A prospective, double-masked, randomized, multicenter, active-controlled, parallel-group, 6-month 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 (MERCURY 3)

NCT03284853

27 May 2020

CLINICAL STUDY PROTOCOL: PG324-CS303

Study Title:	A prospective, double-masked, randomized, multicenter, active-controlled, parallel-group, 6-month 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 **(MERCURY 3)**
Study Number:	PG324-CS303
EudraCT Number:	2015-001528-41
Study Phase:	3
Product Name:	PG324 (netarsudil/latanoprost 0.02%/0.005%) Ophthalmic Solution
Indication:	Reduction of elevated intraocular pressure in subjects with open-angle glaucoma or ocular hypertension
Investigators:	Multi-center
Sponsor:	Aerie Pharmaceuticals Ireland Ltd.
Sponsor Contact:	[redacted]
Medical Monitor:	[redacted]

Version	Date
Original Protocol (Rev 0):	05 December 2016
Amendment 1 (Rev 1)	27 January 2017
Amendment 2 (Rev 2) - UK Specific	07 April 2017
Amendment 3 (Rev 3)	05 June 2017
Amendment 4 (Rev 4)	19 March 2018
Amendment 5 (Rev 5) - Hungary Specific	06 August 2018
Amendment 6 (Rev 6)	27 May 2020

Confidentiality Statement

CLINICAL PROTOCOL APPROVAL FORM

Protocol Title: A prospective, double-masked, randomized, multicenter, active-controlled, parallel-group, 6-month 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 (MERCURY 3)

Study No: PG324-CS303

Original Protocol Date: 05 December 2016

Protocol Version No: Rev 6

Protocol Version Date: 27 May 2020

Contact Information

Aerie Management and Sponsor Safety Officer:

[redacted]

Clinical Operations

[redacted]

[redacted]	[redacted]
Aerie Medical Monitor	[redacted]
Clinical Laboratory	[redacted]
Biostatistics	[redacted]
Data Management	[redacted]

Amendment #1: 27 January 2017

Changes made include the addition of a patient-reported outcome (PRO) tool (health survey questionnaire, SF-36 v.2) and clarification of storage conditions throughout the duration of the study. Modified text is shown here in **bold type**. Specifically:

General / Throughout the document

- Any **corrections to dates and version number**, due to the amendment to the protocol, were made, along with other miscellaneous typographical errors not previously addressed.
- Language has been added to clarify that **any activity conducted by the Sponsor may be carried out by a designee**, if specified and documented.
- **List of Abbreviations has been updated.**
- **Reference** in support of the SF-36 PRO tool has been added.
- An updated version of the PRO tool, **NEI-VFQ-25 added to the appendices** (Appendix 7), replacing the previous version.
- A copy of the additional PRO tool, **SF-36 v.2, added to the Appendices** (Appendix 8).

Synopsis, Sections 2.2, 6.5.1, 7.1.1, 7.1.21 Appendix 1, Appendix 2

- Wherever PRO tools are discussed or described (previously just the Self-Administered National Eye Institute (NEI) Visual Functioning Questionnaire 25 (VFQ-25)), **the Short Form Health Survey Questionnaire 36 (SF-36 v.2) has been added**.
- Clarifying language added that the **PRO tool scores for PG324-treated subjects will be compared to GANFORT®-treated subjects' scores.**

Section 5.10 Handling and Storage of Investigational Product

- Storage conditions for PG324 have been updated such that **IP should be kept at 2°C to 8°C/ 36°F to 46°F, in accordance with the drug label, throughout the study**, including after it has been provided to the subject.

Section 7.1.12 Visit 6, Month 3 08:00 hours and Appendix 1 and Appendix 2

- **Pachymetry added** for consistency with other studies.

Section 8.5.4.4

- New section added detailing the analysis planned for PRO tool, SF-36 v.2.

Appendix 7

- Copy of NEI-VFQ-25 added to replace previous version.

Appendix 8

- Copy of SF-36 v2 added.

None of these changes impact patient safety or exposure to investigational product.

Amendment #2: 07 April 2017 (Country Specific - UK)

Changes made to the Protocol include:

- Any **corrections to dates and version number**, due to the amendment to the protocol.
- Amendment of the investigator requirements in case of emergency unmasking.
- Amendment to the Safety Section with specific reference to reactions not listed in the AR-13324 Ophthalmic Solution (Netarsudil Ophthalmic Solution) / PG324 Ophthalmic Solution Investigator Brochure and/or in Section 4.8 of Ganfort® SmPC.
- Clarification to contraception guidance section with specific reference to sexual abstinence.
- Amendment to the Protocol Deviation section to clarify that Protocol deviations are not acceptable and clarification of Sponsor responsibilities for the assessment and reporting to the MRHA if any non-compliances considered as a serious breach of GCP and the protocol, and other minor clarifications.
- Administrative changes to numeration errors in the summary of changes section for Amendment #1: 27 January 2017.

Modified or added text is shown here in **bold type**. Specifically:

Section 5.5.1 Operational Measures at study sites

WAS: "If the investigator feels it is necessary to unmask a subject's treatment assignment in the event of an emergency situation, the Investigator should promptly contact the Sponsor's medical monitor or Sponsor representative to discuss the rationale for proposal to unmask the subject. A decision will be made as to whether or not the treatment for the subject should be unmasked, preferably after consultation with the Sponsor's Medical Monitor or designee. The treatment assignment will be revealed on a subject-by-subject basis, thus leaving the masking on remaining subject intact.

In an emergency situation in which treatment of an adverse event requires immediate unmasking, and the investigator is unable to promptly contact the Sponsor or Sponsor representative's Medical Monitor, the Investigator may unmask the treatment. The investigator will perform the unmasking through the IWRS or other randomization system. In case of such unmasking in an emergency situation, the investigator should contact the Sponsor/Sponsor representative immediately thereafter and document the unmasking in writing, recording the date, time and reason for unmasking the study drug treatment in the source documentation".

IS: "If the investigator feels it is necessary to unmask a subject's treatment assignment in the event of an emergency situation, the investigator will perform the unmasking through the IWRS or other randomization system. The treatment assignment will be revealed on a subject-by-subject basis, thus leaving the masking on remaining subjects intact.

In case of such unmasking in an emergency situation, the investigator should contact the Sponsor/Sponsor representative immediately thereafter and document the unmasking in writing, recording the date, time and reason for unmasking the study drug treatment in the source documentation".

Section 7.2.1 Adverse Event Definitions

WAS: "Unexpected adverse event or unexpected suspected adverse reaction. An adverse event or suspected adverse reaction is considered ''unexpected'' if it is not listed in the Investigator's Brochure or is not listed at the specificity or severity that has been observed."

IS: "Unexpected adverse event or unexpected suspected adverse reaction. An adverse event or suspected adverse reaction is considered ''unexpected'' if it is not listed in **Section 8.4 of the** Investigator's Brochure **'Reference Safety Information'** or is not listed at the specificity or severity that has been observed".

Section 7.2.5 Expectedness

WAS: "An AE or suspected adverse reaction is considered "unexpected" if it is not listed in the Investigator's Brochure or is not listed at the specificity or severity that has been observed".

IS: "An AE or suspected adverse reaction is considered "unexpected" if it is not listed **in the Section 8.4** of the Investigator's Brochure **'Reference Safety Information'** or is not listed at the specificity or severity that has been observed".

Section 7.2.6 Serious Adverse Events (SAE's) or Serious Unexpected Suspected Adverse Reaction Safety reports (SUSARs)

WAS: "An investigator must immediately report to the Sponsor representative any SAE or serious unexpected suspected adverse reactions within 24 hours of occurrence or being informed of the event, whether or not considered drug related including those listed in the protocol or Investigator Brochure and must include an assessment of whether there is a reasonable possibility that the drug caused the event. Study endpoints that are serious adverse events (e.g., all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the drug and the event (e.g., death from anaphylaxis.

This requirement applies to occurrences observed during the course of the study and within 30 days of last administration of the study medication. In addition, in the case of immediately life-threatening AEs or AEs with fatal outcome, or adverse events that are serious, unexpected (i.e., not in the Clinical Investigator's Brochure) and judged related to the IP, the

Investigator must inform the Sponsor or Sponsor representative by phone within 24 hours of observation or occurrence of the SAE".

IS: "An investigator must immediately report to the Sponsor representative any SAE's within 24 hours of occurrence or being informed of the event, whether or not considered drug related including those listed in the protocol or investigator brochure and must include an assessment of whether there is a reasonable possibility that the drug caused the event. A reaction will be considered unexpected if it is not listed in the Reference Safety Information Section 8.4 in the AR-13324 Ophthalmic Solution (Netarsudil Ophthalmic Solution) / PG324 Ophthalmic Solution Investigator Brochure and/or in Section 4.8 of the GANFORT® SmPC (see Appendix 3). Study endpoints that are serious adverse events (e.g., all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the drug and the event (e.g., death from anaphylaxis).

This requirement applies to occurrences observed during the course of the study and within 30 days of last administration of the study medication. In addition, in the case of immediately life-threatening AEs or AEs with fatal outcome, or adverse events that are serious, unexpected (i.e., not in the Clinical Investigator's Brochure **Reference Safety Information Section 8.4 and /or in Section 4.8 of the GANFORT® SmPC)** and judged related to the IP, the Investigator must inform the Sponsor or Sponsor representative by phone within 24 hours of observation or occurrence of the SAE".

Section 7.2.6 Pregnancy Testing, Prevention and Reporting

WAS: "sexual abstinence"

IS: "sexual abstinence: **sexual abstinence is only considered to be an acceptable method of contraception when defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the trial and the preferred and usual lifestyle of the subject. Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception.**

Male subjects

WAS: "Men with a female partner of childbearing potential must have either had a prior vasectomy or agree to use an effective method of contraception from time of randomization and for 3 months following the last dose of study medication".

Male subjects

IS: "Men with a female partner of childbearing potential must have either had a prior vasectomy or agree to use a **condom as** an effective method of contraception from time of randomization and for 3 months following the last dose of study medication".

Section 11.6 Protocol Deviations

WAS: "Deviations from inclusion and exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

If a protocol deviation is identified by the investigator or through site monitoring activities an immediate submission to the IEC/CEC may be required e.g. 24 or 48 hours. If per country requirements, the protocol deviation is not required to be reported immediately but is still required to be notified to the IEC/CEC, the specific protocol deviation will be added to the annual progress report".

IS: "**Protocol Waivers or any deviations from the** protocol inclusion and exclusion are not allowed because they can potentially jeopardize the scientific integrity of the study regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

If a protocol deviation is identified by the investigator or through site monitoring activities an immediate submission to the IEC/CEC may be required e.g. 24 or 48 hours. **The Sponsor will assess any protocol deviation and decide whether any of these non-compliances should be reported to the relevant competent authority as a serious breach of GCP and the protocol.** If per **the relevant competent authorities' requirements**, the protocol deviation is not required to be reported immediately but is still required to be notified to the IEC/CEC, the specific protocol deviation will be added to the annual progress report."

Amendment #3: 05 June 2017

Changes to the protocol have been made in accordance with observations made by the:

German Federal Institute for Drugs and Medical Devices (BfArM) 23 March 2017:

- New text added to include details of European Medicines Agency (EMA) scientific advice in the protocol as per BfArM request.
- New text added to include rational for the IOP limits used for non-inferiority analysis as discussed with regulatory agencies.
- Expanded rationale for selection of dose selection of netarsudil 0.02% ophthalmic solution.
- New text added to document regarding validation status of NEI visual functioning questionnaire-25 (VFQ-25).
- Inclusion of footnotes from the Clinical Trials Facilitation Group (CTFG) regarding highly effective contraception.
- New text added to clarify how the IMPs under investigation differ and their influence on unmasking.
- Inclusion of guidance for study subjects if a dose of study medication is missed.
- Schedule of events includes IMP dispensation and collection.
- Clarification of investigator responsibilities according to German requirements.

[redacted] 27 March 17:

- Addition of risks associated with the washout period, weekly monitoring of subjects during the washout period and not exceeding a maximum of 8-week washout.
- Only patients capable of giving their consent can participate in the study.

[redacted]

April 2017:

- Addition of inclusion criteria to indicate all subjects included in France are beneficiaries or members of a French social security system.
- Addition of exclusion criteria regarding vulnerable individuals.
- Addition of pregnancy test at Month 3.
- Clarification to the Study Objectives.

[redacted]

- Clarification of the selection the upper limit of intra ocular pressure (IOP) of 25mmHg on treatment and 36mmHg off treatment required for subject inclusion.
- Addition of exclusion of patients previously treated with GANFORT®.
- Updated the exclusion criteria to include all contraindications as per Section 4.3 of the GANFORT® SmPC.
- Inclusion of the reference justification for the washout period for beta blockers, muscarinic agonists and carbonic anhydrase inhibitors in Section 5.7.1 Prior Therapy Washout Period.

- Introduction of drug interactions indicated in the GANFORT® SmPC and the role of the investigator in judging the soundness of treating a study patient despite the concomitant administration of a drug on this list.
- Justification the 30-day period after the study refraining from breast feeding.
- Inclusion of urine pregnancy test for visits at Qualifying visit # 2, Week 2, Week 6, Month 3, Month 4 and Month 5, in addition to Month 6. **Note: The pregnancy test at Qualifying visit #1 has been removed as the Sponsor has added a urine pregnancy test at Screening Visit.**
- Included direction to investigators with respect to monitoring patients with interim visits during the washout period.

General/Throughout the Document

Any corrections to **dates and version number** due to the amendment of the protocol were made, along with other miscellaneous typographical errors identified.

Appendix 2: Procedures

Language has been amended to clarify tonometer validation on at least a monthly basis must be documented.

Appendix 3: Marketed Product Medication Information - GANFORT®

Existing Summary of Product Characteristics replaced with extract from updated SmPC EPAR version 01 June 2017.

