A prospective, double-masked, randomized, multicenter, active-controlled, parallel-group, 6-month study assessing the safety and ocular hypotensive efficacy of PG324 (netarsudil 0.02%/latanoprost 0.005%)[1] Ophthalmic Solution compared to GANFORT® (bimatoprost 0.03%/timolol 0.5%) Ophthalmic Solution in subjects with elevated intraocular pressure (Mercury 3)

[1] "(netarsudil 0.02%/latanoprost 0.005%)" country specific addition to title for Hungary

NCT03284853

26 Aug 2020

STATISTICAL ANALYSIS PLAN
Version 2.0
26 Aug 2020

A prospective, double-masked, randomized, multicenter, active-controlled, parallel-group, 6-month study assessing the safety and ocular hypotensive efficacy of PG324 (netarsudil 0.02%/latanoprost 0.005%)[1] Ophthalmic Solution compared to GANFORT® (bimatoprost 0.03%/timolol 0.5%) Ophthalmic Solution in subjects with elevated intraocular pressure (Mercury 3)

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PROTOCOL NUMBER PG324-CS303

SPONSORED BY

PREPARED BY

DOCUMENT VERSION CONTROL

Version Number	Date	Comments/Changes
0.1	15 June 2018	Draft
0.2	05 June 2019	Second Draft
0.3	27 June 2019	Third Draft
1.0	24 July 2019	Original
2.0	26 August 2020	Version 2.0

APPROVALS

Approved:

[redacted] Date: [redacted]

[redacted] Date: [redacted]

[redacted] Date: [redacted]

[redacted]

Date: [redacted]

[redacted]

Date: [redacted]

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LIST OF ABBREVIATIONS

AE	Adverse Event
ANCOVA	Analysis of Covariance
AR-13324	Netarsudil Mesylate (Drug Substance) / Netarsudil Ophthalmic Solution (Drug Product)
BCVA	Best Corrected Visual Acuity
BOCF	Baseline Observation Carried Forward
BP	Blood Pressure
CI	Confidence Interval
CRF	Case Report Form
CSR	Clinical Study Report
ETDRS	Early Treatment of Diabetic Retinopathy Study
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IOP	Intraocular Pressure
IWR	Interactive Web Response
HR	Heart Rate
LOCF	Last Observation Carried Forward
logMAR	Logarithm of the Minimum Angle of Resolution
IP	Investigational Product
LS Mean	Least Squares Mean
ITT	Intent-to-Treat
IWRS	Interactive Web-based Response System
MCMC	Monte Carlo Markov Chain
MCS	Mental Component Summary
MedDRA	Medical Dictionary for Regulatory Activities
mmHg	Millimeters of Mercury
MMRM	Mixed Model Repeated Measures
OAG	Open-Angle Glaucoma
NEI	National Eye Institute
OHT	Ocular Hypertension
OU	Both eyes
PCS	Physical Component Summary
PG324	Fixed-dose Combination of Netarsudil and Latanoprost
PM	Evening
PP	Per-Protocol
PT	Preferred Term
QD	Once-daily
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SD	Standard Deviation
[redacted]	[redacted]
SE	Standard Error
SF-36 v.2	Short Form (Health Survey Questionnaire, 36 questions, version 2)

SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
VF	Visual Fields
VFQ-25	Visual Function Questionnaire (NEI, 25 questions)

1. PURPOSE OF THE ANALYSES

This statistical analysis plan (SAP) is being developed after review of the Aerie Pharmaceuticals Ireland Ltd., protocol number PG324-CS303 (Amendment 6, dated 27 May 2020 and Amendment 7 dated 27 May 2020 (Country Specific – Hungary)) but before any analyses of the data. The SAP contains detailed information to aid in the performance of the statistical analysis and reporting of the study data for use in the final clinical study report (CSR). This SAP is being written with due consideration of the recommendations outlined in the most recent International Conference on Harmonization (ICH) E9 Guideline entitled: Statistical Principles for Clinical Trials and the most recent ICH E3 Guideline, entitled: Structure and Content of Clinical Study Reports.

This SAP describes the data that will be analyzed and the subject characteristics, efficacy, and safety assessments that will be evaluated. This SAP provides details of the specific statistical methods that will be used. If additional analyses are required to supplement the planned analyses described in this SAP, they may be completed and will be identified in the CSR.

2. PROTOCOL SUMMARY

2.1 Study Objectives

The primary objective of this study is to evaluate:

- The ocular hypotensive efficacy of PG324 Ophthalmic Solution relative to GANFORT® ophthalmic solution at 08:00, 10:00 and 16:00 hours at Week 2, Week 6 and Month 3

The secondary objectives of this study are to evaluate:

- The ocular and systemic safety of PG324 Ophthalmic Solution relative to GANFORT® ophthalmic solution during a 6-month treatment period
- Change in self-administered NEI Visual Functioning Questionnaire- 25 (VFQ-25) score from baseline to study exit for PG324 compared to GANFORT®
- Change in self-administered Short Form Health Survey Questionnaire 36 (SF-36 v2) score from baseline to study exit for PG324 compared to GANFORT®

2.2 Overall Study Design and Plan

This is a 6-month, double-masked, randomized, multicenter, active-controlled, parallel-group study assessing the safety and ocular hypotensive efficacy of PG324 Ophthalmic Solution compared to GANFORT® (bimatoprost 0.03%/timolol 0.5%) Ophthalmic Solution in subjects with elevated intraocular pressure (IOP). All investigational products will be dosed QD (PM). A total of approximately 440 subjects will be enrolled in this study at approximately 70 clinical sites in approximately 11 European Union countries, comprising a total of up to 220 subjects per treatment arm for each of 2 treatment arms. Subjects who are enrolled in this study will be those at least 18 years of age with diagnosed open angle glaucoma (OAG) or ocular hypertension (OHT), who are currently using topical IOP-lowering medication, each of whom meets all inclusion criteria and none of the exclusion criteria.

There will be a total of 9 visits designated as V1 – V9. For visits 3, 4, 5, and 6, the subjects will be evaluated at multiple time points (08:00, 10:00, and 16:00 hours) within the visit day. These time points will be designated as visit x.0, x.1, and x.2 respectively. At Visit 2 the subjects will be evaluated at a single time point (08:00 hours), while at visits 7, 8, and 9, the subjects will be evaluated at a single time point (10:00 hours). At Visit 1 (Screening), the subjects will be evaluated at a single time point with no designated hour. The total treatment period is 180 days, starting at Visit 3 (Day 1), and there are follow-up visits at Week 2, Week 6, and Months 3, 4, 5, and 6.

At Screening (Visit 1), an examination will be conducted, including measurements of heart rate and blood pressure (vital signs), urine pregnancy test (for women of child bearing potential), Visual Function Questionnaire (NEI, 25 questions) (VFQ-25), Short Form (Health Survey Questionnaire, 36 questions, version 2) (SF-36 v.2), and an ophthalmic examination to include ocular symptoms, best corrected visual acuity (BCVA), central corneal thickness by ultrasound

pachymetry (may be taken within 1 week of Visit 1), intraocular pressure (IOP; before pupil dilation), biomicroscopy, and dilated ophthalmoscopy). Visual fields and gonioscopy may be taken up to three months prior to randomization (Visit 3). Subject symptoms will be queried, and blood samples will be taken for clinical chemistry and hematology. All individuals who are qualified for enrollment (per assessment of inclusion/exclusion criteria) will have their current ocular hypotensive therapy reviewed to determine the appropriate washout period, prior to Visit 2, as specified in Section 5.7.1 of the protocol.

At Visit 2 (Qualification #1, Day -7 to -2, 08:00 hours), potential study subjects will be questioned with respect to changes in their health (to be recorded as medical history) and concomitant medication use. Study inclusion/exclusion criteria will be reassessed to confirm eligibility. BCVA, vital signs, urine pregnancy test (women of childbearing potential (who have a washout period that extends beyond 4 weeks), IOP, and biomicroscopy assessments will again be performed. The potential subject must have a post-washout IOP > 20 mmHg in at least one eye and < 36 mmHg in both eyes to qualify for further participation. This is the first of four qualifying IOPs for randomization.

