PROTOCOL TITLE: A Phase 3 Prospective, Randomized, Double-Masked, 12-Week, Parallel Group Study Evaluating the Efficacy and Safety of Latanoprost and Timolol in Pediatric Subjects With Glaucoma

Study Objectives:
Primary Objective: To assess the relative effectiveness of latanoprost 0.005% ophthalmic solution dosed once daily and timolol (0.5% or optionally 0.25% for subjects younger than 3 years old) dosed twice daily in pediatric subjects ≤18 years of age who were diagnosed with pediatric glaucoma. Specifically, to demonstrate that latanoprost is not inferior to timolol (0.5% or optionally 0.25% for subjects younger than 3 years old) within a noninferiority margin of 3 mmHg, with an option of switching to superiority, in the event that the lower limit of the 95% confidence interval (CI) for the treatment difference not only lies above the noninferiority margin but also above zero.

Secondary Objectives:
- To evaluate the safety of latanoprost 0.005% ophthalmic solution dosed once daily and timolol (0.5% or optionally 0.25% for subjects younger than 3 years old) dosed twice daily in pediatric subjects ≤18 years of age who were diagnosed with pediatric glaucoma.
- To compare latanoprost 0.005% ophthalmic solution dosed once daily and timolol (0.5% or optionally 0.25% for subjects younger than 3 years old) dosed twice daily in pediatric subjects ≤18 years of age who were diagnosed with pediatric glaucoma, with respect to the proportion of subjects with at least a 15% lowering of baseline intraocular pressure (IOP) [responder analysis].

METHODS
Study Design:
This was a prospective, randomized, double masked, 12-week, parallel group study of latanoprost and timolol in pediatric subjects with glaucoma. Approximately 120 subjects were planned to be enrolled.

The Baseline visit was conducted 0 to 28 days (4 weeks) after the Screening visit. At the morning (before midday) Baseline visit, a subject's IOP had to be ≥22 mmHg in at least 1 eye. To ensure that systemic exposure was not too high in this pediatric population, enrollment was staged by age groups (0 to 31 mmHg) at the Baseline visit. Subjects were randomly assigned in a 1:1 ratio to 1 of the 2 treatment groups (latanoprost or timolol).

Following randomization, follow-up visits occurred at Weeks 1, 4, and 12. If during the study the Investigator determined that the IOP was not controlled (eg, IOP ≥36 mmHg), therapy could be switched to open-label concomitant therapy of latanoprost 0.005% at approximately 8 PM (± 30 minutes) and timolol 0.5% (or optionally 0.25% for subjects younger than 3 years old) twice daily at approximately 8 AM (± 30 minutes) and 8 PM (±30 minutes). If the therapy was

changed to the concomitant therapy at Weeks 1 or 4, the subject was asked to return to the clinic for a visit at Week 2 or 5 respectively. If at Week 2 or 5 IOP was not adequately controlled (eg, IOP ≥ 36 mmHg), the subject was discontinued. The IOP measurements for all follow-up visits occurred at 10 AM (± 1.5 hours).

The schedule of activities is presented in Table 1.

Number of Subjects (Planned and Analyzed): A total of 120 subjects were planned for the study (including 60 PCG subjects and 60 non-PCG subjects). A total of 139 subjects were assigned to study treatment and 137 subjects (68 in the latanoprost group and 69 in the timolol group) were treated. Subject enrollment by country is summarized in Table 2.

Diagnosis and Main Criteria for Inclusion: Male or female subjects aged 36 weeks to 18 years with a diagnosis of glaucoma and IOP of ≥22 mmHg in at least 1 eye.

Exclusion Criteria: Subjects who required surgery for acute angle closure, had prior cyclodestructive procedures, or had a history of ocular trauma or surgery in either eye within 3 months of the Baseline visit were excluded from the study.

Study Treatment: Study treatments were provided in identical bottles and indistinguishable between latanoprost solution and timolol solution. Vehicle of Xalatan solution was used to make both treatments undistinguishable as timolol treatment was dosed twice daily and latanoprost was dosed once daily (double dummy).

Within each stratum subjects were randomly assigned in a 1:1 ratio to 1 of the 2 treatment groups (latanoprost or timolol): Group 1 received latanoprost vehicle at approximately 8 AM (± 30 minutes) and latanoprost 0.005% at approximately 8 PM (± 30 minutes), and Group 2 received timolol 0.5% (or optionally 0.25% for subjects younger than 3 years old) twice daily at approximately 8 AM (± 30 minutes) and 8 PM (± 30 minutes). Parents or legal guardians (primary caretaker) of subjects administered 1 drop of study medication in each eye once daily in the morning and once daily in the evening for the 84 day treatment duration (administration was to occur at consistent times throughout the study).