Modified or added text is shown here in **bold type**, deleted text is indicated by ~~strikethrough~~. For completeness, changes made in Amendment 2 that address questions raised by the Competent Authorities/Ethics Committees listed above are also included and, shown in ***bold italic type***. Specifically:

Synopsis: Section 2.1 – Primary Objectives; Section 2.2 – Secondary Objectives

WAS:
Primary Objectives:
To evaluate:

- The ocular hypotensive efficacy of PG324 Ophthalmic Solution relative to GANFORT® Ophthalmic solution over a 3-month period.
- The ocular hypotensive safety of PG324 Ophthalmic Solution relative to GANFORT® Ophthalmic solution over a 6-month period.

Secondary Objectives:
To evaluate:

- Change in Self-Administered National Eye Institute (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®.

IS:
Primary Objectives:
To evaluate:

- The ocular hypotensive efficacy of PG324 Ophthalmic Solution relative to GANFORT® Ophthalmic solution over a 3-month period.
- **The** ocular ~~**hypotensive safety of PG324 Ophthalmic Solution relative to GANFORT® Ophthalmic solution over a 6-month period.**~~

Secondary Objectives:
To evaluate:

- **The ocular hypotensive safety of PG324 Ophthalmic Solution relative to GANFORT® Ophthalmic solution over a 6-month period.**
- Change in Self-Administered National Eye Institute (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®.

Synopsis: Section 4.2 – Inclusion Criteria; Section 4.3 – Exclusion Criteria

WAS:
Inclusion Criteria:
10. Men with a female partner of childbearing potential must have either had a prior vasectomy or agree to use effective contraception from time of randomization and for 3 months following the last dose of study medication.

Exclusion Criteria:
4. Treatment-naïve subjects.

5. Known hypersensitivity to any component of the investigational formulations to be used (e.g., benzalkonium chloride etc.) or to fluorescein.

15. Known hypersensitivity or contraindication to β-adrenoceptor antagonists (e.g. Chronic obstructive pulmonary disease or bronchial asthma; abnormally low blood pressure or heart rate; second or third-degree heart block or congestive heart failure; severe diabetes).

18. Women of childbearing potential who are pregnant, nursing, planning a pregnancy, or not using a medically acceptable and highly effective form of birth control. An adult woman is considered to be of childbearing potential unless she is one year post-menopausal or three months post-surgical sterilization.

IS:
Inclusion Criteria:
10. Men with a female partner of childbearing potential must have either had a prior vasectomy or agree to use effective contraception from time of randomization and for 3 months following the last dose of study medication.

11. In France, a subject will be eligible for inclusion in this study only if either affiliated to or as a beneficiary of a social security number.

Exclusion Criteria:
4. Treatment-naïve subjects.

5. **PRIOR TREATMENT WITH GANFORT® TOPICAL EYE DROPS**

6. Known hypersensitivity to any component of the investigational formulations to be used (e.g., benzalkonium chloride etc.) or to fluorescein.

Systemic

15. Known hypersensitivity or contraindication to **GANFORT® (Appendix 3 Marketed Product Medication Information Section 4.3) and t**o β-adrenoceptor antagonists (e.g. Chronic obstructive pulmonary disease or bronchial asthma; abnormally low blood pressure or heart rate; second or third-degree heart block or **congestive heart failure; cardiac failure, cardiac shock** and severe diabetes).

20. Women of childbearing potential who are pregnant, nursing, planning a pregnancy, or not using a medically acceptable and highly effective form of birth control. An adult woman is considered to be of childbearing potential unless she is one year post-menopausal **(1 year without menses with appropriate clinical profile, e.g. age appropriate, > 45 years in the absence of HRT. In questionable cases the subject must have FSH value > 40mIU/mL and an estradiol value < 40pg/mL [< 140pmol/L])** or three months post-surgical sterilization.

21. Vulnerable subjects such as minors, adults under legal protection or unable to express their consent (e.g. hospitalized persons in coma), persons deprived of liberty (prisoners from jails), or persons subject to psychiatric care.

Section 1.2 – Findings from non-clinical and clinical studies

WAS:
Clinical

"The investigations of this concentration (0.02%) and 2 other concentrations (0.01% and 0.04%) in a Phase 2 dose response study (Clinical Study Report AR-13324-CS201) was used in order to define the appropriate concentration of netarsudil ophthalmic solution for the Phase 2 clinical studies of PG324.

A Phase 3 clinical study (AR-13324-CS302) evaluating the safety and efficacy netarsudil 0.02% has been completed. As several different concentrations of netarsudil had already been evaluated with regard to efficacy and safety during netarsudil clinical development, no separate Phase 1 pharmacokinetic studies were conducted with the FDC. Based on the results obtained from the netarsudil program, it was decided to conduct a Phase 2 study with PG324 0.02%. The Phase 2 study (study PG324-CS201) has been completed. Two Phase 3 studies (PG324-CS301 and PG324-CS302) are currently ongoing."

IS:
Clinical
"The investigation of **the efficacy of the 3 doses of netarsudil (0.01%, 0.02% and 0.04%) were evaluated over 7 days. The 0.02% and 0.04% doses showed similar reduction of IOP, which was higher relative to the 0.01% dose. It was therefore concluded that the top of the dose response curve was reached at the 0.02% netarsudil concentration and this was selected as the appropriate concentration of netarsudil ophthalmic solution for further development.**

A Phase 3 clinical study (AR-13324-CS302) evaluating the safety and efficacy netarsudil 0.02% has been completed. **This study compared netarsudil 0.02% Q.D. and BID and Timolol 0.5% BID, and concluded that netarsudil 0.02% Q.D. was safe, generally well tolerated and provided IOP lowering that was non-inferior to timolol in subjects with OAG and OHT. Netarsudil 0.02% BID provided slightly larger IOP reductions but had a less favorable safety profile and therefore netarsudil 0.02% Q.D. was recommended as the dose for clinical use.**

As several different concentrations of netarsudil had already been evaluated with regard to efficacy and safety during netarsudil clinical development, no separate Phase 1 pharmacokinetic studies were conducted with the FDC **PG324**. Based on the results obtained from the netarsudil program, it was decided to conduct a **four arm** Phase 2 study **comparing two doses of PG324 (either 0.01% or 0.02% AR-13324 in combination with 0.005% latanoprost) against AR-13324 0.02% and latanoprost.** The Phase 2 study (study PG324-CS201) has been completed **demonstrating superiority of the PG324 combinations over 0.02% AR-13324 and 0.005% latanoprost alone. PG324 0.02% showed better IOP lowering than 0.01% and was selected for further development in Phase 3.**

Two **pivotal** Phase 3 studies (PG324-CS301 and PG324-CS302) are currently ongoing **comparing PG324 with its components to demonstrate superiority and safety. In addition to these 2 pivotal studies a supportive study will be conducted comparing PG324 to a fixed dose combination therapy containing a prostaglandin analogue (PGA). Following review of the study through scientific advice procedure with the EMA, Aerie Pharmaceuticals has agreed to** GANFORT® **as the comparator. In addition, the EMA has reviewed and accepted the masking procedures as documented in this protocol."**

Section 4.1 – Study Population

WAS:
"A total of approximately 472 subjects will be enrolled in this study at approximately 40 sites in approximately 6 EU countries comprising a total of 236 subjects per each treatment arm for each of the two treatment arms. Subjects enrolled to this study will be those at least 18 years of age with diagnosed OAG or OHT, each of whom meets all the inclusion criteria and none of the inclusion criteria."

IS:
"A total of approximately 472 subjects will be enrolled in this study at approximately 46 sites in approximately 6 EU countries comprising a total of 236 subjects per each treatment arm for each of the two treatment arms. Subjects enrolled to this study will be those at least 18 years of age with diagnosed OAG or OHT, **who are currently using topical IOP- lowering medication. Inclusion criterion 4 specifies that subjects must present with medicated IOP at screening of > 18mmHg and < 25mmHg in both eyes and, in the opinion of the investigator, require a change in IOP therapy. The low limit IOP is based on the guidelines issued by the [redacted] with respect to initiating alternative therapy. The upper limit IOP is selected to exclude subjects who may require more aggressive therapy than a FDC to prevent glaucoma progression. Inclusion criterion 5 states that following a washout period from current IOP therapy, patients must present with an unmedicated IOP of > 20mmHg and < 36mmHg in both eyes at 2 qualification visits at 08:00 hour, 2-7 days apart and at the second qualification visit, have IOP > 17mmHg and < 36mmHg in both eyes at 10:00 and 16:00 hours. The upper limit was chosen to exclude subjects who require a more aggressive therapy than a FDC to prevent glaucomatous damage.**

Subjects MUST meet all the inclusion criteria and none of the exclusion criteria."

Section 5.1 – Description of Treatments

WAS:
5.1.1 Investigational Product
"PG324 Ophthalmic Solution is a sterile, isotonic, buffered aqueous solution containing netarsudil 0.02%, latanoprost 0.005%, boric acid, mannitol, water for injection, and preserved with benzalkonium chloride (0.02%). The product formulation is adjusted to approximately pH 5.

5.1.2 Comparator
GANFORT® (bimatoprost 0.03% / timolol maleate 0.5% ophthalmic solution) is a sterile, buffered aqueous solution containing sodium chloride, sodium phosphate dibasic heptahydrate, and citric acid monohydrate and preserved with benzalkonium chloride (0.005%)."

IS:

5.1.1 Investigational Product

"PG324 Ophthalmic Solution is a sterile, isotonic, buffered aqueous solution containing netarsudil 0.02%, latanoprost 0.005%, boric acid, mannitol, water for injection, and preserved with benzalkonium chloride (0.02%). The product formulation is adjusted to approximately pH 5. **PG324 is a colorless to slightly yellowish solution (PG324 Safety data sheet).**

5.1.2 Comparator

GANFORT® (bimatoprost 0.03% / timolol maleate 0.5% ophthalmic solution) is a sterile, buffered aqueous solution containing sodium chloride, sodium phosphate dibasic heptahydrate, and citric acid monohydrate and preserved with benzalkonium chloride (0.005%). **GANFORT® is a colorless to slightly yellow solution (GANFORT® SmPC)."**

5.2 Treatment of Subjects

WAS:

"Subjects will be randomized to receive IP (PG324 Q.D. or the active comparator (GANFORT® Q.D.). All treatments will be both eyes (OU). Subjects will instill 1 drop of study drug into each eye, one time per day in the evening between 20:00 and 22:00 hours. Doses will be administered by the study subjects. For subjects deemed unable to administer the doses, a guardian or alternative person will be asked to administer the medication. All subjects will administer study treatment for approximately 180 days."

IS:

"Subjects will be randomized to receive IP (PG324 Q.D. or the active comparator (GANFORT® Q.D.). All treatments will be both eyes (OU). Subjects will instill 1 drop of study drug into each eye, one time per day in the evening between 20:00 and 22:00 hours **(including days when the subject is scheduled to visit the study site).** Doses will be administered by the study subjects. For subjects deemed unable to administer the doses, a guardian or alternative person will be asked to administer the medication. All subjects will administer study treatment for approximately 180 days".

5.3 Selection of Timing of Dose for Each Subject

WAS:

"The dose of PG324 selected for this study is based on the positive outcomes seen for PG324 in the PG324-CS201 clinical study. Each IP dose is being administered Q.D. OU in the evening (between 20:00 and 22:00 hours) in this study to allow for estimated peak and trough levels of both netarsudil and latanoprost to be present in ocular tissue at the observation times selected in the clinic for the following morning and the subsequent afternoon. The treatment period is selected on the basis of non-clinical safety studies and regulatory requirements for studies of ophthalmic glaucoma medications."

IS:
"The dose of PG324 selected for this study is based on the positive outcomes seen for PG324 in the PG324-CS201 clinical study. Each IP dose is being administered Q.D. OU in the evening (between 20:00 and 22:00 hours **including days when the subject is scheduled to visit the study site**) in this study to allow for estimated peak and trough levels of both netarsudil and latanoprost to be present in ocular tissue at the observation times selected in the clinic for the following morning and the subsequent afternoon. The treatment period is selected on the basis of non-clinical safety studies and regulatory requirements for studies of ophthalmic glaucoma medications."

Section 5.5 – Masking

WAS:
"Treatment assignments will be masked to the Investigator, the clinical study team, Sponsor/ Sponsor representative working on behalf of the Sponsor, personnel involved in day to day study management, Monitors, Data Managers, and Statisticians), and the subjects for the duration of the study.

Masking of treatment assignment of study supplies is planned to be achieved via both IP packaging/labelling operations and as instructed in the study Pharmacy Manual."

IS:
"The [redacted] through the scientific advice procedure has agreed to the masking procedures documented in this section.

To minimize unmasking due to the differences in bottle closure cap colour, clinical supplies will be packaged in identical outer containers labeled appropriately for clinical trial use as detailed in Section 5.9 of this document.

Differences in the physical characteristics of the PG324 and GANFORT® are minimal and should not pose a significant risk to the masking of the study. Both are essentially colourless liquids of equivalent viscosity which in individual eye drops are indistinguishable to subjects taking part in the study.

Treatment assignments will be masked to the Investigator, the clinical study team, Sponsor/ Sponsor representative working on behalf of the Sponsor, personnel involved in day to day study management, Monitors, Data Managers, and Statisticians), and the subjects for the duration of the study.

Masking of treatment assignment of study supplies is planned to be achieved via both IP packaging/labelling operations and as instructed in the study Pharmacy Manual."

Section 5.6 – Concomitant Medications

WAS:
"Contact lens wear during the study is acceptable. However, subjects must remove their contact lenses at least 30 minutes before instillation of study medication, and not place them in their eye(s) until 30 minutes after instillation.