Qualified subjects will return for Visit 3 (Qualification #2, Baseline, Day 1) 2 to 7 days after Visit 2. At Visit 3.0 (08:00 hours), testing will include recording symptomatology, vital signs, urine pregnancy test (within 7 days prior to randomization), BCVA, IOP, and biomicroscopy assessments. Any symptoms reported at this visit should be entered in the adverse event (AE) CRF. The potential subject must have a post-washout IOP > 20 mmHg in at least one eye and < 36 mmHg in both eyes to qualify for further participation. This is the second of four qualifying IOPs assessments for randomization.

Qualifying subjects will return for two additional visits on this day (Visit 3.1 at 10:00 hours and Visit 3.2 at 16:00 hours) during which symptomatology, IOP, and biomicroscopy assessments will be performed. The subject must have an IOP of > 17 mmHg in at least one eye and < 36 mmHg in both eyes to continue to be qualified. These are the third and the fourth of four qualifying IOPs assessments for randomization.

In summary, the following IOP criteria must be met at the qualifying visits for the subject to qualify for the study:

Visit, Day, Time	IOP Requirement (mmHg)
Visit 1, Screening	≥ 17mmHg in at least one eye and < 28mmHg in both eyes
Visit 2, Day -7 to -2, 8:00 hours	> 20mmHg in at least one eye and < 36mmHg in both eyes
Visit 3.0, Day 1, 8:00 hours	> 20mmHg in at least one eye and < 36mmHg in both eyes
Visit 3.1, Day 1, 10:00 hours	> 17mmHg in at least one eye and < 36mmHg in both eyes
Visit 3.2, Day 1, 16:00 hours	> 17mmHg in at least one eye and < 36mmHg in both eyes

If a subject qualifies in only one eye, it must be the same eye for visits 2, 3.0, 3.1, and 3.2 and this will be the study eye for the duration of the study.

For each qualification visit, individuals who do not meet the IOP requirement may return for up to 2 additional unscheduled qualification visits within 1 week of failing the specific qualification visit. Individuals who screen fail due to IOP being ≥ 36mmHg in either eye (exclusion criterion) may not return for additional qualification visits. Individuals returning at an unscheduled visit within 1 week are required to only re-measure IOP in both eyes. Upon return, such individuals would need to qualify at 08:00, 10:00 and 16:00 hours to continue the study.

For a subject who qualifies in both eyes based on IOP and ocular history, the study eye will be the eye with the higher IOP at 08:00 hours on Visit 3. If both eyes have the same IOP at 08:00 hours on Visit 3, then the right eye will be the study eye. In each subject, both eyes will be treated.

At this point, eligible subjects will be enrolled and assigned to an investigational product through an IWRS system according to a computer-generated randomization list. The first kit removed from an investigational product packer assigned through the IWRS system to the eligible subject will be dispensed unopened to the subject, along with written storage instructions.

Subjects will be instructed to self-administer their masked medication at home between 20:00-22:00 hours (8 PM - 10 PM) beginning with the first dose on the evening of this study visit or no later than within 48 hours of randomization.

Subjects will return for post-treatment Visits 4.0, 4.1, and 4.2 (Week 2 [Day 15]; 08:00, 10:00, and 16:00 hours), Visits 5.0, 5.1, and 5.2 (Week 6 [Day 43]; 08:00, 10:00, and 16:00 hours), Visits 6.0, 6.1, and 6.2 (Month 3 [Day 90]; 08:00, 10:00, and 16:00 hours), Visits 7 (Month 4 [Day 120]; 10:00 hours), Visits 8 (Month 5 [Day 150]; 10:00 hours), and Visits 9 (Month 6 [Day 180]; 10:00 hours). Symptomatology and non-dilated eye examinations including IOP and biomicroscopy will be conducted at all these visits. Vital signs, urine pregnancy test, and BCVA will also be conducted at Visits 4.0, 5.0, 6.0, 7, 8 and 9. Any symptoms reported, or clinical signs observed which have worsened, either from baseline or from previous visits at these post-dose visits, will be recorded as treatment emergent adverse events (TEAE).

Other tests will be performed in addition to those mentioned in the previous paragraph:

1. At Visit 6.0 (Month 3 [Day 90], 08:00 hours), visual fields and pachymetry will be measured. A dilated ophthalmoscopy will be performed at Visit 6.2 (Month 3 [Day 90], 16:00 hours).

2. At Visit 9 (Month 6 [Day 180]), VFQ-25 Questionnaire, SF-36 v.2 Questionnaire, visual fields, a dilated ophthalmoscopy and pachymetry will be assessed. Blood will be drawn for clinical chemistry and hematology labs as well.

A study schedule of events table is presented in Appendix 1.

2.3 Study Population

The study population includes subjects aged 18 years or older with a diagnosis of OAG or OHT. Subjects must present with medicated IOP at screening of ≥ 17mmHg in at least one eye and < 28mmHg in both eyes. In addition, subjects must have an unmedicated (post-washout) IOP

> 20mmHg in at least one eye and < 36 mmHg in both eyes at 2 eligibility visits (08:00 hour), 2-7 days apart and > 17mmHg in at least one eye and < 36 mmHg in both eyes at 10:00 and 16:00 hours at the second qualification visit in both eyes. If a subject qualifies in only one eye, it must be the same eye for all qualification visits, except screening. Corrected visual acuity in each eye must be +1.0 logMAR or better by early treatment of diabetic retinopathy study (ETDRS). The subject must also be willing to give signed inform consent and follow study instructions. The specific inclusion and exclusion criteria can be found in Sections 4.2 and 4.3 of the study protocol.

2.4 Treatment Regimens

There will be 2 treatments in this study:

- PG324 (Netarsudil 0.02% and latanoprost 0.005%) Ophthalmic Solution
- GANFORT® (bimatoprost 0.03% / timolol maleate 0.5% ophthalmic solution)

Subjects will be instructed to self-administer their masked medication once a day (QD) in the evening between 20:00 – 22:00 hours (8pm - 10pm). All treatments will be dosed in both eyes (OU). The treatment period will be 180 days.

2.5 Treatment Group Assignments or Randomization

A randomization code for allocating the treatments was prepared by an independent biostatistician, who was not involved in the day-to-day conduct of the study and provided in confidence to the unmasked clinical supply manager at Aerie and the Interactive Web Response (IWR) system personnel. At Visit 3.2 (Day 1), qualified subjects will be randomized in a 1:1 ratio to receive PG324 or GANFORT (stratified by investigative site and by maximum baseline IOP [< 25 mmHg vs ≥ 25 mmHg]). Treatment assignments were masked to the Investigator, the Sponsor team members involved in the day-to-day oversight of the clinical study and employees of the CRO administrating the study for the Sponsor, and the study subjects. At the end of the study, the randomized treatment assignments will be presented in a data listing.

2.6 Sample Size Determination

Assuming no difference between PG324 Ophthalmic Solution Q.D. and GANFORT® Q.D., a two -tailed alpha of 0.05 (2-sided 95% CI) at each of 9-time points, a common standard deviation (SD) of 3.5mmHg, and a correlation between time points of 0.60 or less, 200 intent-to-treat subjects per arm are necessary to have 85% power to show clinical non-inferiority (as defined above) of PG324 Ophthalmic Solution Q.D. to GANFORT® Q.D. in the mean change from baseline IOP. To account for the potential of additional variability in the primary efficacy outcome due to multiple imputations of missing data, up to 220 subjects per arm will be randomized.

3. GENERAL ANALYSIS AND REPORTING CONVENTIONS

This section discusses general policies to be employed in the analysis and reporting of the data from the study. Departures from these general policies may be given in the specific detailed sections of this SAP. When this situation occurs, the rules set forth in the specific section take precedence over the general policies.