Efficacy Endpoints:

Primary Endpoint:
- Mean change from baseline IOP in the study eye at Week 12.

Secondary Endpoints:
- Mean IOP change from baseline in the study at each visit (Week 1, Week 4, Week 12 and Weeks 2 or 5 when applicable).

• Mean IOP level in the study eye at each visit (Baseline, Week 1, Week 4, Week 12 and Weeks 2 or 5 when applicable).
• Proportion of subjects with at least a 15% IOP reduction from baseline in the study eye (for responder analysis).
• Proportion of subjects discontinuing therapy due to a drug-related adverse experience.

Safety Evaluations: Safety evaluations included assessment of adverse events (AEs), visual acuity and refraction, conjunctival hyperemia, pachymetry, pupil diameter, corneal diameter, biomicroscopy (anterior segment), gonioscopy, biomicroscopy posterior segment (ophthalmoscopy), visual field, vital signs measurements, and a measurement of alertness.

Statistical Methods: The intention to treat (ITT) population was defined as all subjects who were randomized into the study and received at least 1 dose of study medication. The per protocol (PP) population was restricted to subjects with no major protocol violations who received at least 1 week of study medication and had at least Week 1 IOP measurements during the 12-week treatment period.

The primary efficacy endpoint was the mean IOP change from baseline in the study eye at Week 12. For subjects who switched to open-label concomitant therapy or discontinued study prior to Week 12, their last IOP measurements prior to the switch or study discontinuation was used to impute the IOP value at Week 12 using the Last Observation Carried Forward (LOCF) method. This applied to both the PP and ITT populations.

For the primary endpoint, an analysis of covariance (ANCOVA) model with treatment and baseline diagnosis as factors and baseline IOP as a covariate was used to estimate the difference in IOP reduction at Week 12 between latanoprost and timolol. The corresponding p-value and 95% CI of the mean difference were also calculated.

Before the ANCOVA model was fitted for the primary efficacy endpoint, a test for parallelism was performed to ensure the ANCOVA model without the interaction terms among treatment group, baseline diagnosis and baseline IOP was appropriate for the primary efficacy data analysis. Note: The results indicated that a statistical model with heterogeneous regression slopes for different treatment groups within different diagnosis subgroups would be a better fit to the study data.

The primary efficacy analysis population for determination of non-inferiority was based on the PP population and the primary efficacy analysis population for determination of superiority was based on the ITT population.

Secondary Endpoint Analyses:
The same ANCOVA model with treatment and baseline diagnosis as factors and baseline IOP

as a covariate was used to estimate the difference in IOP reduction at each visit between latanoprost and timolol. The corresponding p-value and 95% CI of the mean difference was also calculated.

If a subject's IOP reduction in the study eye was greater than or equal to a 15% reduction from baseline at both Weeks 4 and 12, then this subject was classified as a responder. A subject with an IOP reduction in the study eye less than 15% reduction was classified as a nonresponder.

Subgroup Analyses: All efficacy analyses were also performed for the PCG and non-PCG subgroups within the PP and ITT populations.

For the subgroup analyses within the baseline diagnosis groups (PCG and non-PCG), the ANCOVA model had only treatment as the factor and baseline IOP as a covariate. For the responder analysis, a Pearson's chi-square test was used to evaluate the treatment difference.

RESULTS

Subject Disposition and Demography: Subject disposition is summarized in Table 3. All 137 of the subjects treated in this study were evaluable for inclusion in the ITT population and the safety population; 77% of the subjects assigned to study treatment were included in the PP population.

Most subjects treated completed the study. In the latanoprost group, none of the 4 subject discontinuations were considered by the Investigator as being related to study drug treatment. Approximately 12% of subjects switched to open-label treatment. While 3 subjects in the timolol group discontinued due to lack of efficacy, no subject in the latanoprost group discontinued for this reason (Table 4).

Demographic characteristics and diagnosis are presented in Table 5.

Efficacy Results:

The least-squares (LS) mean of IOP reduction was 7.2 mmHg in the latanoprost treated group and 5.7 mmHg in the timolol group. The LS mean difference was 1.5 mmHg in favor of latanoprost. The lower bound of the 95% CI of the difference between the LS means was -0.81 mmHg, which was above the pre-specified non-inferiority margin of -3 mmHg demonstrating the noninferiority of latanoprost to timolol. The LS mean difference (1.5 mmHg in favor of latanoprost) was also similar to the arithmetic mean difference (1.3 mmHg in favor of latanoprost). Results from this primary efficacy endpoint analysis are presented in Table 6 for the study eye in the PP population.