Use of all medications should be documented on the appropriate CRF. Investigators are encouraged to contact the Sponsor/Sponsor representative for any questions regarding allowed medications. Judgment of continued study participation by the subject, and inclusion of this subject's subsequent visits in the safety and efficacy analysis will be made by the Sponsor."

IS:
"Contact lens wear during the study is acceptable. However, subjects must remove their contact lenses at least 30 minutes before instillation of study medication, and not place them in their eye(s) until 30 minutes after instillation.

As detailed in the GANFORT® SmPC Section 4.5 (Appendix 3) there is a potential for additive effects resulting in hypotension, and/or marked bradycardia when ophthalmic solution containing beta-blockers (timolol) is administered concomitantly with oral calcium channel blockers, guanethidine, beta-adrenergic blocking agents (prohibited see above), parasympathomimetics, anti-arrhythmics (including amiodarone) and digitalis glycosides.

Potentiated systemic beta-blockade (e.g., decreased heart rate, depression) has been reported during combined treatment with CYP2D6 inhibitors (e.g. quinidine, fluoxetine, paroxetine) and timolol.

Mydriasis resulting from concomitant use of ophthalmic beta-blockers and adrenaline (epinephrine which is prohibited) has been reported occasionally.

Beta-adrenergic blocking agents and epinephrine are not permitted to be used concomitantly during the subject's participation in the study. Concomitant use of the other medications is at the discretion of the investigator who must assess if the subject should participate in the study based on the potential interactions listed in Section 4.5 of the GANFORT® SmPC.

Use of all medications should be documented on the appropriate CRF. Investigators are encouraged to contact the Sponsor/Sponsor representative for any questions regarding allowed medications. Judgment of continued study participation by the subject, and inclusion of this subject's subsequent visits in the safety and efficacy analysis will be made by the Sponsor."

Section 5.7.1 – Prior Washout Period

WAS:
"Subjects must undergo a minimum washout period as specified in Table 1.
For prostaglandins the minimum washout period should be not less than 4 weeks and it may be extended if deemed necessary in investigator opinion.

If washout is to be extended beyond 8 weeks (56 days) for logistical or other reasons, the Sponsor should be contacted. (Stewart 2001)."

Table 1 reference – Hughes 2005.

IS:
"Subjects must undergo a minimum washout period as specified in Table 1.
For prostaglandins the minimum washout period should be not less than 4 weeks and it may be extended if deemed necessary in investigator opinion.

Washout should not extend beyond 8 weeks (56 days). **If for logistical or other reasons the period needs to be extended beyond 8 weeks (56 days),** the Sponsor should be contacted.

The risks associated with a wash period are increase in IOP requiring immediate intervention. Therefore, the investigator must monitor the subject regularly during the washout period, ideally every week."

Table 1 references – **Stewart 2001,** Hughes 2005, **and** [redacted] **November 2011**

Section 5.8 – Treatment Compliance

WAS:
"All subjects will be instructed on the importance of following the once-daily dosing regimen. Dosing should occur in the evening between 20:00 and 22:00 hours. As no commercially available method is readily available for direct, single-container monitoring of treatment adherence with multi-dose ophthalmic products, no formal measure of treatment compliance is planned. Subjects should be reminded at all visits to dose every evening. In addition, subjects will be provided with a paper and electronic dosing reminder."

IS:
"All subjects will be instructed on the importance of following the once-daily dosing regimen. Dosing should occur in the evening between 20:00 and 22:00 hours. As no commercially available method is readily available for direct, single-container monitoring of treatment adherence with multi-dose ophthalmic products, no formal measure of treatment compliance is planned. Subjects should be reminded at all visits to dose every evening. In addition, subjects will be provided with a paper and electronic dosing reminder.

If a dose of study medication is missed the subject should take the next dose as planned. The dose of study medication should not exceed one drop daily."

Section 6.1 – Informed Consent

WAS:
"Prior to any study procedures, the study will be discussed with each subject and subjects wishing to participate must give written informed consent…At the end of the interview, the subject should be given time to reflect. Subjects and/or legally authorized representative then will be required to sign and date the informed consent form."

IS:
"Prior to any study procedures, the study will be discussed with each subject and subjects wishing to participate must give written informed consent…At the end of the interview, the subject should be given time to reflect. Subjects ~~**and/or legally authorized representative**~~ then will be required to sign and date the informed consent form."

Section 7.1.1 – Visit 1 (Screening visit)

WAS:
"The following procedures will be performed:

- Heart rate and blood pressure
- Best Corrected Visual Acuity"

IS:
"The following procedures will be performed:

- **Confirm eligibility per inclusion and exclusion criteria**
- Heart rate and blood pressure
- **Urine pregnancy test: All females of childbearing potential must have a negative urine pregnancy prior to commencement of washout period**
- Best corrected visual acuity"

Section 7.1.1.1 – Evaluation of eye-drop instillation performance

WAS:
"Subjects (or legally authorized representative for subjects deemed unable to administer) will be provided a bottle of commercially available, multi-dose, non-medicated artificial tears in a room with access to water and soap…If the subject (guardian or alternative person) cannot demonstrate proper delivery of the eye drop, or if staff member feels that the individual will be unable to do so consistently, then the subject will be excluded from further study participation."

IS:
"Subjects (or **guardian or care giver** for subjects deemed unable to administer) will be provided a bottle of commercially available, multi-dose, non-medicated artificial tears in a room with access to water and soap…If the subject (guardian or alternative person) cannot demonstrate proper delivery of the eye drop, or if staff member feels that the individual will be unable to do so consistently, then the subject will be excluded from further study participation."

Section 7.1.1.2 – Washout

WAS:
"As noted in Section 5.7.1, as current use of at least one ocular hypotensive medication is an inclusion criterion, a washout period is required for those who meet other qualifications for enrollment. The investigator is encouraged to have interim visits during the washout period for IOP measurement for individuals for whom the washout period may be a risk for further glaucomatous progression."

IS:
"As noted in Section 5.7.1, as current use of at least one ocular hypotensive medication is an inclusion criterion, a washout period is required for those who meet other qualifications for enrollment. The investigator **must perform** interim visits, **ideally at weekly intervals,** during the washout period for IOP measurement."

Section 7.1.2 Visit 2 (Qualifying visit #1 for 08.00 hours IOP and safety measurements)

WAS:
The following procedures will be performed

- Heart rate and blood pressure
- Pregnancy test: All females of childbearing potential must have a negative urine pregnancy test result within 7 days prior to randomization
- Symptomology: Individuals will be asked "How are you feeling"…….

IS:
- Heart rate and blood pressure
- Symptomology: Individuals will be asked "How are you feeling"…..

Section 7.1.3 -Visit 3.0 (Qualifying visit #2 for 08.00 hours IOP and safety measurements)

WAS:
The following procedures will be performed

- Heart rate and blood pressure
- Symptomology: Individuals will be asked "How are you feeling"…….

IS:

- Heart rate and blood pressure
- **Urine pregnancy test: All females of childbearing potential must have a negative urine pregnancy test result within 7 days prior to randomization**
- Symptomology: Individuals will be asked "How are you feeling**"…..**

Section 7.1.6 – Visit 4.0 (Week 2); Section 7.1.9 – Visit 5.0 (Week 6); Section 7.1.12 – Visit 6.0 (Month 3); Section 7.1.15 – Visit 7.0 (Month 4); Section 7.1.18 – Visit 8.0 (Month 5)

WAS:
"Subjects will return to the Investigator's office. The subject will be questioned about any missed doses and any changes in their health or concomitant medication use. Subjects will be examined and each examination will include:

- Heart rate and blood pressure
- Symptomatology: Individuals will be asked "How are you feeling?""

IS:
"Subjects will return to the Investigator's office. The subject will be questioned about any missed doses and any changes in their health or concomitant medication use.

Subjects will be examined and each examination will include:

- Heart rate and blood pressure
- **Urine pregnancy test (female subjects of childbearing potential as applicable)**
- Symptomatology: Individuals will be asked "How are you feeling?""

Section 7.2.3 Severity

WAS:
"For example, a change in severity may go from mild to severe or from severe to moderate. In either case, the start and stop dates should be recorded."

IS:
"For example, a change in severity may go from mild to severe or from severe to moderate. In **both** cases, the start and stop dates should be recorded."

Section 7.2.6 – Serious Adverse Events (SAEs) or Serious Unexpected Suspected Adverse Reaction Safety Reports (SUSARs)

WAS:
"Highly acceptable contraceptive methods when used consistently and in accordance with both the product label and the instructions of the physician, are as follows (Clinical Trials Facilitation Group 2014):

- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:

  - oral
  - intravaginal
  - transdermal

- progestogen-only hormonal contraception associated with inhibition of ovulation.
  - oral
  - injectable
  - implantable

- intrauterine device (IUD)
- intrauterine hormone-releasing system (IUS)
- bilateral tubal occlusion
- vasectomised partner

Sexual abstinence: ***sexual abstinence is only considered to be an acceptable method of contraception when defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the trial and the preferred and usual lifestyle of the subject. Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception.***

Female subjects who are lactating must discontinue nursing prior to the first dose of IP and must refrain from nursing throughout the treatment period and for 30 days following the last dose of IP.

Male subjects

Men with a female partner of childbearing potential must have either had a prior vasectomy or agree to use ***a condom as*** an effective method of contraception from time of randomization and for 3 months following the last dose of study medication. A combination of male condom with either cap, diaphragm or sponge with spermicide (double barrier methods) are also considered acceptable,….."

IS:
"Highly acceptable contraceptive methods when used consistently and in accordance with both the product label and the instructions of the physician, are as follows (Clinical Trials Facilitation Group 2014):

- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation. **Due to lack of systemic absorption of netarsudil and no systemic effects seen with latanoprost, PG324 is not expected to lower the effectiveness of hormonal contraception**
  - oral
  - intravaginal
  - transdermal

- progestogen-only hormonal contraception associated with inhibition of ovulation. **Due to lack of systemic absorption of netarsudil and no systemic effects seen with latanoprost, PG324 is not expected to lower the effectiveness of hormonal contraception**
  - oral
  - injectable
  - implantable **(considered to have low user dependency)**

- intrauterine device (IUD)
- intrauterine hormone-releasing system (IUS) **(considered to have low user dependency)**
- bilateral tubal occlusion **(considered to have low user dependency)**

Vasectomised partner ***(is considered as having lower user dependency and highly effective birth control method providing that the partner is the sole sexual partner of the women of childbearing potential and that the vasectomized partner has received a medical assessment of the surgical success).***

Sexual abstinence: sexual abstinence is only considered to be an acceptable method of contraception when defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the trial and the preferred and usual lifestyle of the subject. Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception.

Female subjects who are lactating must discontinue nursing prior to the first dose of IP and must refrain from nursing throughout the treatment period and for 30 days following the last dose of IP.

Male subjects

Men with a female partner of childbearing potential must have either had a prior vasectomy or agree to use a condom as an effective method of contraception from time of randomization and for 3 months following the last dose of study medication. **A combination of male condom with either cap, diaphragm or sponge with spermicide (double barrier methods) are also considered acceptable, but not highly effective, birth control methods.** A combination of male condom with either cap, diaphragm or sponge with spermicide (double barrier methods) is also considered acceptable,….."

Section 8.1 – Primary Hypotheses

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

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

The non-inferiority (NI) margin specified in the protocol was based on advice received from EMA through the scientific advice procedure (EMA/CHMP/SAWP/588765/2016) on 15 September 2016. In addition to the 1.5 mmHg margin at all time points specified in the draft protocol submitted to EMA for comment, advice was given that in accordance with the European Glaucoma Society's (EGS) Glaucoma Guideline a difference of 1 mmHg in IOP was considered to also be clinically relevant and therefore a NI margin no larger than this at the majority of time points should be included in the protocol.

As agreed with the USA FDA at the end of Phase 2 meeting for netarsudil (AR-13324) in accordance with the agency's draft guidance paragraph 16 (recommended Sep 2008; Revised Feb 2014, Dec 2014, Mar 2015)."

Section 13 REFERENCES

WAS:

7. Collaborative Normal-Tension Glaucoma Study Group. The effectiveness of intraocular pressure reduction in the treatment of normal-tension glaucoma. Am J Ophthalmol 1998; 126:498-505.
8. Ferris FL, Freidlin V, Kassoff A, et al. Relative letter and position difficulty on visusal acuity charts from the early Treatment Diabetic Retinopathy Study. Am J Ophthalmol 1993; 116:735-40.

IS:

7. Collaborative Normal-Tension Glaucoma Study Group. The effectiveness of intraocular pressure reduction in the treatment of normal-tension glaucoma. Am J Ophthalmol 1998; 126:498-505.
8. **European Glaucoma Society, Tip of the Month, November 2011, Ann Hoste, Antwerp.**
9. Ferris FL, Freidlin V, Kassoff A, et al. Relative letter and position difficulty on visual acuity charts from the early Treatment Diabetic Retinopathy Study. Am J Ophthalmol 1993; 116:735-40.

Appendix 1 – Schedule of Visits and Examinations

WAS:
"Urine Pregnancy Test at Visit 2 (Qualification #1) and Visit 9.0 (Month 6 [Day 180])"

IS:
"Urine Pregnancy Test at **Visit 1 (Screening visit), Visit 3.0 (Qualifying Visit #2), Visit 4.0**

(Day 15), Visit 5.0 (week 6) Visit 6.0 (Month 3 [Day 90]), Visit 7.0 (Month 4 [Day 120]), Visit 8.0 (Month 5 [Day150]), and Visit 9.0 (Month 6 [Day 180])"

WAS:
9. Collect used kit(s) dispensed during the previous visit

IS:
9. Collect used kit(s) dispensed during the previous visit

10. Per Section 5.2 and 5.3, subjects are required to administer IP on all days of the study, including days of study visits

Appendix 2 – Procedures:

Procedures: Biomicroscopy and measurement of Intraocular pressure (IOP)

WAS: "Tonometer calibration on at least a monthly basis will be documented."