All continuous study assessments will be summarized by treatment and time point (as applicable) using descriptive statistics (n, mean, median, standard deviation (SD), minimum, and maximum). All categorical study assessments will be summarized by treatment and time point (as applicable) using frequency counts and percentages.

All study data will be listed by treatment, subject, visit, and time point (as applicable).

In Protocol versions prior to Protocol Amendment 4, there were 3 time points (8:00, 10:00 and 16:00) for Visits 7, 8, and 9 (Month 4, Month 5 and Month 6). IOP and biomicroscopy assessments were measured at all timepoints for subject visits prior to Protocol Amendment 4; however, these assessments will only be performed at one time point (10:00 hours) for subject visits after Protocol Amendment 4. For summaries and analyses of Visits 7, 8, and 9 (Month 4, Month 5 and Month 6), only the assessment at 10:00 hours will be included if subjects have multiple timepoint assessments at a visit. The assessments at 08:00 and 16:00 hours will be listed in data listings only.

Hypothesis testing, unless otherwise indicated, will be performed at a 2-sided 0.05 significance level. Where applicable, two-sided 95% confidence intervals will be reported. All p-values will be displayed to four decimal places, with p-values less than 0.0001 presented as '<0.0001' and p-values greater than 0.9999 presented as '>0.9999'. Differences between PG324 and GANFORT will be calculated as PG324 – GANFORT.

For diurnally adjusted IOP, baseline will refer to the time-relevant measure at Visits 3.0 through 3.2 (e.g. IOP at 08:00 hours at Visit 3.0 will be the baseline for 08:00 hours at Visits 4.0, 5.0, and 6.0, etc.; IOP at 10:00 hours at Visit 3.1 will be the baseline for 10:00 hours at Visits 4.1, 5.1, and 6.1, etc.). For mean diurnal IOP, baseline will refer to the mean diurnal IOP at Visit 3. For all other variables, baseline is defined as the last measurement prior to the first dose of study medication. Change from baseline will be calculated as follow-up visit – baseline visit.

The unit of analysis for efficacy will be the study eye.

All study data will be listed by subject, treatment, and time point (as applicable). In the listings, individual subjects will be identified by a combination of site number and subject number, e.g., XXX-YYY, where XXX is the site number and YYY is the subject number.

All data analysis will be performed by [redacted] after the study is completed and the database has been locked and released for un-masking. Statistical programming and analyses will be performed using SAS® Version 9.4 or higher. Output will be provided in rtf format for tables and pdf format for tables, listings, and figures.

4. ANALYSIS POPULATIONS

4.1 Randomized Population

The randomized population will include all subjects who were randomized to treatment. Baseline variables and demographic characteristics will be summarized for this population.

4.2 Intent-to-Treat Population (ITT)

The ITT population will include all randomized subjects who have received at least one dose of study medication. This population will be the primary population for efficacy analyses and will be used to summarize all efficacy variables and will summarize subjects as randomized.

4.3 Per-protocol Population (PP)

The PP population is a subset of the ITT population, which will include those subjects (and their visits) who do not have major protocol deviations likely to seriously affect the primary outcome of the study as judged by a masked evaluation prior to the unmasking of the study treatment. This population will be the secondary population for efficacy analyses and will be used to summarize a subset of efficacy variables. If the PP and ITT populations are exactly the same, then additional efficacy analyses on the PP population will not be performed. The PP population will summarize subjects as treated.

4.4 Safety Population

The safety population will include all randomized subjects who have received at least one dose of study medication. This population will be used to summarize safety variables and will summarize subjects as treated.

5. STUDY SUBJECTS

5.1 Disposition of Subjects

Subject randomization, analysis populations, study completion, and withdrawal from the study will be summarized and listed for all randomized subjects. The summary table will include the numbers of subjects randomized and included in the analysis populations by randomized treatment group for the ITT population and by actual treatment group for the PP and Safety populations. It will also include the numbers of subjects who completed and discontinued from the study. The reasons for subject discontinuation and test agent discontinuation will be summarized for the applicable subjects. Reasons for subject discontinuation will include adverse event (AE), withdrawal of consent, non-compliance lost to follow-up, lack of efficacy, disallowed concurrent medication, investigator decision, protocol violation, death, and an "other" category for reasons other than those previously listed.

By-subject listings will include randomization information, actual treatment assigned, first and last dose dates, exposure, study eye, and analysis population inclusion. For subjects who prematurely discontinue following randomization, an additional by-subject listing will be provided that shows treatment assignment, gender, age, date of last visit, date of last dose, treatment duration at time of discontinuation, study day of discontinuation, and reason for discontinuation. Study day of discontinuation will be calculated as (date of discontinuation – date of Visit 3 date +1). Note that date of first dose is not collected but will be assumed to be the Visit 3 date. Treatment duration will be calculated as the (Date of Last Dose – Visit 3 Date + 1).

5.2 Protocol Deviations

Protocol deviations will be evaluated for all subjects. Major protocol violations will be judged by a masked evaluation and summarized in writing prior to the unmasking of the study treatment, for the purpose of selecting the PP population. All subjects having a protocol deviation will be identified in a subject data listing. The number and percentage of subjects with any deviations, any major or minor deviations, related to COVID-19 will be summarized by treatment group along with the disposition data. A separate data listing for COVID-19 related protocol deviations will be provided.

Failure to meet all Protocol Inclusion Criteria or meeting any Exclusion Criterion will also be considered for categorization as a major Protocol Deviation. Inclusion and Exclusion Criteria will be presented in a by-subject listing.

6. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

6.1 Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized by treatment group and listed for the randomized population. Demographic parameters will include gender, iris color, age in years at signing of informed consent form (ICF), race, ethnicity, prior hypotensive therapy, and time on current hypotensive therapy. Baseline characteristics will include study eye diagnosis of OHT or OAG, length of time since study eye diagnosis of OHT or OAG, study eye IOP at screening, and study eye mean diurnal IOP at baseline. Additionally, means for both the study eye and the fellow eye will be summarized separately for the baseline ocular measurements of deviation in visual fields, central corneal thickness, and cup-to-disc ratio.

Age will be reported in years and calculated in SAS using the formula:

Age = Floor ((ICFDT – DOB) / 365.25)

ICFDT is the date the subject signed the informed consent, DOB is the subject's date of birth, and Floor takes the integer part of the result.

Tests of differences between the treatment groups will be performed for both demographic and baseline characteristics. Categorical responses will be tested using Fisher's exact tests. Continuous measures will be tested using an analysis of variance model with treatment as the only explanatory variable.

6.2 Prior and Concomitant Medications

All medications which the subject has taken within 30 days prior to randomization and during the study will be recorded on the CRF. The name of the drug, dose, route of administration, duration of treatment, and indication will be recorded for each medication. For combination products (e.g., Contac®), the brand name is required. For non-combination products, the generic name is desired. The use of routine ophthalmic diagnostic pharmaceutical agents (e.g., fluorescein and local anesthetic) will be allowed, and individual documentation not required. Any change in dosing parameters should also be recorded on the CRF.

All prior and concomitant medications will be coded to preferred drug names and therapeutic drug class using the *WHO Drug Dictionary* (Version: March 2017). Use of concomitant medications will be summarized for each therapeutic drug class and each preferred drug name by treatment group. Subjects will be counted only once under each therapeutic drug class and preferred term for which they have used at least one concomitant medication. All prior and concomitant medication data will also be listed.

The class of prior hypotensive therapy, summarized on the baseline characteristic table and listed on the washout medication listing, will also be derived from the coded medication data. Classes include the following: Prostaglandins, β-adrenoceptor antagonists, adrenergic agonists (including α-agonists such as brimonidine and apraclonidine), Muscarinic agonists (e.g., pilocarpine), and Carbonic anhydrase inhibitors (topical or oral). For the summary table, categories will be: combination therapy, prostaglandins (monotherapy), other (monotherapy. Additionally, the

following two classes will be summarized: prior prostaglandin therapy and no prior prostaglandin therapy.

