve patients using bimatoprost 0.01% compared with bimatoprost 0.03%.[11] In that analysis, which also utilized a large pharmacy claims database and calculated days' supply using the drop count technique, mean PDC values were 0.53 among bimatoprost 0.01% users and 0.44 among bimatoprost 0.03% users (P <.001) in the first year of therapy.[11] In the present study, mean PDC was higher in both treatment groups over 1 year of therapy, which may be expected in a PGA treatment-experienced (ie, latanoprost) population, as was used here, compared with the PGA treatment-naïve population of the prior study. The definition of continuous enrollment in the present study included a pharmacy fill each month; consequently, the sample may be more compliant overall than those in the prior study.

As noted, a significantly higher proportion of bimatoprost 0.01% users (52.2% vs 45.5%) were persistent to their index therapy over the 1-year postindex period, with no gap in treatment that was >30 days. In comparison, a study of persistence to PGA therapy over 1 year among topical ocular hypotensive treatment-naïve patients found 43% of patients treated with bimatoprost 0.03% were persistent to therapy, slightly lower than latanoprost-experienced patients in the current study.[18] Latanoprost users had the highest proportion of persistent patients in that study (50%), which was slightly lower than the present study's 52.2% persistent bimatoprost 0.01% population. The current study's persistence results are also comparable to those of a large database study conducted in Canada with PGA treatment-naïve patients.[19] In that study, patients were treated with bimatoprost 0.03%, latanoprost, or travoprost. At 1 year, 57.4% of patients were persistent (patients were categorized by use of PGA monotherapy vs PGA plus adjunctive [non-PGA] therapy, not by type of PGA). Patients who remained on either the index PGA or switched to an alternative PGA were considered persistent, which may account for the slightly higher estimate reported by Iskedjian and colleagues.

The current study has several strengths. The data source (LRx) was larger than the pharmaceutical claims database (Source Lx) that was utilized in the prior analysis of treatment-naïve bimatoprost users.[11] Next, days' supply estimation from prescription claims can be subject to error, potentially affecting adherence and persistence estimates that use days' supply as recorded by the pharmacy. Use of the drop count method allowed some control for differences in bottle size and the volume of medication dispensed, thereby allowing for a more accurate estimate of

Figure 3. Time to Nonpersistence



Log rank P <.001.

adherence.[14] Also, the use of 3 different measures of treatment compliance, including PDC (adherence), monthly proportion of patients on treatment (treatment status), and proportion of patients continuously on treatment over 12 months (persistence), allowed for a thorough analysis comparing compliance with bimatoprost 0.01% versus with bimatoprost 0.03% therapy. Consistent findings across all of these measures support the evidence of superior compliance with bimatoprost 0.01% compared with bimatoprost 0.03% among latanoprost-experienced patients.

Limitations

As with any retrospective study utilizing administrative claims data, the current analysis has several limitations. First, medical claims were not available to assess patient comorbidity nor were IOP measurements available to assess disease severity. Therefore, it was not possible to assess if there were any clinical imbalances between the bimatoprost 0.01% and bimatoprost 0.03% cohorts. Second, allowing adjunctive glaucoma medication use following the index date could have adversely influenced patient adherence and persistence with study medication, since there is literature suggesting that with adjunctive therapy comes greater complexity of treatment and reduced adherence.[9,20] However, there is no evidence to date that adjunctive treatment rates differ between the bimatoprost formulations.

Next, prescription refills were assumed to be taken with perfect adherence since information on medication-taking behavior is unknown in this pharmacy claims-based analysis. The assumption that medication possession is equivalent to utilization of medication is incorrect if patients sought a refill without utilizing the full supply on hand or made dosing errors by incorrectly administering the drops. These concerns, however, were not expected to differ between the treatment cohorts.

Lastly, the pre-index proxy eligibility criteria required that patients have a prescription filled for any medication in each of the prior 18 months. Although this may have biased the results toward higher adherence and persistence to bimatoprost overall, the magnitude of the observed differences between the cohorts would not be affected.

CONCLUSIONS

In conclusion, by using more recent real-world data and a larger patient population, the results of this analysis confirm prior findings of superior adherence and persistence for bimatoprost 0.01% compared with bimatoprost 0.03% users in PGA treatment-naïve patients[10,11,21] and presents new information that the difference is maintained among latanoprost-experienced patients.

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