IS: "Tonometer **validation** on at least a monthly basis will be documented."

Procedures: Self-Administered NEI Visual Functioning Questionnaire-25 (VFQ-25)

WAS:
"Translations of the NEI Visual Functioning Questionnaire -25 (VFQ-25), if available, will be provided for participating centers in non-English-speaking countries."

IS:
"Translations of the NEI Visual Functioning Questionnaire -25 (VFQ-25), if available, will be provided for participating centers in non-English-speaking countries."

The NEI Visual Functioning Questionnaire-25 (VFQ-25) is a validated VFQ-25 and reliable 25-item version of the 51-item National Eye Institute Visual Function Questionnaire (NEI-VFQ). It is especially useful in settings such as clinical trials, where interview length is a critical consideration (Mangione 2001)."

Appendix 5 – Investigator's Obligations

WAS:
"The Investigator is obligated to:

A. In the event of a serious adverse experience, whether related to the use of the study medication or device or not…"

IS:
"**An Investigator for the PG324-CS303 study must be a physician duly qualified to practice medicine.** The Investigator is obligated to:

A. **Questioning (evaluation of) examination regarding, as well as collection and documentation of, adverse events and efficacy parameters.** In the event of a serious adverse experience, whether related to the use of the study medication or device or not…"

Amendment #4: 19 March 2018

Changes have been made to the protocol based on feedback from Investigators. The changes made reflect current clinical practice. The changes are as follows:

1. Changes to the following inclusion and exclusion criteria have been made based on feedback from Investigators to reflect current clinical practice and facilitate patient screening:

    a. Revision to medicated IOP required for a subject to enter screening from > 18mmHg and < 25mmHg in both eyes to ≥ 17mmHg in at least one eye and < 28mmHg in both eyes.

    b. Clarification of the GANFORT® exclusion criteria.

    c. Revision of the criteria regarding prior systemic medications (including corticosteroids) that affect IOP.

    d. Clarification of the use of topical steroids.

2. Changes to Section 5.6 Concomitant medications to clarify the use of steroids by various routes.

3. To allow investigators at their discretion record images of ocular events.

4. Removal of the requirement at Visits 7, 8, and 9 to measure IOP at 08:00 and 16:00. All assessments previously required to be performed at 08:00 and 16:00 visits will now be performed at one 10:00 visit.

5. Increase window for 08:00 IOP assessments to +/- 1 hour.

In addition to the feedback from investigators the following changes have been made:

1. From the time that the subject gives written consent events that occur will be recorded as adverse events and not as previously stated as medical history until the time of randomization.

2. Updated references to ICH E6 (R2) throughout.

3. Abbreviation QD changed to Q.D. throughout.

4. To clarify that Investigational Product will be administered to both eyes for the duration of the study.

5. [redacted] has changed name to [redacted]. [redacted]arch has been updated to the new company name [redacted] throughout.

Other changes have been made to correct typographical errors and inconsistences.

Modified or added text is shown below in **bold type**, deleted text is indicated by ~~strikethrough~~.

Synopsis, Section 4.2 – Subject Inclusion Criteria, Section 4.3 – Subject Exclusion Criteria

Primary Objectives

WAS:
"To evaluate:

- The ocular hypotensive efficacy of PG324 Ophthalmic Solution relative to GANFORT® Ophthalmic Solution ~~over a 3-month period~~".

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".**

Study Design

WAS:
"Procedures conducted at each of Study Visits 3-9 will include safety measures and efficacy measurements, including IOP assessments at the following time points **at a study visit: 08:00, 10:00, and 16:00 hours; …"**

IS:
"Procedures conducted at each of Study Visits 3-9 will include safety measures and efficacy measurements, including IOP assessments at the following time points **at study visits 3-6: 08:00, 10:00, and 16:00 hours, and 10:00 hours only at visits 7-9; …"**

Inclusion Criteria

WAS:
4. Medicated intraocular pressure > 18mmHg and < 25mmHg in both eyes at screening visit.
5. Unmedicated (post-washout) IOP > 20mmHg and < 36mmHg in both eyes at 2 qualification visits at 08:00 hour, 2-7 days apart. At the second qualification visit, have IOP > 17mmHg and < 36mmHg in both eyes at 10:00 and 16:00 hours. Note: For purposes of determining eligibility of subjects to be enrolled the non–integral IOP mean number will be used. Any non-integral mean IOP number should not be rounded.

IS:
4. Medicated intraocular pressure **≥ 17mmHg in at least one eye** and < 28mmHg **in both eyes** at the screening visit.

5. Unmedicated (post-washout) IOP > 20mmHg **in at least one eye** and < 36mmHg in both eyes at 2 qualification visits at 08:00 hour, 2-7 days apart. At the second qualification visit, have IOP > 17mmHg **in at least one eye** and < 36mmHg in both eyes at 10:00 and 16:00 hours. Note: For purposes of determining eligibility of subjects to be enrolled the non–integral IOP mean number will be used. Any non-integral mean IOP number should not be rounded. **If only one eye qualifies at second qualification visit it MUST be the same eye that qualified on the first visit and this will be the study eye for the duration of the study.**

Exclusion Criteria

WAS:
3. Intraocular pressure…Note: fixed dose combination medications, for the purpose of this exclusion criterion, count as one medication.

IS:
3. Intraocular pressure… Note: fixed dose combination medications, for the purpose of this exclusion criterion, count as one medication. **However, subjects currently taking 2 fixed dose combination products are excluded."**

WAS:
5. Prior treatment with GANFORT® topical eye drops.

IS:
5. Prior treatment with GANFORT® topical eye drops **where the subjects IOP did not achieve the target IOP and was considered either a therapeutic failure or to have insufficient response. Subjects currently (immediately prior to screening visit) being treated with GANFORT® are excluded from the study.**"

WAS:
10. Recent or current evidence of ocular infection or inflammation in either eye. Current evidence of clinically significant blepharitis, conjunctivitis, keratitis, current evidence or history of herpes simplex or zoster keratitis in either eye at screening, in either eye at screening.

IS:
10. Recent or current evidence of ocular infection or inflammation in either eye. Current evidence of clinically significant blepharitis, conjunctivitis, keratitis, current evidence or history of herpes simplex or **zoster keratitis in either eye at screening.**

WAS:
11. Use of ocular medication in either eye of any kind within 30 days of screening and throughout the study, with the exception of a) ocular hypotensive medications (which must be washed out according to the provided schedule), b) lid scrubs (which may be used prior to, but not after, screening), c) lubricating drops for dry eye (which may be used throughout the study), as prescribed by the Investigator.

IS:
11. Use of ocular medication in either eye of any kind within 30 days of screening and throughout the study, with the exception of a) ocular hypotensive medications **which must be the same medication for 30 days prior to screening** (which must be washed out according to the provided schedule), b) lid scrubs (which may be used prior to, but not after, screening), c) lubricating drops for dry eye (which may be used throughout the study), as prescribed by the Investigator.

WAS:
18. Systemic medication that could have a substantial effect on IOP within 30 days prior to screening, or anticipated during the study, including any corticosteroid-containing drug regardless of route of administration.

19. Women of childbearing potential…

IS:
18. Systemic medication **including corticosteroid containing drugs** that could have a substantial effect on IOP **which HAVE NOT been maintained at a consistent dose and regime** within 30 days prior to screening **and are anticipated to change in dose and/or regimen during the study.**"

19. **Use of topical steroid containing medications on the face or in or around the eyes will exclude the subject (see Section 5.6 concomitant medications).**

20. Women of childbearing potential…"

Efficacy Assessments

WAS:
Secondary efficacy outcomes will be comparison of PG324 Ophthalmic Solution relative 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
- ~~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~~

IS:
Secondary efficacy outcomes will be comparison of PG324 Ophthalmic Solution relative 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

Section 1.2 – Findings from Non-clinical and Clinical Studies

WAS:
"Two pivotal Phase 3 studies (PG324-CS301 and PG324-CS302) are currently ongoing…"

IS:
"Two pivotal Phase 3 studies (PG324-CS301 and PG324-CS302) **have been completed…"**

Section 1.3 – Risks and Benefits to Human Subjects

WAS:
"(Clinical Study Reports AR-13324-CS101, AR-13324-CS102, AR-13324-CS201, AR-13324-CS202, AR-13324-CS301, PG324-CS201 and AR-13324-CS302)"

IS:
"(Clinical Study Reports AR-13324-CS101, AR-13324-CS102, AR-13324-CS201, AR-13324-CS202, AR-13324-CS301, PG324-CS201 and AR-13324-CS302, **AR-13324-CS304**, **PG324-CS301 and PG324-CS302**)"

Section 3.1 – Overall Study Design and Plan

WAS:
"Subsequent visits at Month 4, Month 5 and Month 6 will focus primarily on safety and will include IOP measurements at 08:00, 10:00 and 16:00 hours."

IS:
"Subsequent visits at Month 4, Month 5 and Month 6 will focus primarily on safety and will include IOP measurements at 10:00 hours."

Section 4.1 – Study Population

WAS:
"A total of approximately 472 subjects will be enrolled in this study at approximately 40 sites in approximately 6 EU countries".

IS:
"A total of approximately 472 subjects will be enrolled in this study at approximately **60** sites in approximately **12** EU countries**"**.

Section 5.6 – Concomitant Medications

WAS:

- "Any corticosteroid containing systemic drug is disallowed during the study regardless of route of administration".

IS:

- **"Routine (e.g. daily) and intermittent use of topical medication containing steroids on the face or topical eye drops containing steroids is NOT permitted at any time during the study."**

WAS:
"Systemic therapy with agents other than corticosteroids that could have an effect on IOP is to be consistent in dose, regimen and agent within the 30 days prior to screening and throughout the study."

IS:
"Systemic therapy with agents **including** corticosteroids that could **influence** IOP is to be consistent in dose, regimen and agent within the 30 days prior to screening and throughout the study…

Intermittent use of topical steroids for certain skin conditions (but not on the face) may be permitted following consultation with and approval from the Medical Monitor if dosing has been intermittent for 90 days prior to screening and no alteration to the dosing regimen is anticipated during the 6-month study participation."

Section 5.7.1

WAS:
"Prior Therapy Washout period"

Subjects must undergo a minimum washout period as specified in Table 1.
For prostaglandins the minimum washout period should be not less than 4 weeks and it may be extended if deemed necessary in investigator opinion."

IS:
"Prior Therapy Washout period"

To qualify subjects must have been taking the same IOP lowering medication for 30 days prior to screening. Subjects must undergo a minimum washout period as specified in Table 1. For prostaglandins the minimum washout period should be not less than 4 weeks and it may be extended if deemed necessary in investigator opinion."

WAS:
"If for logistical or other reasons, the period needs to be extended beyond 8 weeks (56 days), the Sponsor should be contacted."

IS:
"If for logistical or other reasons, the **washout** period needs to be extended beyond 8 weeks (56 days), the Sponsor should be contacted. **Washout period can start at any time following the screening visit but the period between the screening (visit 1) and qualification 1 (visit 2) MUST not exceed 56 days.**"

Section 5.11.5 – Actions after Discontinuation

WAS:
"For the subject who chooses to withdraw consent or who is non-compliant, every possible effort should be made by the Investigator to assure there is a final visit that includes all examinations listed for Visit 9.0 (Exit) and dilated ophthalmoscopy."

IS:
"For the subject who chooses to withdraw consent or who is non-compliant, every possible effort should be made by the Investigator to assure there is a final visit that includes all examinations listed for Visit 9.0 (Exit) and dilated ophthalmoscopy.

Subjects should not take part in another clinical trial within 30 days of withdrawing or completing the study."

Section 7.1.1 – Visit 1 (Screening Visit)

WAS:
- Pregnancy test: women of childbearing potential must have a negative urine pregnancy prior to commencement of washout period.

IS:
- Pregnancy test: women of childbearing potential must have a negative urine pregnancy **test** prior to commencement of washout period.

WAS:
- "Dilated ophthalmoscopy: Medicated IOP must be > 18mmHg and < 25mmHg in both eyes at screening visit."

IS:
- Dilated ophthalmoscopy **(including cup:disc ratio)**: Medicated IOP must be **≥ 17mmHg in at least one eye** and **< 28mmHg** in both eyes at screening visit.

WAS:
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) so long as the results of the clinical labs are available for that subject prior to Visit 3 (Qualification Visit #2).

IS:
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).

Section 7.1.1.2

WAS:
As noted in Section 5.7.1, as current use of at least one ocular hypotensive medication is an inclusion criterion, a washout period is required for those who meet other qualifications for enrollment. The investigator must perform interim visits, ideally at weekly intervals, during the washout period for IOP measurement.

IS:
As noted in Section 5.7.1, as current use of at least one ocular hypotensive medication is an inclusion criterion, a washout period is required for those who meet other qualifications for enrollment. The investigator must perform interim visits, ideally at weekly intervals, during the washout period for IOP measurement.

In addition, all women of childbearing potential will have a pregnancy test performed during the washout period if the washout period extends beyond 4 weeks.

Section 7.1.2 – Visit 2 (Qualifying Visit 1, 08:00) and Section 7.1.3 (Qualifying Visit 2, 08:00).

WAS:
"Any change in the individual's Visit 1 health status should be recorded on the Medical History page of the eCRF (e.g., the subject has been diagnosed with cancer)"

IS:
"Any change should be recorded on the Adverse Event page of the CRF."

Addition of the following bullet:

- **Recording of any AEs.**

Section 7.1.2 – Visit 2 (Qualifying Visit #1, 08:00), Section 7.1.3 – Visit 3.0 (Qualifying Visit #2, 08:00), Section 7.1.6 – Visit 4.0 (Day 15, 08:00), Section 7.1.9 – Visit 5.0 (Day 43, 08:00), Section 7.1.12 – Visit 6.0 (Day 90, 08:00)

WAS:
- A non-dilated eye examination will be performed, including pupil size, IOP measurements and biomicroscopy. IOP must be measured within 30 minutes of the nominal time (i.e., 07:30 to 08:30 hours).