6.3 Medical and Ocular History

A medical and ocular history will be collected at screening, including diagnosis, start date, and stop date (as applicable) or ongoing. For ocular history, the applicable eye(s) will be noted. Any change in the individual's baseline health status that occur after the subject signs the informed consent until 30 days after the last dose of investigational product should be reported as adverse events.

Ocular surgery and laser procedures will also be collected at screening including the procedure description, procedure date, and affected eye(s).

All medical history and ocular surgery/laser procedures data will be presented in a by-subject listing. Medical and ocular history will be coded to preferred terms and system organ class using the MedDRA Dictionary (Version: 20.0). Medical and ocular histories will be summarized for each system organ class and each preferred term by treatment group. Subjects will be counted only once under each system organ class and preferred term for which they have at least one medical/ocular history.

Study eye diagnosis will be derived from the coded ocular history data. The preferred terms of "Ocular hypertension" and "Open angle glaucoma" will be matched to the study eye selection page of the CRF. Analyses based on study diagnosis will use this definition.

7. MEASUREMENTS OF TREATMENT COMPLIANCE

All subjects will be instructed to follow once a day dosing regimen in the evening between 20:00 – 22:00 hours (8pm - 10pm). All treatments will be dosed in both eyes (OU). No formal measure of treatment compliance is planned.

8. EFFICACY EVALUATION

8.1 Overview of Efficacy Analysis Issues

8.1.1 Handling of Dropouts or Missing Data

Any missing, unused, or spurious data will be noted in the final statistical report. Analyses will be performed primarily on the ITT population with multiple imputation techniques (e.g., Monte Carlo Markov Chain) used to impute missing data and secondarily using: observed data only, last observation carried forward (LOCF) where LOCF will be performed using time-relevant measures (i.e. from the same time point of the most recent visit with a non-missing value); and baseline observation carried forward (BOCF) using time-relevant measures to determine the robustness of results.

8.1.2 Multicenter Studies

This study will have approximately 70 different sites enrolling and treating subjects. Due to the low sample size from most sites, country will be included in the assessment. The homogeneity of treatment effect across investigative sites will be examined by a model containing the additional factors of investigative countries and its interaction with treatment for the primary IOP efficacy endpoint.

8.1.3 Assessment Time Windows

In general, it is intended that all safety and efficacy data (with some exceptions) will be summarized at each time point collected regardless of assessment time windows. Because subjects may have an early termination visit at any time or may have unscheduled visits, the following conventions will be implemented.

For all safety data, the visit date or start date (e.g., adverse events) will be used to calculate study day, defined as the number of days from the day of first dose. The day of first dose (Visit 3) is considered study day 1, so study day will be computed as (date of data – Visit 3 + 1). However, if the visit date or start date happens before the date of first dose, study day will be computed as (date of data – Visit 3). Study day will be presented in listings for medical history, concomitant medications, and adverse events.

In all by-visit safety assessments, end of study visits and early termination visits will be combined in order to present all data available for each subject; early termination visits will not be windowed into the nearest fitting study visit. Each subject will have one end of study visit. For efficacy outcomes, early termination data will not be combined with end of study visit information as the timing of the outcome measure is integral to the analysis. Instead, the efficacy outcome will be windowed into the nearest study visit, where each follow-up visit through Month 5 has a ± 3-day window. The Month 6 visit has a ± 7-day window.

8.2 Efficacy Variables and Primary Hypotheses

1. The primary efficacy outcome will be the comparison of PG324 to GANFORT for:

- Mean IOP within a treatment group at 08:00, 10:00, and 16:00 hours at the Week 2, Week 6, and Month 3 study visits

2. Secondary efficacy endpoints will include the comparison of PG324 to GANFORT for:
   - Mean diurnal IOP within a treatment group at each post-treatment visit
   - Mean change from diurnally adjusted baseline IOP at each post-treatment time point
   - Mean change from baseline in diurnal IOP at each post-treatment visit
   - Mean percent change from diurnally adjusted baseline IOP at each post-treatment time point
   - Mean percent change from baseline in diurnal IOP at each post-treatment visit
   - Percentages of subjects achieving pre-specified mean, mean change, and percent mean change diurnal IOP levels at each post-treatment time point:
     - Diurnal mean IOP of ≤22, ≤21, ≤20, ≤19, ≤18, ≤17, ≤16, ≤15, ≤14
     - IOP reduction from baseline of ≥2, ≥4, ≥6, ≥8, ≥10, ≥12 (IOP reduction at a visit from baseline was calculated as IOP [baseline] - IOP [visit], using mean [integral or non-integral] IOP values)
     - IOP percent reduction from baseline of ≥5, ≥10, ≥15, ≥20, ≥25, ≥30, ≥35, ≥40 (IOP percent reduction at a visit from baseline was calculated as [IOP reduction from baseline / IOP (baseline)] * 100%)

3. The primary hypotheses are:

- H_0: The difference between study eyes treated with PG324 and study eyes treated with GANFORT (PG324 - GANFORT), in mean IOP at the following time points: 08:00, 10:00, and 16:00 hours at the Week 2, Week 6, and Month 3 Visits, is > 1.5 mmHg for at least one time point over all visits or is > 1.0 mmHg for a majority of time points over all visits.

- H_1: The difference between study eyes treated with PG324 and study eyes treated with GANFORT (PG324 - GANFORT), in mean IOP at the following time points: 08:00, 10:00, and 16:00 hours at the Week 2, Week 6, and Month 3 Visits, is ≤ 1.5 mmHg for all visits and is ≤ 1.0 mmHg for a majority of time points over all visits.

Clinical non-inferiority will be concluded if the upper limit of the 95% CIs around the difference (PG324 - GANFORT) is ≤ 1.5 mmHg at all time points and ≤ 1.0 mmHg at the majority of time points through Month 3.

8.3 Analysis Methods

All continuous study assessments will be summarized by treatment and time point (as applicable) using descriptive statistics (n, mean, median, SD, minimum, and maximum). All categorical study assessments will be summarized by treatment and time point (as applicable) using frequency counts and percentages. All statistical tests will be performed at a 2-sided 5% significance level. For the IOP measurements, 2-sided tests and 2-sided 95% confidence intervals will be reported.

Mean diurnal IOP values will be constructed by averaging the three IOP measurements on each of Week 2, Week 6, and Month 3. Mean diurnal baseline IOP will be constructed as the average of the three Day 1 IOP measurements. Mean change from mean baseline diurnal IOP will be created by taking the average of the three time points on each of Week 2, Week 6, and Month 3and subtracting the mean baseline diurnal IOP measurement.

For diurnally adjusted IOP measures, baseline will refer to the time-relevant measure at Visits 3.0 through 3.2 (e.g., IOP at 08:00 hours at Visit 3.0 will be the baseline for 08:00 hours at Visits 4.0, 5.0, and 6.0; IOP at 10:00 hours at Visit 3.1 will be the baseline for 10:00 hours at Visits 4.1, 5.1, 6.1, 7, 8, and 9). IOP at 16:00 hours at Visit 3.2 will be the baseline for 16:00 hours at Visits 4.2, 5.2, and 6.2). For mean diurnal IOP, baseline will refer to the mean diurnal IOP at Visit 3. For all other variables, baseline is defined as the last measurement prior to the first dose of study medication. Change from baseline will be calculated as follow-up visit – baseline visit.

Percent change from diurnally adjusted baseline IOP will be determined by dividing the change from diurnally adjusted baseline by the corresponding baseline IOP value, such that a negative change from baseline will produce a negative percent change from baseline.