Results from primary efficacy endpoint analysis in the ITT population are presented in Table 7. The LS mean difference was 1.07 mmHg in favor of latanoprost. Although this difference was

less than that achieved for the PP population the same trend was noted. The lower bound of the 95% CI of the difference between the LS means was -0.89 mmHg, which is consistent with the results analyzed in PP population and is also above the pre-specified noninferiority margin of -3 mmHg.

Secondary Analyses:
IOP Reduction: Mean IOP and IOP reduction (without LOCF imputation) in the study eye at each visit (Weeks 1, 4, and 12), excluding observations collected after switching to open-label concomitant therapy, are summarized in Table 8 for the PP population. Mean IOP reduction in the latanoprost group was similar to or numerically greater than the timolol group at each study visit (Weeks 1, 4, and 12). Results at Week 12 (missing data not imputed) were supportive of results achieved at Week 12 for the primary endpoint using a LOCF approach.

Responder Analyses: The proportion of responders (subjects whose IOP reduction in the study eye was greater than or equal to a 15% reduction from Baseline at both Weeks 4 and 12) excluding observations collected after switching to open-label therapy in the PP population is summarized in Table 9. The proportion of responders was 60% in the latanoprost group and 52% in the timolol group.

Diagnosis Subgroups: PCG versus non-PCG:
IOP reduction: The mean IOP reduction at Week 12 for the PCG subgroup was 5.9 mmHg in the latanoprost group and 5.3 mmHg in the timolol group (Table 10); for the non-PCG subgroup the mean reductions at Week 12 were 8.4 and 6.3 mmHg, respectively (Table 11). The lower bounds of the 95% CI of the difference between the LS means in both diagnosis subgroups were above -3 mmHg.

Responder Analysis: The proportion of responders for the PCG subgroup was 50% in the latanoprost group and 46% in the timolol group; for the non-PCG subgroup the proportion of responders was 72% and 57%, respectively (Table 12).

Safety Results: The most common AEs were nasopharyngitis and headache. The incidence of conjunctival hyperemia (both eyes and study eye) was low. Non serious AEs experienced by ≥2% of subjects are presented in Table 13.

Most treatment-related AEs were only noted for 1 subject each; conjunctival hyperemia was the only treatment-related AE reported for >1 subject (0 in the latanoprost group and 3 subjects in the timolol group). Treatment related AEs are presented in Table 14.

A total of 9 subjects experienced serious adverse events (SAEs): 2 subjects (2.9%) in the latanoprost group and 7 subjects (10.1%) in the timolol group. Three of these events (developmental glaucoma and eye hemorrhage in 1 subject and pneumonia in a second subject),

were considered by the Investigator as being at least possibly related to study medication and the subjects were withdrawn from the study. Treatment emergent SAEs are presented in Table 15.

Discontinuations: Five subjects (1 subject in the latanoprost group and 4 subjects in the timolol group) discontinued the study due to AEs. One of these discontinuations due to an AE (visual acuity reduced) was considered by the Investigator as being possibly related to study drug (timolol) treatment (Table 16). There were no dose reductions or temporary discontinuations due to AEs during this study.

Deaths: There were no deaths during the study.

Most subjects had normal conjunctival hyperemia scores in the study eye at baseline and in most cases scores were unchanged from baseline. No clinically meaningful changes from baseline results were noted for other safety parameters including visual acuity, central corneal thickness levels, pupil diameter, corneal diameter, visual field testing, biomicroscopy (anterior segment), angle gradings measured via gonioscopy, aqueous flare, cells in the anterior chamber, or ophthalmoscopy (posterior segment), vital signs, or alertness scores.

CONCLUSIONS:
In this prospective, randomized, double-masked, 12-week, parallel-group study of latanoprost and timolol in pediatric subjects with glaucoma ≤18 years old:
- Latanoprost 0.005% ophthalmic solution dosed once daily was not inferior (within a noninferiority margin of 3 mmHg in IOP measurement) to timolol 0.5% (or optionally 0.25% for subjects younger than 3 years old) dosed twice daily.
- There was no statistically significant difference in the proportion of subjects with a 15% or more IOP reduction at both Weeks 4 and 12 (responders); response rates in the latanoprost and timolol groups in the PP population were 60% and 52%, respectively, with a p-value of 0.33.
- Latanoprost demonstrated IOP reduction in both the PCG and non-PCG subgroups. When comparing the proportion of responders between the treatment groups the response rates in the PCG subgroup were 50% in the latanoprost group and 46% in the timolol group; in the non-PCG subgroup the response rates were 72% and 57%, respectively.
- Latanoprost 0.005% ophthalmic solution was well-tolerated and the safety profile was favorable.