IS:

- A non-dilated eye examination will be performed, including ~~pupil size,~~ IOP measurements and biomicroscopy. IOP must be measured within **60** minutes of the nominal time (i.e., **07:00 to 09:00** hours).

Section 7.1.3 – Visit 3.0 (Qualifying Visit #2, 08:00), 7.1.4 – Visit 3.1 (Day 1, 10:00) and 7.1.5 – Visit 3.2 (Day 1, 16:00),

WAS:
"Individuals who screen fail due to IOP being > 36mmHg in both eyes (exclusion criterion) MAY NOT return for additional qualification visits."

IS:
"Individuals who screen fail due to IOP being > 36mmHg in **either eye** (exclusion criterion) MAY NOT return for additional qualification visits."

Section 7.1.2 – Visit 2 (Qualifying Visit #1, 08:00 hours IOP and safety measurements)

WAS:
"For further evaluation in the study, at this time, unmedicated (post-washout) IOP must be > 20mmHg and < 36mmHg in both eyes. This is the first of the four qualifying IOPs for randomization.

Individuals who screen fail due to IOP being > 36mmHg in both eyes (exclusion criterion) MAY NOT return for additional qualification visits."

IS:
"For further evaluation in the study, at this time, unmedicated (post-washout) IOP must be > 20mmHg **in at least one eye** and < 36mmHg **in** both eyes. This is the first of the four qualifying IOPs for randomization.

"Individuals who screen fail due to IOP being > 36mmHg in **either eye** (exclusion criterion) MAY NOT return for additional qualification visits."

Addition of the following bullet:

- **Pregnancy test: Women of childbearing potential (who have a washout period that extends beyond 4 weeks)**

Section 7.1.3 – Visit 3.0 (Qualifying Visit #2, Day 1, for IOP and safety measurements at 08:00 hours)

WAS:
"For further evaluation in the study, at this time, (08.00 hours) unmedicated (post-washout) IOP must be > 20mmHg and < 36mmHg in both eyes. This is the first of the four qualifying IOPs for randomization.

Individuals who screen fail due to IOP being > 36mmHg in both eyes (exclusion criterion) MAY NOT return for additional qualification visits."

IS:
"For further evaluation in the study, at this time (08.00 hours), **unmedicated (post-washout) IOP must be > 20mmHg in at least one eye and < 36mmHg in both eyes.** This is the second of the four qualifying IOPs for randomization."

Individuals who screen fail due to IOP being > 36mmHg in **either eye** (exclusion criterion) MAY NOT return for additional qualification visits.

If one eye qualifies at the second qualification visit, it MUST be the same eye as in previous qualification visit (Visit 2 qualifying visit #1) and this will be the study eye for the duration of the study.''

Section 7.1.4 – Visit 3.1 (Day 1, for IOP and safety measurements at 10:00 hours)

WAS:
"For further evaluation in the study, at this time, (10.00 hours, Day 1) unmedicated (post-washout) IOP must be > 17mmHg and < 36mmHg in both eyes. This is the third of the four qualifying IOPs for randomization.

Individuals who screen fail due to IOP being > 36mmHg in both eyes (exclusion criterion) MAY NOT return for additional qualification visits."

IS:
"For further evaluation in the study, at this time, unmedicated (post-washout) IOP must be > 17mmHg **in at least one eye** and < 36mmHg in both eyes. This is the third of the four qualifying IOPs for randomization.

Individuals who screen fail due to IOP being > 36mmHg in **either** eye (exclusion criterion) MAY NOT return for additional qualification visits. **If one eye qualifies it MUST be the same eye as Visit 2.0 and Visit 3.0.**"

Section 7.1.5 – Visit 3.2 (Day 1, for IOP and safety measurements at 16:00 hours)

WAS:
For further evaluation in the study, at this time, (16.00 hours, Day 1) unmedicated (post-washout) IOP must be > 17mmHg and < 36mmHg in both eyes. This is the fourth of the four qualifying IOPs for randomization.

Individuals who screen fail due to IOP being > 36mmHg in both eyes (exclusion criterion) MAY NOT return for additional qualification visits.

IS:
For further evaluation in the study, at this time (16.00 hours Day 1), unmedicated (post-washout) IOP must be > 17mmHg **in at least one eye** and < 36mmHg in both eyes. This is the fourth of the four qualifying IOPs for randomization.

Individuals who screen fail due to IOP being > 36mmHg in **either** eye (exclusion criterion) MAY NOT return for additional qualification visits. **If one eye qualifies it MUST be the same eye as Visit 2.0, Visit 3.0 and Visit 3.1.**

Section 7.1.4 Visit 3.1 (QUAL 2, IOP 10:00), Section 7.1.7 Visit 4.1 (W2 IOP 10:00), Section 7.1.10 Visit 5.1 (W6 IOP 10:00) Section 7.1.13 Visit 6.1 (M3 IOP 10:00)

WAS:
A non-dilated eye examination will be performed, including IOP measurements and biomicroscopy. IOP must be measured within 30 minutes of the nominal time (i.e., 09:30 to 10:30 hours).

IS:
A non-dilated eye examination will be performed, including IOP measurements and biomicroscopy. IOP must be measured within 30 minutes of the nominal time (i.e., 09:30 to 10:30 hours). **PLEASE NOTE, the minimum time between IOP measurements is 60 minutes. For example, if the previous IOP measurement was taken at 09:00, the IOP at this visit should not be measured before 10:00.**

Section 7.1.5 Visit 3.2 (day 1, for IOP and safety measurements at 16.00 hours)

WAS:
Subjects will be:

Instructed to administer their masked medication OU at home between 20.00-22.00 hours beginning with their first dose on the evening of this study visit.

IS:
Subjects will be:

Instructed to administer their masked medication **to both eyes** (OU) at home between 20:00 – 22:00 hours beginning with their first dose on the evening of this study visit **or no later than within 48 hours of randomization.**

Section 7.1.5 – Visit 3.2 (Day 1, 16:00)

WAS:
"As noted in Section 4.2, subjects must qualify in both eyes based upon IOP and ocular history for a subject who qualifies…In each subject, BOTH eyes will be treated."

IS:
"**For subjects that** qualify in both eyes based upon IOP and ocular history ~~for a subject who qualifies~~…In **all subjects**, BOTH eyes will be treated."

Sections 7.1.6 – Visit 4.0 (Day 15, 08:00), Section 7.1.9 – Visit 5.0 (Day 43, 08:00), Section 7.1.12 – Visit 6.0 (Day 90, 08:00), Section 7.1.15 – Visit 7.0 (Month 4, 10:00), Section 7.1.16 – Visit 8.0 (Month 5, 10:00) and Section 7.1.17 – Visit 9.0 (Month 6, 10:00)

WAS:
- "Urine pregnancy test (women of childbearing potential as applicable)."

IS:
- "Urine pregnancy test **for** women of childbearing potential."

Section 7.1.6 – Visit 4.0 (Day 15, 08:00) to Section 7.1.17 – Visit 9.0 (Month 6, 10:00) (all on-treatment visits)

WAS:
- "Recording of any AEs."

IS:
- "Recording of any AEs. **At the investigator's discretion photography of any ocular events."**

Section 7.1.15 – Visit 7.0 (Month 4, 10:00), Section 7.1.16 – Visit 8.0 (Month 5, 10:00), Section 7.1.17 – Visit 9.0 (Month 6, 10:00)

WAS:
- A non-dilated eye examination will be performed, including pupil size, IOP measurements and biomicroscopy. IOP must be measured within 30 minutes of the nominal time (i.e., 07:30 to 08:30 hours).

IS:
- A non-dilated eye examination will be performed, including IOP measurements and biomicroscopy. IOP must be measured within 30 minutes of the nominal time (i.e., **09:30 to 10:30** hours).

Visit 7 (Month 4), Visit 8 (Month 5), Visit 9 (Month 6)

WAS:
- Sections 7.1.15 – 7.1.17 (Month 4 [Day 120] 08:00 – 16:00)
- Sections 7.1.18 – 7.1.20 (Month 5 [Day 150] 08:00 – 16:00)
- Sections 7.1.21 – 7.1.23 (Month 6 [Day 180] 08:00 – 16:00)

IS:

- Section 7.1.15 (Month 4 [Day 120], 10:00)
- Section 7.1.16 (Month 5 [Day 150], 10:00)
- Section 7.1.17 (Month 6 [Day 180], 10:00)
- Section 7.1.18 (Unscheduled Visits)
- Section 7.1.19 (Instructions for Completion of Case Report Forms)

Sections 7.1.15 Visit 7.0 (Month 4) and 7.1.16 Visit 8 (Month 5)

Added text as follows:

TO:
"Two new subject kits, from the assigned safety extension subject packer, each containing 1 bottle will be dispensed to the subject by the unmasked site staff, along with dosing and storage instructions. Subjects will be:

- Instructed to continue to administer their masked medication to both eyes (OU) at home between 20:00 – 22:00 hours (taking the daily evening dose on that day).

- Instructed to return to the office with their study medication on Month 5 or Month 6 (Day 180)."

Delete text:

WAS:

~~"Subjects are allowed to leave the investigator's office, and eat and drink without restrictions. However, individuals are not to consume alcohol or engage in strenuous exercise"~~

Section 7.1.19 – Instructions for completion of Case Report Forms

WAS:
"At each subject visit, the appropriate CRFs must be completed. Whenever a CRF is used, be sure to provide all information requested including subject identification number and initials~~,~~ name or number of Investigator, date(s), etc."

IS:
"At each subject visit, the appropriate CRFs must be completed. Whenever a CRF is used, be sure to provide all information requested including subject identification number ~~and initials,~~ name or number of Investigator, date(s), etc."

Section 7.2.1 Adverse Event Definitions

WAS:
"Note: If an event occurs during the washout period (prior to subject enrollment and the commencement of study medication), it should be recorded as ~~part of the Medical History and not as an adverse event. As noted in section 7.1.2, any change in their Visit 1 (Screening)~~

~~health status should be recorded on the Medical History page of the eCRF (e.g., the subject has been diagnosed with cancer)~~"

IS:
"Note: If an event occurs during the washout period (prior to subject enrollment and the commencement of study medication), it should be recorded as an adverse event."

Section 7.2 – Performing Adverse Events Assessments

WAS:
"Adverse events should be documented from the time the subject receives the first dose of Investigational Product until 30 days after the last dose of study drug.
…
Documentation of adverse events/adverse reactions include start date and stop date, severity, action(s) taken, seriousness and outcome."

IS:
"Adverse events should be documented from the time the subject **signs the informed consent** until 30 days after the last dose of **Investigational Product**.
…
Documentation of adverse events/adverse reactions include start date and stop date, severity, action(s) taken, seriousness and outcome. **Investigators at their discretion may also take photographs of ocular events to provide additional documentation of adverse events. These images can only be shared with the sponsor if the subject has provided permission to do so by signing the appropriate consent documentation.**"

Section 7.2.1 – Adverse Event Definition

WAS:
"Note: If an event occurs during the washout period (prior to subject enrollment and the commencement of study medication), it should be recorded as ~~part of the Medical History and not as~~ an adverse event."

IS:
"Note: If an event occurs during the washout period (prior to subject enrollment and the commencement of study medication), **it should be recorded as an adverse event**."

Section 7.2.2 – Timing for Reporting of Adverse Events

WAS:
"AEs should be documented from the time the subject ~~receives the first dose of investigational product~~ until subject participation in the study has been completed."

IS:
"AEs should be documented from the time **the subject signs and dates the subject consent form** until subject participation in the study has been completed."

Section 7.2.3 – Severity

WAS:
"For example, a change in severity may go from mild to severe or from severe to moderate. In either case, the start and stop dates should be recorded."

IS:
"For example, a change in severity may go from mild to severe or from severe to moderate. In **both cases**, the start and stop dates should be recorded."

Section 7.2.6 – Serious Adverse Events (SAEs) or Serious Unexpected Suspected Adverse Reaction Safety Reports (SUSARs)

WAS:
Procedurally, for this study, the Investigator will report the event to INC Drug Safety. An SAE report should be completed and faxed or emailed directly to INC Drug Safety as indicted below, using the study-specific SAE fax coversheet.

IS:
Procedurally, for this study, the Investigator will report the event to [redacted] Drug Safety. An SAE report should be completed and faxed or emailed directly to [redacted]**th** Drug Safety, using the study-specific SAE fax coversheet. **The SAE fax/email cover page is included in attachment 1 of the Safety Management Plan (SMP) together with all relevant fax numbers and email addresses.**

Removed phone numbers for all countries.

Section 13.2 Internal References

Added completed clinical study reports.

IS:

8. AR-13324-CS304 Clinical Study Report: A double masked, randomized, multi-center, active controlled, parallel 6-month study with a 3-month interim analysis assessing the ocular hypotensive efficacy and safety of AR-13324 Ophthalmic Solution, 0.02% QD compared to Timolol Maleate Ophthalmic Solution, 0.5% BID in patients with elevated intraocular pressure (2017)

10. PG324-CS301 Clinical Study Report: A prospective, double-masked, randomized, multi-center, active-controlled, parallel-group 12-month study assessing the safety and ocular hypotensive efficacy of PG324 Ophthalmic Solution compared to AR-13324 Ophthalmic Solution, 0.02% and Latanoprost Ophthalmic Solution, 0.005% in subjects with elevated intraocular pressure (2018)

11. PG324-CS302 Clinical Study Report: A prospective, double-masked, randomized, multi-center, active-controlled, parallel-group, 3-month study assessing the safety and

ocular hypotensive efficacy of PG324 Ophthalmic Solution compared to AR-13324 Ophthalmic Solution, 0.02% and Latanoprost Ophthalmic Solution, 0.005% in subjects with elevated intraocular pressure (2018)

Appendix 1 – Schedule of Visits and Examinations

- Updated table and footers to reflect changes identified in section 7 of this protocol; added cup-to-disc ratio exam

Appendix 2 – Procedures

Procedures: Visual Acuity

IS:

- "If the individual is unreliable on two visual fields, the Investigator should consider that this individual is not appropriate for study entry.
- ~~Complete visual field reports will be provided to the Sponsor, with subject names removed."~~

Procedures: Photography

IS:

"At the investigator's discretion images of treatment emergent events may be taken. Events such as corneal verticillata or conjunctival hemorrhage can be imaged using a slit lamp mounted camera system using the investigator's normal practice. Subjects must confirm by checking the relevant section on the patient information and consent form that images can be taken and shared with the sponsor.