All primary and secondary efficacy variables, along with the planned analysis methods for those variables, are given in Table 8-1. These analyses will be performed for the ITT population for all efficacy variables and PP population for selected efficacy variables. The ITT population will be used for all efficacy subgroup analyses. Note that each subject will have one eye designated as the study eye. Only study eyes will be evaluated for all the efficacy measures; however, both eyes will be treated. Fellow eyes will be evaluated separately for the primary analysis of the primary efficacy measure.

Table 8-1 Summary of Efficacy Variables and Analysis Methods

	Two Sample T-test[a]	ANCOVA[b]	MMRM[c]	Fisher's Exact Test[d]	Analysis Population	Missing Data Imputation
Primary Analysis						
Mean IOP at each time point at Week 2, Week 6, and Month 3		X			ITT	MCMC
Secondary Analyses						
Mean IOP at each time point at Week 2, Week 6, and Month 3		X			ITT	LOCF, BOCF, Observed data
	X				ITT, PP	MCMC, LOCF, BOCF, Observed data
		X			PP	MCMC, LOCF, BOCF, Observed data
			X		ITT	Observed data
Mean diurnal IOP at Week 2, Week 6, and Month 3	X	X			ITT, PP	MCMC, LOCF, BOCF, Observed data
Mean change from diurnally adjusted baseline IOP at each post-treatment time point	X				ITT, PP	MCMC, LOCF, BOCF, Observed data
Mean change from baseline in diurnal IOP at Week 2, Week 6, and Month 3	X				ITT, PP	MCMC, LOCF, BOCF, Observed data
Mean percent change from diurnally adjusted baseline IOP at each post-treatment time point	X				ITT, PP	Observed data
Percentages of subjects achieving pre-specified mean, mean change, and percent mean change diurnal IOP levels				X	ITT, PP	Observed data

[a] Two Sample T-test comparing actual mean IOP value at each time point between PG324 and GANFORT.

[b] ANCOVA model including treatment as the main effect and baseline as the covariate. Individual models will be fit for each visit and time point.

[c] Mixed Model Repeated Measures analysis including treatment as the main effect, and baseline IOP, visit, time point, treatment*visit, treatment*time point, visit*time point, and treatment*visit*time point as model terms. Repeated measures will be used to account for the correlation among measures within a subject. The model will include all post-dose visits and time points.

[d] Fisher's exact test comparing the incidence in each category at each time point between PG324 and GANFORT.

8.3.1 Primary Efficacy Analyses

The primary analysis of the primary outcome will employ a linear model with IOP at the given visit and time point as the response, baseline IOP as a covariate, and treatment as a main effect factor at each time point (08:00, 10:00, and 16:00 hours at the Week 2, Week 6, and Month 3 Visits), using the intent-to-treat population with multiple imputation techniques (e.g., Monte Carlo Markov Chain) used to impute missing data. Each time point within each visit will be modeled separately. The least squares mean differences (PG324 – GANFORT) will be presented as well as 2-sided 95% confidence intervals (CIs) and p-values. Clinical non-inferiority for PG324 will be concluded if the upper limit of the 95% CIs around the difference (PG324 – GANFORT) is ≤1.5 mmHg at all 9 time points through Month 3 and is ≤1.0 mmHg at a majority of time points (at least 5 of 9) through Month 3.

The following SAS code will be used for multiple imputations using the Monte-Carlo Markov Chain method, where a separate model will be fit for each time point at each visit.

```
proc mi data = indata seed = 48669 out = outdata1;
  mcmc initial = em;
  var trt01pn baseline IOP;
run;
```

where

- *indata* is the name of the input dataset
- *outdata* is the name of the output dataset
- *trt01pn* is the name of the treatment group variable in numeric format
- *baseline* captures the baseline IOP for the given time point
- *IOP* is the name of the IOP measure.

Five complete data sets will be generated from the above code. Each complete data set will be used to analyze this primary efficacy endpoint separately using analysis of variance. Then, the SAS procedure MIANALYZE will be used to analyze the results from the 5 complete data sets to generate a combined inference. The following SAS code will be used:

```
ods output diffs = outdata2;
proc mixed data = outdata1;
  class trt01pn;
  model IOP=trt01pn baseline;
  lsmeans trt01pn / cl pdiff;
  by _Imputation_;
run;

proc sort data=outdata2;
  by trt01pn _trt01pn;
run;

ods output ParameterEstimates = outdata3;
proc mianalyze data = outdata2 alpha = 0.05;
```

```
        by trt01pn _trt01pn;
        modeleffects estimate;
        stderr stderr;
    run;
```

where

- *IOP* is the name of the IOP measure
- *trt01pn* is the name of the treatment group variable in numeric format
- *outdata2* is the name of the output dataset that contains the statistical results of the differences between treatment groups
- *outdata3* is the name of the output dataset that contains summary and inferential statistics.

8.3.2 Secondary Efficacy Analyses

The secondary efficacy analyses will include repeating the primary efficacy analysis on all subjects and additional analyses of the primary efficacy endpoint as well as other analyses of the secondary endpoints, as outlined below.

The primary efficacy analysis will be repeated on the ITT population using observed data only, last observation carried forward (LOCF) where LOCF will be performed using time-relevant measures; and baseline observation carried forward (BOCF) using time-relevant measures to determine the robustness of results. Additionally, the above analyses will be repeated on the PP population to determine robustness of results.

Secondary analyses of the primary endpoint will be completed using individual two-sample t-tests and 95% t-distribution confidence intervals for each comparison (PG324 vs GANFORT) at each time point (08:00, 10:00, and 16:00 at the Week 2, Week 6 and Month 3 Visits) using the ITT and PP populations. Similar analyses will be completed on the secondary endpoints: mean IOP measure at Month 4, Month 5, and Month 6 visits and mean diurnal IOP and change from baseline diurnal IOP measures based on the ITT and PP populations. Models adjusting for baseline will only be performed on the mean IOP response variable as inference is identical between this response and the change from baseline IOP response variable in such a model based on the ITT and PP populations.

Additionally, for the mean IOP values at each time point, mixed model repeated measures will be run with baseline as the covariate; treatment, visit, time point, treatment by visit, treatment by time point, visit by time point, and treatment by visit by time point as the fixed effect factors; and subject as the random effect, repeated measure. An unstructured covariance structure will be used to model the within subject, between visit and time point variances. This allows for different variances and covariances within and between time points and visits. The treatment by visit, treatment by time point, visit by time point, and treatment by visit by time point interactions allow for a different rate of change in IOP in the different treatment arms among visits and time points. This model will be run including the Week 2, Week 6, and Month 3 visits based on the ITT population.

Percent change from diurnally adjusted baseline IOP at each time point will be analyzed using two-sample t-tests, between PG324 and GANFORT, at each time point and visit, including two-sample t-tests and 95% t-distribution confidence intervals on the difference (PG324 – GANFORT). The analysis will be based on the ITT and PP populations.

Analyses of IOP will also include summarizing the number and percentage of study eyes achieving mean diurnal IOP reduction from baseline of ≥ 4 to ≥ 12 mmHg in 2 mmHg increments and percent reduction from baseline of ≥ 5% to ≥ 40% in 5% increments at Week 2, Week 6, and Month 3. Additionally, the number and percentage of study eyes attaining a mean diurnal IOP of ≤ 22 to ≤ 14 mmHg in 1 mmHg increments will be summarized at Week 2, Week 6, and Month 3. Fisher's exact test (2-sided p-values) will be used to test the pair wise differences between treatment groups for each category at each visit. These analyses will be presented for both the ITT and PP populations with observed data only.