Images should be stored electronically ideally in an uncompressed JPEG format identifying the subject by site and subject identification number only and date image acquired."

Amendment #5: 06 August 2018 (Country Specific – Hungary)

Changes to the protocol have been made in accordance with observations made by the [redacted]. The changes are as follows:

- **An amendment to the study title to clarify that PG324 is a fixed dose combination of netarsudil and latanoprost.**

Study Title

WAS:
A prospective, double-masked, randomized, multicenter, active-controlled, parallel-group, 6-month 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 (**MERCURY 3**)

IS:
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%) Ophthalmic Solution compared to GANFORT® (bimatoprost 0.03%/timolol 0.5%) Ophthalmic Solution in subjects with elevated intraocular pressure (**MERCURY 3**)

- **Any corrections to dates and version number, due to the amendment to the protocol**

Amendment #6: 27 May 2020

Changes have been made primarily to reflect updates that will be made to the statistical analysis plan (SAP), and a decision to stop screening activities when the study was >90% enrolled. The decision to stop screening was not the result of any safety concerns, but a Sponsor administrative decision.

Synopsis:

- **Study Population:** Sample size updated FROM 472 TO "**up to 440**"; and FROM 236/arm TO "**up to 220 per arm**"

- **Statistical Methods:** Primary efficacy analysis population changed FROM per protocol (PP) TO **intent-to-treat (ITT);** ADDED "**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."**

Section 3.1; Section 4.1 and Figure 1: Sample size updated FROM 472 TO **"up to 440"**

Section 5.6: Corrected typographical error so systemic use of **beta-adrenergic blocking agents are NOT prohibited** provided the dose is stable

Section 5.11.7: Study is completed when… changed FROM planned enrollment has been completed, and all the enrolled subjects have completed the study TO **…when the last visit of the last subject has completed at the last site of all the countries taking part in the study.**

Updated reference to GANFORT® SmPC listed concomitant medications due to recent updates to the SmPC coming into effect; REMOVED beta adrenergic blocking agents as a prohibited concomitant medication

Section 8.2: Primary efficacy analysis population changed FROM per protocol (PP) TO **intent-to-treat (ITT);** ADDED; **"…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."**

Section 8.5.3: Primary efficacy analysis population changed FROM per protocol (PP) TO **intent-to-treat (ITT)**

Section 11.3: For source data verification…..data will be changed FROM 100% TO 80% source verified

Appendix 3 UPDATED to latest version of GANFORT® SmPC

Other changes have been made to correct typographical errors and inconsistences.

SYNOPSIS

Sponsor:
Aerie Pharmaceuticals Ireland Ltd.

Name of Finished Product: PG324 Ophthalmic Solution

Name of Active Ingredients: netarsudil and latanoprost

Study Title:
A prospective, double-masked, randomized, multicenter, active-controlled, parallel-group,6-month 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 (MERCURY 3)

Study Number: PG324-CS303

Study Phase: Phase 3

Primary Objectives:
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.

Secondary Objectives:
To evaluate:

- The ocular and systemic safety of PG324 Ophthalmic Solution relative to GANFORT® Ophthalmic Solution over a 6-month period.
- Change in Self-Administered National Eye Institute (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®.

Study Design:
This will be a 6-month, double-masked, randomized, multicenter, active-controlled, parallel-group efficacy and safety trial for reduction of elevated intraocular pressure (IOP) with PG324 Ophthalmic Solution compared to GANFORT® Ophthalmic solution, in subjects at least 18 years of age with open angle glaucoma (OAG) or ocular hypertension (OHT).
All investigational products (IP) will be dosed in both eyes once daily/ Q.D. (PM). Subjects eligible to be enrolled in this study will be those with a diagnosis of either open angle glaucoma (OAG) or ocular hypertension (OHT) that are on treatment with a topical ocular hypotensive medication. Subjects who agree to participate in this study and are enrolled in the study will attend a total of 9 study visits: Screening Visit, Qualification Visit #1, Qualification Visit #2/Day 1 (baseline), Week 2 (Day 15), Week 6 (Day 43), Month 3 (Day 90), Month 4 (Day 120), Month 5 (Day 150) and Month 6 (Day 180).
Subjects will be required to washout of their pre-study ocular hypotensive medication for a prescribed period (up to 4 weeks or longer), depending on the medication, prior to attending Qualification Visit #1. Subjects eligible to be enrolled in this study must meet all inclusion criteria and none of the exclusion criteria at each of the Screening Visit and Qualification Visits #1 and #2. Subjects will receive a baseline eye examination including IOP measurements at the Screening Visit and Qualification Visits #1 and #2 and, if deemed eligible, will be enrolled at Qualification Visit #2 and assigned to 1 of 2 IPs in a 1:1 ratio according to a computer-generated randomization list. Randomization will take place using interactive web-based response system (IWRS) methodology and will stratify subjects by site and by maximum baseline IOP (< 25mmHg vs ≥ 25mmHg).
Randomized subjects will dose the assigned IP in both eyes Q.D. in the evening beginning on Day 1 and up to and including the evening prior to the Month 6 study visit. Procedures conducted at each of Study Visits 3-9 will include safety measures and efficacy measurements, including IOP assessments at the following time points at study visits 3-6: 08:00, 10:00, and 16:00 hours, and 10:00 hours only at visits 7-9; IOP assessments at visits 7 (Month 4), 8 (Month 5) and 9 (Month 6) will not be part of the primary efficacy analysis of this study. Following completion of the Month 6 study visit procedures, subjects will exit the study. For subjects who discontinue early, every possible effort will be made to assure there is a final visit that includes all examinations listed for Visit 9.0 (Month 6) and dilated ophthalmoscopy.

Inclusion criteria:
Subjects have to meet all of the following criteria at screening and qualification visits to enter into the study:

1. Must be 18 years of age or older.
2. Diagnosis of OAG or OHT in both eyes (OAG in one eye and OHT in the fellow eye is acceptable).
3. Subjects insufficiently controlled and/or subjects considered in need for combination therapy by the investigators.
4. Medicated intraocular pressure ≥ 17mmHg in at least one eye and < 28mmHg in both eyes at the screening visit.
5. Unmedicated (post-washout) IOP > 20mmHg in at least one eye and < 36mmHg in both eyes at 2 qualification visits at 08:00 hour, 2-7 days apart. At the second qualification visit, have IOP > 17mmHg in at least one eye and < 36mmHg in both eyes at 10:00 and 16:00 hours. Note: For purposes of determining eligibility of subjects to be enrolled the non–integral IOP mean number will be used. Any non-integral mean IOP number should not be rounded. If only one eye qualifies at the second qualification visit it MUST be the same eye that qualified on the first visit and this will be the study eye for the duration of the study.
6. Best corrected visual acuity +1.0 logMAR or better by ETDRS in each eye (equivalent to 20/200 or better Snellen visual acuity in each eye).
7. Be able and willing to give signed informed consent and follow study instructions.
8. Women must be either of non-childbearing potential, or women with childbearing potential and men with reproductive potential must be willing to practice acceptable methods of birth control during the study.
9. Women of childbearing potential must have a negative urine pregnancy test within 7 days of first dose of study treatment and agree to use highly effective contraception during the study and for 3 months after the last dose of study medication.
10. Men with a female partner of childbearing potential must have either had a prior vasectomy or agree to use effective form of contraception from time of randomization and for 3months following the last dose of study medication.
11. In France, a subject will be eligible for inclusion in this study only if either affiliated to or as a beneficiary of a social security number.

Exclusion criteria:
Subjects meeting any of the following criteria during screening or qualification evaluations (e.g., at the time of randomization) will be excluded from entry into the study:

Ophthalmic:

1. Clinically significant ocular disease (e.g. corneal edema, uveitis, or severe keratoconjunctivitis sicca) which might interfere with interpretation of the study efficacy endpoints or with safety assessments, including subjects with glaucomatous damage so severe that washout of ocular hypotensive medications for 4 weeks or longer if needed is not judged safe as it would put the subject at risk for further vision loss.
2. Pseudoexfoliation or pigment dispersion component glaucoma, history of angle closure glaucoma, or narrow angles (i.e., Grade 2 Shaffer (Chan Ry 1981) or less; extreme narrow angle with complete or partial closure). Note: Previous laser peripheral iridotomy is NOT acceptable.
3. Intraocular pressure ≥ 36mmHg (unmedicated) in either eye (individuals who are excluded for this criterion are not allowed to attempt requalification), or use of more than two ocular hypotensive medications within 30 days of screening. Note: fixed dose combination medications, for the purpose of this exclusion criterion, count as one medication. However, subjects currently taking 2 fixed dose combination products are excluded.
4. Treatment-naïve subjects.
5. Prior treatment with GANFORT® topical eye drops where the subjects IOP did not achieve the target IOP and was considered either a therapeutic failure or to have insufficient response. Subjects currently (immediately prior to screening visit) being treated with GANFORT® are excluded from the study.
6. Known hypersensitivity to any component of the investigational formulations to be used (e.g., benzalkonium chloride etc.) or to fluorescein.
7. Previous glaucoma intraocular surgery, including SLT or ALT in either eye.
8. Refractive surgery in either eye (e.g., radial keratotomy, PRK, LASIK, corneal cross-linking, keratoplasty).

9. Ocular trauma within the six months prior to screening, or ocular surgery or non-refractive laser treatment within the three months prior to screening.
10. Recent or current evidence of ocular infection or inflammation in either eye. Current evidence of clinically significant blepharitis, conjunctivitis, keratitis, current evidence or history of herpes simplex or zoster keratitis in either eye at screening.
11. Use of ocular medication in either eye of any kind within 30 days of screening and throughout the study, with the exception of a) ocular hypotensive medications which must have been the same medication for 30 days prior to screening (which must be washed out according to the provided schedule), b) lid scrubs (which may be used prior to, but not after, screening), c) lubricating drops for dry eye (which may be used throughout the study) as prescribed by the Investigator.
12. Mean central corneal thickness greater than 620µm at screening.
13. Any abnormality preventing reliable Goldmann applanation tonometry of either eye (e.g., keratoconus).

Systemic:

14. Clinically significant abnormalities in laboratory tests at screening.
15. Known hypersensitivity or contraindication to GANFORT® (Appendix 3 Marketed Product Medication Information Section 4.3) and to β-adrenoceptor antagonists (e.g. Chronic obstructive pulmonary disease or bronchial asthma; abnormally low blood pressure or heart rate; second or third-degree heart block or congestive heart failure; cardiac failure, cardiac shock and severe diabetes).
16. Clinically significant systemic disease which might interfere with the study.
17. Participation in any investigational study within 30 days prior to screening.
18. Systemic medication including corticosteroid containing drugs that could have a substantial effect on IOP which HAVE NOT been maintained at a consistent dose and regime within 30 days prior to screening and are anticipated to change in dose and/or regimen during the study.
19. Use of topical steroid containing medications on the face or in or around the eyes will exclude the subject (see section 5.6 concomitant medications).
20. Women of childbearing potential who are pregnant, nursing, planning a pregnancy, or not using a medically acceptable and highly effective form of birth control. An adult woman is considered to be of childbearing potential unless she is one year post-menopausal (1 year without menses with appropriate clinical profile, e.g. age appropriate, > 45 years in the absence of HRT. In questionable cases the subject must have FSH value > 40mIU/mL and an estradiol value < 40pg/mL (< 140pmol/L)) or three months post-surgical sterilization.
21. Vulnerable subjects such as minors, adults under legal protection or unable to express their consent (e.g. hospitalized persons in coma), persons deprived of liberty (prisoners from jails), or persons subject to psychiatric care.

Study Population:

A total of up to 440 subjects will be enrolled in this study at approximately 60 clinical sites, comprising a total of up to 220 subjects per treatment arm for each of 2 treatment arms. Subjects will be at least 18 years of age diagnosed with OAG or OHT, each of whom meets all inclusion criteria and none of the exclusion criteria.

Investigational Product, Dose, and Mode of Administration:

- PG324 Ophthalmic Solution, 1 drop once daily (Q.D.) each evening (PM) in both eyes (OU).
- GANFORT®, 1 drop once daily (Q.D.) each evening (PM), in both eyes (OU).

Duration of Treatment:

All subjects will administer Investigational Product for approximately 180 days.

Efficacy Assessments:

Efficacy will be evaluated by:

- IOP measurements at 08:00, 10:00, and 16:00 hours at baseline and at Week 2 (Day 15), Week 6 (Day 43), and Month 3 (Day 90) by Goldmann Applanation Tonometry.

The primary efficacy outcome will be comparison of PG324 Ophthalmic Solution relative to GANFORT® for:

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

Secondary efficacy outcomes will be comparison of PG324 Ophthalmic Solution relative 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 in diurnal IOP levels

Other secondary efficacy analyses may be carried out as described in the study Statistical Analysis Plan.

Safety Assessments:
The primary safety measures in both eyes of enrolled subjects will be:

- Ocular symptoms/adverse events.
- Pachymetry and gonioscopy.
- ETDRS corrected visual acuity.
- Objective findings of biomicroscopic examinations (i.e., anterior segment examinations including evaluation of cornea, conjunctiva, lids, and lens).
- Visual field and cup-disc ratio measurements.
- Dilated ophthalmoscopy.

Other safety assessments will be:

- Systemic safety assessments as measured by heart rate, blood pressure, and clinical laboratory evaluations (including hematology and clinical chemistry).
- Pregnancy testing (for women of childbearing potential).
- Change in Self-Administered NEI Visual Functioning Questionnaire-25 (VFQ-25) score from baseline to study exit (Mangione 2001).
- Change in Self-Administered Short Form Health Survey Questionnaire 36 (SF-36 v.2) score from baseline to study exit (Ware 2000).

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

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 SD of 3.5mmHg, and a correlation between time points of 0.60 or less 200 ITT 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

Date of Original Protocol: 05 December 2016
Date of Version (Protocol Amendment 1): 27 January 2017
Date of Version (Protocol Amendment 2) – UK Specific: 07 April 2017
Date of Version (Protocol Amendment 3): 05 June 2017
Date of Version (Protocol Amendment 4): 19 March 2018
Date of Version (Protocol Amendment 5) – Hungary Specific: 06 August 2018
Date of Version (Protocol Amendment 6): 27 May 2020

Prepared in: Microsoft Word 2016

TABLE OF CONTENTS

TABLE OF TABLES

TABLE OF FIGURES

LIST OF APPENDICES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Description
AE	Adverse Event
ALT	Argon laser trabeculoplasty
AM	Morning
AR-13324	Netarsudil mesylate (drug substance) / netarsudil ophthalmic solution (drug product)
BID	Twice-daily
BOCF	Baseline observation carried forward
BP	Blood pressure
CEC	Competent Ethics Committee
CFR	Code of Federal Regulations
CTFG	Clinical Trials Facilitation Group
CI	Confidence Interval
CRF	Case Report Form
EDC	Electronic Data Capture
ETDRS	Early Treatment of Diabetic Retinopathy Study
EU	European Union
FDA	Food and Drug Administration
FDC	Fixed-dose combination
GCP	Good Clinical Practice
HR	Heart rate
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IND	Investigational New Drug
IOP	Intraocular Pressure
IP	Investigational Product
ITT	Intent-To-Treat
IWRS	Interactive web-based response system
LASIK	Laser-Assisted In-Situ Keratomileusis
LDPE	Low-density polyethylene
LOCF	Last observation carried forward
logMAR	Logarithm of the minimum angle resolvable
MedDRA	Medical Dictionary for Regulatory Activities
mmHg	Millimeters of mercury
mL	Milliliter
NEI	National Eye Institute
OAG	Open-angle glaucoma
OHT	Ocular hypertension
OTC	Over-the-counter
OU	Both Eyes
PG324	Fixed-dose combination of netarsudil and latanoprost
PM	Evening
PP	Per protocol
PRK	Photorefractive keratectomy
PRO	Patient-reported outcome

PT	Preferred term
Q.D.	Once-daily
ROCK	Rho kinase
SAE	Serious Adverse Event
SD	Standard Deviation
SF-36 v.2	Short Form (Health Survey Questionnaire, 36 questions, version 2)
SLT	Selective laser trabeculoplasty
SOC	System/Organ/Class
SSAR	Serious Suspected Adverse Reaction
SUSAR	Serious Unexpected Suspected Adverse Reaction
US	United States
VA	Visual Acuity
VFQ	Visual Function Questionnaire (NEI, 25 questions)

1. INTRODUCTION

1.1 Investigational Product

Glaucoma is a progressive optic neuropathy that causes characteristic loss of visual fields and can eventually lead to blindness. A major risk factor for glaucomatous visual field loss is elevated intraocular pressure (AGIS 2000).

The need for improved efficacy of glaucoma medications is supported by several clinical studies. Studies such as the Early Manifest Glaucoma Trial (Heijl 2002), the Ocular Hypertension Treatment Study (Kass 2002; Kass 2010), and the Collaborative Normal Tension Glaucoma Study Group (Collaborative Normal-Tension Glaucoma Study Group 1998) support the general conclusion that every millimeter of reduction in IOP is significant for delaying disease progression. This conclusion holds true not only for high risk ocular hypertensive and glaucoma subjects with elevated IOPs but also for glaucoma subjects with IOPs in the normal range. Thus, the goal for treating subjects should be to lower IOP to the point that it prevents further damage to the optic nerve and achieve this without sacrificing safety or convenience. For many individuals with glaucoma, current IOP-lowering medications are not sufficiently effective as monotherapy to achieve target IOP and the majority of glaucoma patients often need more than one drug to reach their target IOP (Lichter 2001). Increasing complexity of the dosing regimen often leads to decreased compliance with dosing. Fixed-dose combination (FDC) products such as Simbrinza® Ophthalmic Solution help simplify dosing regimens by providing two medications in a single bottle, but some FDC products marketed in the EU require twice-daily dosing. An FDC product that would provide the same efficacy as co-administration of two medications with the convenience of once daily (Q.D.) dosing may allow for better compliance from these patients.

Inhibitors of Rho kinase (ROCK) have emerged as a new class of IOP-lowering agents and are currently being tested in the clinic (Chen 2011; Kopczynski 2014). Netarsudil mesylate (AR-13324) is a novel Rho kinase and norepinephrine transporter inhibitor developed at Aerie Pharmaceuticals, Inc. for topical ophthalmic use for lowering IOP. In both rabbit and monkey studies, netarsudil produces large reductions in IOP with a longer duration of action than reported for previously characterized Rho kinase inhibitors. Netarsudil Ophthalmic Solution has been shown to provide significant IOP lowering when dosed once-daily in the evening (AR-13324-CS202), and reduces IOP potentially through several mechanisms: increasing trabecular outflow (Wang 2014), decreasing aqueous humor production (Wang 2015), and reducing episcleral venous pressure (Kiel 2015). The ability to reduce aqueous production may be related to netarsudil *in vitro* inhibitory activity against monoamine transporters, including the norepinephrine transporter.

Prostaglandin analogues are highly effective at lowering IOP when dosed once daily in the evening, primarily acting on uveoscleral outflow. Because netarsudil lowers IOP through different mechanisms of action than prostaglandin analogues, netarsudil should provide additional IOP-lowering efficacy when used in combination with a prostaglandin analogue. An FDC of netarsudil and latanoprost, PG324 (PG324 Ophthalmic Solution), was therefore

tested as a topical solution to include the known latanoprost mechanism of increasing uveoscleral outflow. Based on this rationale, a fixed-dose combination of AR-13324 (0.01% or 0.02%) and latanoprost (0.005%) dosed Q.D. (PM) was investigated in a double-masked, parallel-group study (Lewis 2015; PG324-CS201). In this study PG324 0.02% provided clinically relevant and statistically superior ocular hypotensive efficacy relative to its individual active components at the same concentrations. The only safety finding of note was transient asymptomatic conjunctival hyperemia which was of mild severity approximately 80% of the time when it occurred.

The present investigation is designed to evaluate PG324 in a controlled study compared to a fixed dose combination of bimatoprost and timolol (GANFORT®, Bimatoprost 0.03% and timolol maleate 0.5% ophthalmic solution, GANFORT®) in a study of 6 months duration.

1.2 Findings from Non-Clinical and Clinical Studies

Non-Clinical

Proof of concept for netarsudil in lowering IOP was established in primary pharmacology studies in 2 species, rabbits and monkeys. Safety pharmacology (central nervous system and cardiovascular) of netarsudil was investigated in rats and dogs. Pharmacokinetics/bio distribution of netarsudil was assessed after systemic and ocular administration of netarsudil. Ocular toxicity was investigated in studies up to 6 months in rabbits and up to 9 months in monkeys. Repeated dose toxicity of systemically administered netarsudil was investigated in studies up to 28 days in rats and dogs. The non-clinical program for netarsudil also included a standard range of genotoxicity tests.

PG324 is a FDC of one approved drug (latanoprost) and one unapproved drug at an advanced stage of development (netarsudil), which has undergone non-clinical testing as summarized above. In primary pharmacology studies in 2 species, rabbits and monkeys, the topically applied FDC product PG324 was effective in lowering IOP. The non-clinical programs for PG324 further included a 3-month ocular toxicity study in rabbits. In this study, the addition of latanoprost had no unexpected consequences of toxicological significance.

Clinical

The clinical development of netarsudil ophthalmic solution monotherapy is significant as it relates to clinical development of PG324 in a number of respects, including pharmacokinetics, tolerability and dose-response investigations. The assessment of the ocular and systemic safety of netarsudil 0.02% in Phase 1 clinical study (AR-13324-CS101) and Phase 1 Clinical study (Clinical Study Report AR-13324-CS102) has been completed. The investigation of the efficacy of the 3 doses of netarsudil (0.01%, 0.02% and 0.04%) were evaluated over 7 days (AR-13324-CS201). The 0.02% and 0.04% doses showed similar reduction of IOP, which was higher relative to the 0.01% dose. It was therefore concluded that the top of the dose response curve was reached at the 0.02% netarsudil concentration and this was selected as the appropriate concentration of netarsudil ophthalmic solution for further development.

A Phase 3 clinical study (AR-13324-CS302) evaluating the safety and efficacy netarsudil 0.02% has been completed. This study compared netarsudil 0.02% Q.D. and BID and Timolol 0.5% BID, and concluded that netarsudil 0.02% Q.D. was safe, generally well tolerated and provided IOP lowering that was non-inferior to timolol in subjects with OAG and OHT. Netarsudil 0.02% BID provided slightly larger IOP reductions but had a less favourable safety profile and therefore netarsudil 0.02% Q.D. was recommended as the dose for clinical use.

As several different concentrations of netarsudil had already been evaluated with regard to efficacy and safety during netarsudil clinical development, no separate Phase 1 pharmacokinetic studies were conducted with the FDC PG324. Based on the results obtained from the netarsudil program, it was decided to conduct a four arm Phase 2 study comparing two doses of PG324 (either 0.01% or 0.02% AR-13324 in combination with 0.005% latanoprost) against AR-13324 0.02% and latanoprost. The Phase 2 study (PG324-CS201) has been completed demonstrating superiority of the PG324 combinations over 0.02% AR-13324 and 0.005% latanoprost alone. PG324 0.02% showed better IOP lowering than 0.01% and was selected for further development in Phase 3.

Two pivotal Phase 3 studies (PG324-CS301 and PG324-CS302) have been completed comparing PG324 with its components to demonstrate superiority and safety. In addition to these 2 pivotal studies a supportive study will be conducted comparing PG324 to a fixed dose combination therapy containing a prostaglandin analogue (PGA). Following review of the study through scientific advice procedure with the EMA, Aerie Pharmaceuticals have agreed to GANFORT® as the comparator. In addition, the EMA has reviewed and accepted the masking procedures as documented in this protocol.

Detailed information on nonclinical and clinical studies completed with netarsudil and PG324 is provided in the Investigator's Brochure.

1.3 Risks and Benefits to Human Subjects

As no other FDCs of this class are approved, and only early stage clinical experience is available, the risks and benefits are not well understood at this time. Given the pharmacology of this class of agents and the results of previous Phase 1, Phase 2, and Phase 3 clinical studies by the Sponsor (Clinical Study Reports AR-13324-CS101, AR-13324-CS102, AR-13324-CS201, AR-13324-CS202, AR-13324-CS301, PG324-CS201, AR-13324-CS302, AR-13324-CS304, PG324-CS301 and PG324-CS302), it is expected that adverse events seen in clinical trials individually with latanoprost and netarsudil-containing ophthalmic formulations may be observed with PG324. The reader should refer to the Investigator's Brochure for more detailed information on potential risks due to use of netarsudil and PG324 ophthalmic solutions.

The major potential benefit from exposure to PG324 is reduction in IOP in subjects with open angle glaucoma or ocular hypertension. A sequela of reduced IOP could be slowing of disease progression and preservation of vision in subjects for longer times when measured over periods of months to years.