8.4 Examination of Subgroups

Subgroup analyses based upon pre-study characteristics include:

- Age: <65 years, ≥65 years
- Gender: Male, Female
- Race: Caucasian, Other
- Iris Color: Blue/Grey/Green, Brown/Black, Hazel
- Maximum baseline IOP value: <22 mmHg, <23 mmHg, <24 mmHg, < 25 mmHg, <26 mmHg, <27 mmHg, <30 mmHg, <32 mmHg
- Prior hypotensive medication experience category 1: Combination Therapy, Prostaglandin (monotherapy), Other (monotherapy),
- Prior hypotensive medication experience category 2: Prior Prostaglandin, No Prior Prostaglandin
- Country

For each subgroup, except those defined by unmedicated baseline IOP, IOP will be compared at each post-dose time point between treatment groups (using an ANCOVA model with treatment as the main effect, baseline IOP and subgroup as covariates, and the interaction of treatment by subgroup. The least squares mean differences (PG324 – GANFORT) will be presented as well as 2-sided 95% confidence intervals (CIs) and p-values. These subgroup examinations are based on the ITT population and use observed data only.

An analysis of investigative country will also be included as a subgroup analysis. The homogeneity of treatment effect across investigative regions will be examined using a similar model as the above subgroup analyses. Results will be presented in tabular form. This analysis is based on the ITT population and use observed data only.

Subgroup analyses based upon country will be completed for Austria, Belgium, Czech R, France, Germany, Hungary, Italy, Latvia, Poland, Spain, and UK. The analysis of these IOP subgroups will be completed using only the primary endpoint analysis strategy.

Subgroup analyses based upon maximum unmedicated baseline IOP in the study eye additionally will be completed for maximum baseline IOP <22 mmHg, <23 mmHg, <24 mmHg, <25 mmHg, >=25 mmHg, <26 mmHg, <27 mmHg, <30 mmHg, and <32 mmHg. The analysis of these IOP subgroups will be completed using only the primary endpoint analysis strategy.

9. SAFETY EVALUATION

9.1 Overview of Safety Analysis Methods

The assessment of safety and tolerability is the secondary objective of this study. All safety analyses will be carried out using the Safety Population and will include the study eye and fellow eye separately, where applicable. All tabular summaries will be provided primarily for all subjects.

The assessment of safety will be evaluated by:

- Adverse events
- Heart rate and blood pressure
- Biomicroscopy of anterior segment including evaluation of cornea, conjunctiva and anterior chamber. (Fluorescein staining to be used.)
- Dilated ophthalmoscopy
- Best Corrected ETDRS Visual Acuity
- Visual fields
- Pachymetry
- IOP
- Clinical chemistry and hematology laboratory findings
- Pregnancy testing (for women of childbearing potential)
- Change in Self-Administered NEI Visual Functioning Questionnaire-25 (VFQ) score from baseline to study exit
- Change in Self-Administered Short Form Health Survey Questionnaire 36 (SF-36 V.2) score from baseline to study exit

All safety variables will be descriptively summarized by treatment group at each assessment time and for relevant changes from baseline.

For complete inclusion of subjects who withdraw from the study early, the End of Study visit for safety outcomes will be defined as either Visit 9 or Early Discontinuation.

For the first interim analysis, the Month 3 visit for safety outcomes will be defined as either Visit 6 or Early Discontinuation.

9.2 Extent of Exposure

Summary statistics will be presented for treatment exposure. Treatment exposure will be defined as the number of days that the subject was exposed to study treatment as calculated using the formula:

Treatment exposure = Date of Last Dose – Visit 3 Date + 1.

9.3 Adverse Events

An adverse event is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. All AEs occurring during the study (i.e. once the subject has received one dose of study drug) will be defined as treatment emergent adverse events (TEAEs) and must be documented, regardless of the assumption of causal relationship, on the respective AE CRF. All adverse events should be documented from the time the subject signs the informed consent until 30 days after the last dose of investigational product. If a subject has ongoing AEs at the time of study completion, the ongoing AEs must be followed-up and provided appropriate medical care until the event has resolved or stabilized. Documentation of AEs includes onset date, severity, action(s) taken, study medication relationship, outcome, resolution date, and seriousness. AE data post study completion date may be included in the CSR.

Verbatim descriptions of AEs will be mapped to MedDRA (version: 20.0) thesaurus terms and be presented in a data listing. Treatment emergent AEs, those that occur after the first dose of study medication, will be summarized by treatment group using frequencies and proportions for each system organ class (SOC) and preferred term (PT) within each SOC. A separate summary will be presented for AEs that are related to the study drug (marked as "possibly related" or "related" in the CRF). For these summaries, Fisher's exact tests will be used to test the difference in proportions of subjects with each AE between treatment groups, SOC, and PT. Another table will be presented summarizing AEs by maximum severity. Additional summaries will be presented for serious AEs and AEs leading to study treatment discontinuation.

An overall summary table will be developed to report the number of events and the incidence of subjects having at least one event in the following categories:

- TEAEs
- Ocular TEAEs
- Non-Ocular TEAEs
- Serious TEAEs (SAEs)
- Treatment-Related TEAEs (reported as possibly related or related to the study drug)
- Treatment-Related SAEs
- TEAEs by maximum severity
- TEAEs leading to study drug discontinuation
- TEAEs resulting in death

While the overall summary of TEAEs will present both the number of TEAEs and the incidence of TEAEs, the other summaries will only report the incidence of TEAEs. When reporting the number of TEAEs, if the same TEAE occurs for a subject on multiple occasions the event will be counted once for each occurrence. When reporting the incidence, a subject will only be counted once if they ever experience an event within the SOC and ever experience the individual PT. Summaries will be performed using the actual treatment received.

9.4 Deaths, Serious Adverse Events, and Other Significant Adverse Events

An adverse event is considered "serious" if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes: Death, a life-threatening adverse event, patient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Serious adverse events and deaths will be listed and summarized separately for the Safety population. Separate listings will also be provided for the COVID-19 related AEs, and COVID-19 related SAEs.

9.5 Clinical Laboratory Evaluation

Clinical laboratory results, including clinical chemistry and hematology, will be presented in data listings. Abnormal results, those above or below the normal range, will be flagged with "H" (high), "HP" (high panic), "L" (low) or "LP" (low panic) based on the laboratory ranges provided by the lab and included in the listings. Descriptive statistics will be used to summarize continuous measures and will be presented in tabular form including change from baseline to the Month 6 visit. Shifts from baseline to the Month 6 visit will also be presented in tabular form for clinical chemistries and hematology parameters by treatment group and laboratory domain. Summary tables also will be presented for the number of subjects with abnormal values within each laboratory parameter at the end of the study. Clinical laboratory results, including clinical chemistry, hematology, and urine pregnancy test will also be listed by subject.

9.6 Vital Signs, Ophthalmic Exam Findings, and Other Safety Outcomes

9.6.1 Vital Signs

Heart rate and blood pressure will be listed by treatment group, subject, and visit including observed values and changes from baseline. Measurements and change from baseline measurements will be summarized by treatment group and visit. Paired t-tests will be used to test within treatment group changes from baseline in vital sign parameters. Two-sided 95% Cis and p-values will be provided.

9.6.2 Intraocular Pressure

Intraocular pressure will be presented in data listings. Intraocular pressure data will be summarized at each visit and time point using continuous summaries, including change from baseline, for both the study eye and the fellow eye, the number and percentage of subjects who had change from baseline $\geq$ 10 mmHg.

9.6.3 Visual Acuity

Visual acuity scores will be presented in data listings. Subjects who lost three or more lines will be presented in an additional listing. Visual acuity data will be summarized at each visit using continuous summaries, including change from baseline, for both the study eye and the fellow eye. Additionally, discrete summaries of the worst change from baseline will be presented for both the study eye and the fellow eye with the following groupings based on the logMAR scores: 0 or less, >0 to +0.09, +0.10 to +0.19, +0.20 to 0.29, +0.30 or more.

9.6.4 Dilated Ophthalmoscopy and Cup-to-Disc Ratio

Dilated ophthalmoscopy and cup-to-disc ratio results from Screening and Months 3 and 6 will be presented in data listings. A separate listing will be created for those subjects with a criterion change, defined as a change from "Normal" to "Abnormal" or a change from "Abnormal – Not Clinically Significant" to "Abnormal – Clinically Significant". Frequencies and percentages of normal, abnormal ophthalmoscopy results will be created for the following fields: Retina, Macula, Choroid, Optic Nerve, and Vitreous Humor. Abnormal results will further be broken down by clinical significance. A shift table of study eye and fellow eye ophthalmoscopy results will also be presented by treatment group.

Vertical cup-to-disc ratio at Screening will be summarized for the study eye and for the fellow eye by treatment group in the baseline characteristics table. Additionally, vertical cup-to-disc ratio will be summarized at follow-up visits and change from baseline to follow-up visits using continuous summary statistics. A listing of subjects with increases of ≥ 0.2 in either eye at end of study will be presented.

9.6.5 Biomicroscopy

Biomicroscopy results will be listed for both eyes at each visit. A separate listing will be presented for subjects with a criterion change, defined as a +1 unit increase from baseline. Summaries of biomicroscopy results will also be presented for study eyes and fellow eyes by treatment group, visit, and time point in tabular form.

A summary table of the number and percentage of subjects with at least a +1 unit increase in score from baseline will be presented by region, finding, time point and eye (study eye and fellow eye). In addition to each time point, there will be summaries for "At the Final Visit" and "At Any Visit".

Additionally, for Conjunctival Hyperemia, the proportion of subjects with a one severity grade increase from baseline will be compared between Day 15 and Day 90 at each time point within a treatment arm using McNemar's test. Another summary table will be presented with the number and percentage of subjects who had a finding judged to be clinically significant by region, finding, time point and eye (study eye and fellow eye). Fisher's exact tests will be used to compare incidence between treatment groups in both tables. Additionally, Conjunctival Hyperemia will be presented using continuous summary statistics for each visit, for the change from baseline to each post-baseline visit, and for the change from Day 15 to Day 90 visit (which will use time-specific differences [e.g. 08:00 at Day 90 – 08:00 at Day 15]). Differences

between treatment groups will be tested using two-sample t-tests as well as Wilcoxon rank sum tests.

Other summaries for Conjunctival Hyperemia:

Number and percentage of subjects with at least a clinically significant increase from baseline in conjunctival hyperemia will be presented by treatment group. Clinically significant increase is defined as ≥ 1 unit score change from baseline in either eye, with baseline defined as the maximum score prior to first dose of study medication (any time point).

Proportion of subjects with sporadic or non-sporadic conjunctival hyperemia will be presented for all subjects with conjunctival hyperemia who completed the study. Non-sporadic is defined as an event that started on/before Week 2 and stopped after study exit or is ongoing at exit.

Proportion of subjects with treatment-emergent conjunctival hyperemia by number of consecutive visits (e.g. 0, 1, 2, etc.) will be presented by treatment group. For example, subjects with the event that did not cover any visit are counted in 0 visit. Subjects with the event that covered only 1 visit are counted in 1. Subjects with the event onset at Visit 3 and covered Visits 4 to 6 are counted in 4.

9.6.6 Visual Field Examination, Pachymetry, and Gonioscopy

Visual field examination results will be collected at Screening and Months 3 and 6 and listed for each subject. Visual field mean deviation (dB) will be summarized using continuous summary statistics for the Screening and Months 3 and 6 visits as well as change from Screening to Months 3 and 6 by treatment group for the study eye and fellow eye separately.

Central corneal thickness, collected at Screening and Months 3 and 6 will be listed for each subject. Central corneal thickness will be summarized using continuous summary statistics for the Screening and Months 3 and 6 visits as well as change from Screening to Months 3 and 6 by treatment group for the study eye and fellow eye separately. The study eye and fellow eye means at screening will also be summarized by treatment group and included with baseline characteristics.

Gonioscopy will be collected at screening for each eye and listed for each subject. Possible values will be Open Angle, Narrow Angle, and Closed Angle.

10. VISUAL FUNCTION AND QUALITY OF LIFE QUESTIONNAIRES

10.1 Visual Function Questionnaire (NEI, 25 questions)

The VFQ-25 consists of a base set of 25 vision-targeted questions representing 11 vision-related constructs, plus an additional single-item general health rating question.

Table 10.1 Step 1: Recoding of Items

Question Numbers	Original Item Score[a]	Recoded Value
1, 3, 4, 15c[b]	1	100
	2	75
	3	50
	4	25
	5	0
2	1	100
	2	80
	3	60
	4	40
	5	20
	6	0
5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 16, 16a	1	100
	2	75
	3	50
	4	25
	5	0
	6	*
17, 18, 19, 20, 21, 22, 23, 24, 25	1	0
	2	25
	3	50
	4	75
	5	100

[a]Refer to protocol for the original item score
[b]Question 15c has four-response levels, but is expended to five-levels using question 15b.
Note: If 15b=1 then 15c should be recoded to 0.
If 15b=2, then 15c should be recoded to missing.
If 15b=3, then 15c should be recoded to missing.
*Response choice "6" indicates that the person does not perform the activity because of non-vision related problems. If this choice is selected, the item is coded as "missing".

Table 10.2 Step 2: Averaging Items to Generate VFQ-25 Sub-Scales

Sub-Scale	Number of items	Items to be averaged (after recoding per Table 10.1)
General Health	1	1

General Vision	1	2
Ocular Pain	2	4, 19
Near Activities	3	5, 6, 7
Distance Activities	3	8, 9, 14
Vision Specific:		
Social Functioning	2	11, 13
Mental Health	4	3, 21, 22, 25
Role Difficulties	2	17, 18
Dependency	3	20, 23, 24
Driving	3	15c, 16, 16a
Color Vision	1	12
Peripheral Vision	1	10

If the respondent is missing one of the items within a sub-scale, the subject's score will be equal to the average of the non-missing items.

To calculate an overall composite score for VFQ-25, simply average all the vision-target sub-scale scores, excluding the General Health sub-scale.

A higher sub-scale score or overall composite score indicates a better perception of health.

The VFQ-25 sub-scale scores and overall composite score will be summarized for the Screening, Month 6 and Month 6/Early Discontinuation visits, including change from Screening to Month 6 and change from Screening to Month 6/Early Discontinuation using continuous summary statistics. Paired t-tests will be used to primarily analyze the mean change from Screening to Month 6 and Month 6/Early Discontinuation within a treatment group; additionally, the non-parametric Wilcoxon signed-rank test will be used secondarily to analyze the change from Screening to Month 6 and Month 6/Early Discontinuation. Two-sample t-tests will be used to primarily analyze the difference in the mean scores between treatments at Screening, Month 6, Month 6/Early Discontinuation and change from Screening to Month 6 and Month 6/Early Discontinuation; additionally, the non-parametric Wilcoxon rank-sum test will be used secondarily to analyze the differences in scores between treatments.

Analyses will be performed using the safety population.

10.2 Health Survey Questionnaire, 36 Questions, Version 2 (Short Form)

The SF-36 is a generic health survey with 36 items that measure functional health and well-being from the subject's perspective.

The survey is grouped into 8 dimensions: physical functioning (PF), role-physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role-emotional (RE), and mental health (MH). From the eight health dimensions, a physical component summary (PCS) measure, which is the aggregate score of the PF; RP; BP and GH scales, and mental component summary (MCS) measure, which is the aggregate score of the VT; SF; RE and MH scales, measures are derived. A higher dimension or component summary score indicates a better perception of health.

The dimension scores, physical component summary score and mental component summary score will be derived using a certified scoring software (PRO CoRE) provided by Optum, an external vendor. The maximum data recovery option will be used as the imputation method for missing data. The software applies a value to a scale item rendered missing if at least one of the items in that scale has valid data. A scale receives a "missing" score only if all the items in that scale are missing. PCS and MCS are calculated when at least seven of the eight profile scales have valid data, either actual or estimated. However, to calculate PCS, the PF scale must be one of the seven scales having valid data. Also, to calculate MCS, the MH scale must be one of the seven scales having valid data.

The dimension scores and physical and mental health composite summary scores will be summarized for the Screening, Month 6, and Month 6/Early Discontinuation visits, including change from Screening to Month 6 and change from Screening to Month 6/Early Discontinuation using continuous summary statistics using observed data only. Paired t-tests will be used to primarily analyze the mean change from Screening to Month 6 and Month 6/Early Discontinuation within a treatment group; additionally, the non-parametric Wilcoxon signed-rank test will be used to secondarily analyze the change from Screening to Month 6 and Month 6/Early Discontinuation. Two-sample t-tests will be used to primarily analyze the difference in the mean scores between treatments at Screening, Month 6, Month 6/Early Discontinuation and change from Screening to Month 6 and Month 6/Early Discontinuation; additionally, the non-parametric Wilcoxon rank-sum test will be used to secondarily analyze the differences in scores between treatments.

Analyses will be performed using the safety population.

11. PHARMACOKINETIC EVALUATION

Not applicable.

12. OTHER ANALYSES

Any additional analyses conducted will be considered exploratory and enumerated in the CSR.

13. INTERIM ANALYSES AND DATA MONITORING

When all subjects have completed three months of treatment, the Sponsor biostatistical representative will unmask the study to analyze the 3-month efficacy and safety data. No other study personnel other than the biostatistician; SAS programmers; and [redacted] will be unmasked to the individual subject treatment assignments and demographic information to perform the 3-month efficacy and safety data analysis and further exploratory data analysis as necessary. This is the primary efficacy analysis of the study and therefore no alpha adjustment for this interim analysis will be implemented. The interim analysis will be completed at an overall 2-sided alpha of 5%, with each of the pairwise comparisons of PG-324 to GANFORT. For the efficacy interim analyses, analyses will be limited to data available through 3 months of treatment. Additionally, key adverse event summaries will be limited to data available through 3 months.

14. CHANGES TO THE ANALYSES PLANNED IN THE PROTOCOL

No changes to the analyses that are planned in the protocol.

15. REFERENCES

US Federal Register. (1998) International Conference on Harmonization; Guidance for Industry: Statistical Principles for Clinical Trials. Department of Health and Human Services: Food and Drug Administration. Federal Register, Vol. 63, No. 179, September 16, 1998, page 49583. (E9)

US Federal Register. (1996) International Conference on Harmonization; Guidance for Industry: Structure and Content of Clinical Study Reports. Department of Health and Human Services: Food and Drug Administration. Federal Register Vol. 61, July 17, 1996, page 37320. (E3)

16. APPENDICES

Appendix 1 Schedule of Visits and Examinations

Day (D)/ Week (W)/ Month (M)	Screening	Qual. #1 (Day -7 to -2)	Qual. #2 D1			W2 (Day 15±3)			W6 (Day 43±3)			M3 (Day 90±3)			M4 (Day 120±3), M5 (Day 150±3)	M6 (Day180±7)
Visit	**1**	**2**	**3.0**	**3.1**	**3.2**	**4.0**	**4.1**	**4.2**	**5.0**	**5.1**	**5.2**	**6.0**	**6.1**	**6.2**	**7.0 + 8.0**	**9.0**
Hour (XY = XY:00)		08	08	10	16	08	10	16	08	10	16	08	10	16	10	10
Informed Consent	X															
Inclusion/Exclusion	X	X	X	X	X											
Washout[1]	X															
Demography	X															
Medical/Ophthalmic History	X	X	X													
Concomitant Medications	X	X	X			X			X			X			X	X
HR/BP	X	X	X			X			X			X			X	X
Urine Pregnancy Test [11]	X	X	X			X			X			X			X	X
Clinical Labs (Chem/ Hem)[2]	X															X
Symptoms/AEs[3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Visual Acuity (ETDRS)	X	X	X			X			X			X			X	X
IOP[4]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Biomicroscopy	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Gonioscopy[5]/Pachymetry[6]	G/P											P				P
Visual Field[7]	X											X				X
Ophthalmoscopy (dilated)	X													X		X
Cup:disc ratio	X													X		X
Eye-Drop Instillation Evaluation	X															
VFQ-25 questionnaire	X															X
SF-36 v.2 questionnaire	X															X
Study Medications Dispensed[9]					X			X			X			X	X	
Study Medications Collected[8]						X			X			X			X	X
Study Completed																X

Abbreviations: D=Day; W = Week; M = Month; HR/BP = heart rate/blood pressure; Chem/ Hem = Chemistry/Hematology; A = Early Treatment of

Diabetic Retinopathy Study; IOP = Intraocular pressure; G = Gonioscopy; P = Pachymetry; Self-Admin = Self-Administered

Early Discontinuation: Visit 9.0 procedures are to be completed plus a dilated ophthalmoscopy examination.

Visit Requirements: IOP measurements at all visits are to be made within ±1 hour of the protocol-specified times of 08:00, and ±½ hour of 10:00 and 16:00 hours with the exception of the screening visit.

1. Subjects must undergo a minimum washout period of current ocular hypotensive medication(s).
2. For subjects who are unable or unwilling to have blood drawn for clinical labs at Visit 1 (screening), the blood sample may be drawn at Visit 2 (Qualification Visit #1) **or** during the washout period at a visit where interim IOP measurements are being performed so long as the results of the clinical labs are available for that subject prior to Visit 3 (Qualification Visit #2).
3. Ocular symptoms: Subjects will be queried at each visit "How are you feeling?" and treatment emergent AEs beginning at Visit 4 (Qualification Visit #2) will be documented on the AE form. Additional symptoms reported after screening and before randomization will be documented on the medical history form. AEs will be recorded for every study visit (i.e., at 0800, 10.00, and 16:00 hours) as needed.
4. Individuals returning at an unscheduled visit within 1 week are required to only re-measure IOP in both eyes.
5. Gonioscopy evaluation up to 3 months prior to randomization is acceptable.
6. Pachymetry Evaluation at screening visit or within one week prior to screening visit, and at Month 3 (or within 1 week of Month 3 study visit).
7. Entry visual field evaluation up to 3 months prior to randomization is acceptable. Visual field collection must meet the requirement for automated threshold visual field assessment (e.g., 30-2 or 24-2 Humphrey or Octopus perimetry) and reliability.
8. Collect used kit(s) dispensed during the previous visit.
9. Per Section 5.2 and 5.3, subjects are required to administer IP on all days of the study, including days of study visits. In addition, per section 7.1.5 IP will be dispensed within 48 hours of the randomization visit.
10. At the investigator's discretion photography of ocular events, such as corneal verticillata, conjunctival hemorrhage.
11. For women of child bearing potential, a pregnancy test will be performed every 4 weeks during study participation. This will include a pregnancy test during the washout period, if the washout period extends beyond 4 weeks.

17. ATTACHMENTS

- PG324-CS303 Listing Shells
- PG324-CS303 Table Shells

18. REVISION HISTORY

Documentation of revision to the SAP will commence after approval of the Final version 1.0.

Section #	Description of Change	Rationale
2.6	Updated to "…200 intent-to-treat subjects per arm…"	Change based on protocol amend 6
4.2	Updated to "…This population will be the primary population for efficacy analyses…"	Change based on protocol amend 6
4.3	Updated to "…This population will be the secondary population for efficacy analyses and will be used to summarize a subset of efficacy variables…"	Change based on protocol amend 6
5.2	Added COVID-19 related protocol deviations to subject disposition summary table and a separate listing	Change based on FDA Guidance for Statistical Considerations for Clinical Trials During COVID-19 Public Health Emergency
8.3, Table 8-1, 8.4	Updated the previous ITT/PP population to be PP/ITT population	Population switched based on protocol amend 6
9.4	Added COVID-19 related AE and SAE listings	Change based on FDA Guidance for Statistical Considerations for Clinical Trials During COVID-19 Public Health Emergency
9.6.5	More descriptions of summary tables for conjunctival hyperemia	Added for analysis completeness