2. STUDY OBJECTIVES

2.1 Primary 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

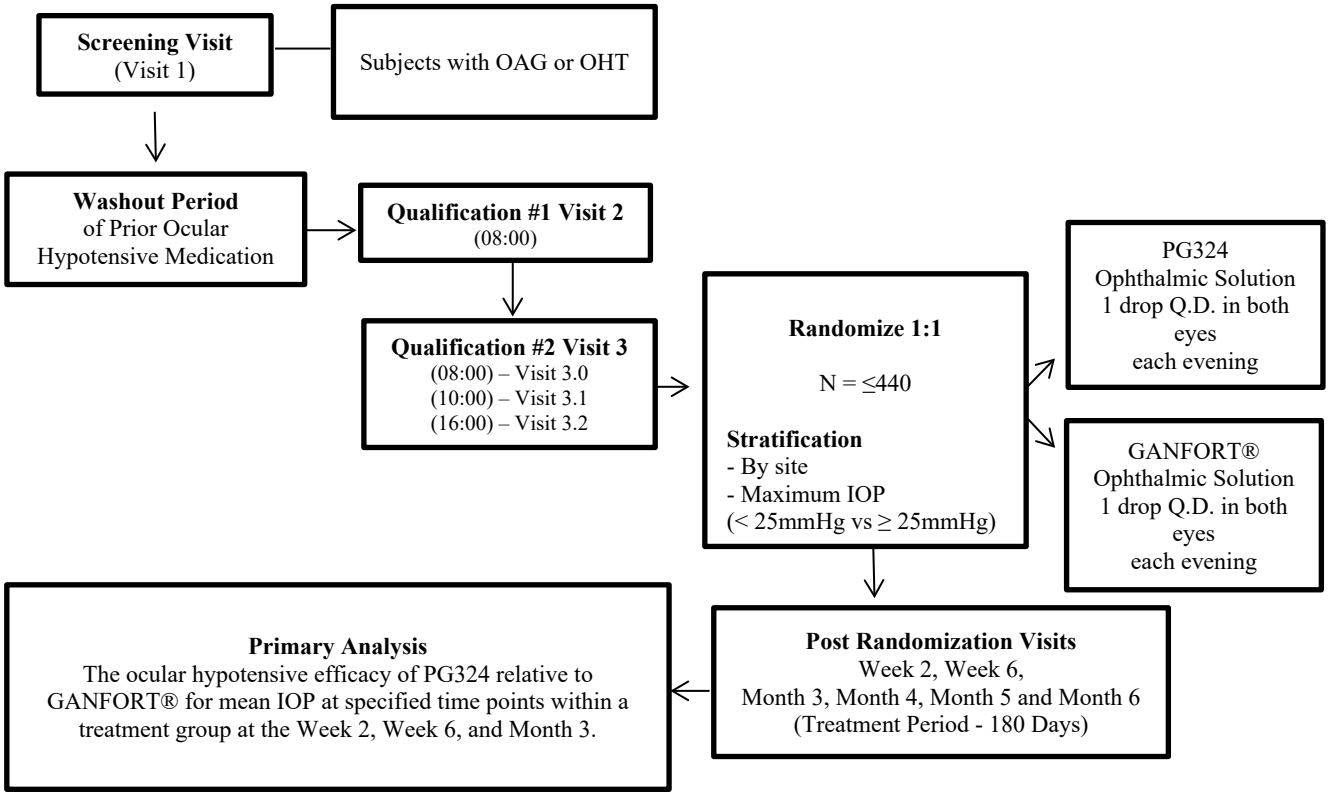
2.2 Secondary Objectives

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®

3. STUDY DESIGN

Figure 1 Study Design



3.1 Overall Study Design and Plan

This is a 6-month, double-masked, randomized, multicenter, active-controlled, parallel-group efficacy and safety trial for reduction of elevated IOP with PG324 Ophthalmic Solution compared to GANFORT® Ophthalmic Solution, in subjects at least 18 years of age with OAG or OHT.

Subjects eligible to be enrolled in this study will be those with a diagnosis of either OAG or OHT that are on treatment with a topical ocular hypotensive medication. Up to 440 subjects will be enrolled in this study.

Participating subjects who have signed a consent form will attend up to 9 study visits. The study duration for an enrolled subject will be approximately 180 days from Visit 1 (Screening) to the last visit (Visit 9 [Day 180 ± 7 days]). Visit 1 will occur up to approximately 4 weeks prior to Visit 2 [Qualification Visit #1], depending on the washout period required for previous IOP medication. Eligible subjects who have met all the inclusion criteria and none of the exclusion criteria will be enrolled and assigned masked study medication at Qualification Visit # 2. Eligible subjects will be randomized in a 1:1 ratio to receive PG324 or GANFORT® stratified by investigative site and maximum baseline IOP < 25mmHg vs ≥ 25mmHg.

Randomized subjects will dose the assigned investigational product (IP) as a single drop in both eyes once daily (Q.D.) in the evening (between 20:00 and 22:00 hours) beginning on Day 1 and up to and including the evening prior to the Month 6 study visit. Significant effort will be made to ensure adequate masking of all IP for both subjects and clinical staff. For subjects deemed unable to self-administer, a guardian or an alternative person will be asked to administer the medication.

Enrolled subjects will return on Week 2, Week 6, Month 3, Month 4, Month 5 and Month 6 for efficacy and/or safety assessments. Efficacy assessments for the first 3 months of the study will focus on careful monitoring of IOP at each study visit at 3 different times (08:00, 10:00 and 16:00 hours) during each study visit. These data will be used to evaluate the primary efficacy endpoint of mean IOP at 08:00, 10:00 and 16:00 hours at the Week 2, Week 6 and Month 3 study visits.

Subsequent visits at Month 4, Month 5 and Month 6 will focus primarily on safety and will include IOP measurements at 10:00 hours.

At each study visit, multiple ocular and systemic safety assessments will be conducted including some or all of the following: systemic safety assessments (heart rate, blood pressure and clinical laboratory evaluations [including hematology,]) pregnancy testing (for women of childbearing potential) ocular symptoms/ adverse events, ETDRS corrected visual acuity, objective findings of biomicroscopic evaluations (i.e. anterior segment evaluations including evaluation of cornea, conjunctiva and lens), visual field and cup disc ratio measurements, dilated ophthalmoscopic examination and Quality of Life assessments.

For subjects who discontinue early, every possible effort will be made to assure there is a final visit that includes all examinations listed for Visit 9.0 (Month 6) and dilated ophthalmoscopy.

3.2 Rationale for Study Design and Dosing Regimen

In order to further evaluate the non-inferiority of the FDC PG324 relative to the ocular hypotensive efficacy of an approved FDC product in subjects with elevated IOP and to generate additional safety data for PG324, a parallel group, double-masked, 2 arm study design was selected.

As the intended route of administration for PG324 Ophthalmic Solution is topical ocular, this is the route to be used in this study. The dosage regimen selected for this study is based on study PG324-CS201 (Bacharach 2015) the treatment period and dosing frequency is selected on the basis of preclinical safety studies with PG324 and regulatory requirements for demonstration of ocular hypotensive efficacy.

3.3 Expected Duration of Subject Participation

Each subject is planned to undergo a washout period of their current ocular hypotensive medications, followed by approximately 180 days of treatment with IP. A temporary study treatment interruption may be permitted at the request of the Investigator on a case-by-case basis and following consultation with the Sponsor/Sponsor representative.

4. STUDY POPULATION SELECTION

4.1 Study Population

A total of approximately 440 subjects will be enrolled in this study at approximately 60 sites in approximately 12 EU countries comprising a total of up-to 220 subjects per each treatment arm for each of the two treatment arms. Subjects enrolled to this study will be those at least 18 years of age with diagnosed OAG or OHT, who are currently using topical IOP-lowering medication. Inclusion criterion 4 specifies that subjects must present with medicated IOP at screening of ≥ 17mmHg in at least one eye and < 28mmHg in both eye and, in the opinion of the investigator, require a change in IOP therapy. The lower limit IOP is based on the guidelines issued by the European Glaucoma Society and current clinical practice in Europe with respect to initiating alternative therapy. The upper limit IOP is selected to exclude subjects who may require more aggressive therapy than a FDC to prevent glaucoma progression. Inclusion criterion 5 states that following a washout period from current IOP therapy, patients must present with an unmedicated IOP of > 20mmHg in at least one eye and < 36mmHg in both eyes at 2 qualification visits at 08:00 hour, 2-7 days apart and at the second qualification visit, have IOP > 17mmHg in at least one eye and < 36mmHg in both eyes at 10:00 and 16:00 hours. The upper limit was chosen to exclude subjects who require a more aggressive therapy than a FDC to prevent glaucomatous damage.

Subjects MUST meet all the inclusion criteria and none of the exclusion criteria.

Planned enrollment numbers are higher than statistically required for demonstrating efficacy (approximately 200 intent-to-treat subjects per arm for 85% power) 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. Over-enrollment is to be undertaken only after communication between the investigational site and the Sponsor representative.

4.2 Subject Inclusion Criteria

Subjects must qualify in at least one eye. See Section 8.4 for more information on statistical analysis of the study eye. **ALL TREATMENTS WILL BE DOSED TO BOTH EYES. (OU)**

Subjects have to meet all of the following criteria at screening and qualification visits to enter into the study:

1. Must be 18 years of age or older.

2. Diagnosis of OAG or OHT in both eyes (OAG in one eye and OHT in the fellow eye is acceptable).

3. Subjects insufficiently controlled and/or subjects considered in need for combination therapy by the investigators.

4. Medicated intraocular pressure ≧ 17 mmHg in at least one eye and < 28mmHg in both eyes at screening visit.

5. Unmedicated (post-washout) IOP >20mmHg in at least one eye and < 36mmHg in both eyes at 2 qualification visits at 08:00 hour, 2-7 days apart. At the second qualification visit, have IOP >17mmHg in at least one eye and < 36mmHg in both eyes at 10:00 and 16:00 hours. **Note: For purposes of determining eligibility of subjects to be enrolled, the non-integral IOP mean number will be used. Any non-integral mean IOP number should not be rounded.** If only one eye qualifies at the second qualification visit it MUST be the same eye that qualified on the first visit and this will be the study eye for the duration of the study.

6. Best corrected visual acuity +1.0 logMAR or better by ETDRS in each eye (equivalent to 20/200 or better Snellen visual acuity in each eye).

7. Be able and willing to give signed informed consent and follow study instruction.

8. Women must be either of non-childbearing potential, or women with childbearing potential and men with reproductive potential must be willing to practice acceptable methods of birth control during the study.

9. Women of childbearing potential must have a negative urine pregnancy test within 7 days of first dose of study treatment and agree to use highly effective contraception during the study and for 3 months after the last dose of study medication.

10. Men with a female partner of childbearing potential must have either had a prior vasectomy or agree to use an effective form of contraception from time of randomization and for 3 months following the last dose of study medication.

11. In France, a subject will be eligible for inclusion in this study only if either affiliated to or as a beneficiary of a social security number.

4.3 Subject Exclusion Criteria

Individuals with the following characteristics will be excluded from the study:

Ophthalmic:

1. Clinically significant ocular disease (e.g., corneal edema, uveitis, or severe keratoconjunctivitis sicca) which might interfere with interpretation of the study efficacy endpoints or with safety assessments, including subjects with glaucomatous damage so severe that washout of ocular hypotensive medications for 4 weeks or longer if needed is not judged safe as it would put the subject at risk for further vision loss.

2. Pseudoexfoliation or pigment dispersion component glaucoma, history of angle closure glaucoma, or narrow angles i.e. Grade 2 Shaffer (Chan 1981) or less extreme narrow angle with complete or partial closure. Note: Previous laser peripheral iridotomy is NOT acceptable.

3. Intraocular pressure ≥ 36mmHg (unmedicated) in either eye (individuals who are excluded for this criterion are not allowed to attempt requalification), or use of more than two ocular hypotensive medications within 30 days of screening. Note: fixed dose combination medications, for the purpose of this exclusion criterion, count as one medication. However, subjects currently taking 2 fixed dose combination products are excluded.

4. Treatment-naïve subjects.

5. Prior treatment with GANFORT® topical eye drops where the subjects IOP did not achieve the target IOP and was considered either a therapeutic failure or to have insufficient response. Subjects currently (immediately prior to screening visit) being treated with GANFORT® are excluded from the study.

6. Known hypersensitivity to any component of the investigational formulations to be used (e.g., benzalkonium chloride) or to fluorescein.

7. Previous glaucoma intraocular surgery, including SLT or ALT in either eye.

8. Refractive surgery in either eye (e.g., radial keratotomy, PRK, LASIK, corneal cross-linking, keratoplasty).

9. Ocular trauma within the six months prior to screening, or ocular surgery or non-refractive laser treatment within the three months prior to screening.

10. Recent or current evidence of ocular infection or inflammation in either eye. Current evidence of clinically significant blepharitis, conjunctivitis, keratitis, current evidence or history of herpes simplex or zoster keratitis in either eye at screening.

11. Use of ocular medication in either eye of any kind within 30 days of screening and throughout the study, with the exception of a) ocular hypotensive medications which must have been the same medication for 30 days prior to screening (which must be washed out according to the provided schedule), b) lid scrubs (which may be used prior to, but not after, screening), c) lubricating drops for dry eye (which may be used throughout the study), as prescribed by the Investigator.

12. Mean central corneal thickness greater than 620µm at screening.

13. Any abnormality preventing reliable Goldmann applanation tonometry of either eye (e.g., keratoconus).

Systemic:

14. Clinically significant abnormalities in laboratory tests at screening.

15. Known hypersensitivity or contraindication to GANFORT® (Appendix 3 Marketed Product Medication Information Section 4.3) and to β-adrenoceptor antagonists (e.g. Chronic obstructive pulmonary disease or bronchial asthma; abnormally low blood pressure or heart rate; second or third-degree heart block or congestive heart failure, cardiac failure, cardiac shock and severe diabetes).

16. Clinically significant systemic disease which might interfere with the study.

17. Participation in any investigational study within 30 days prior to screening.

18. Systemic medication including corticosteroid containing drugs that could have a substantial effect on IOP which HAVE NOT been maintained at a consistent dose and regime within 30 days prior to screening, and are anticipated to change in dose and/or regime during the study.

19. Use of topical steroid containing medications on the face or in or around the eyes will exclude the subject (see Section 5.6 Concomitant Medications).

20. Women of childbearing potential who are pregnant, nursing, planning a pregnancy, or not using a medically acceptable and highly effective form of birth control. An adult woman is considered to be of childbearing potential unless she is one year post-menopausal (1

year without menses with appropriate clinical profile, e.g. age appropriate, > 45 years in the absence of HRT. In questionable cases the subject must have FSH value ≥ 40mIU/mL and an estradiol value < 40pg/mL (< 140pmol/L)) or three months post-surgical sterilization.

21. Vulnerable subjects such as minors, adults under legal protection or unable to express their consent (e.g. hospitalized persons in coma), persons deprived of liberty (prisoners from jails), or persons subject to psychiatric care.

5. STUDY TREATMENTS

5.1 Description of Treatments

5.1.1 Investigational Product

PG324 Ophthalmic Solution is a sterile, isotonic, buffered aqueous solution containing netarsudil 0.02%, latanoprost 0.005%, boric acid, mannitol, water for injection, and preserved with benzalkonium chloride (0.02%). The product formulation is adjusted to approximately pH 5. PG324 is a colorless to slightly yellowish solution (PG324 Safety data sheet).

5.1.2 Comparator

GANFORT® (bimatoprost 0.03% / timolol maleate 0.5% ophthalmic solution) is a sterile, buffered aqueous solution containing sodium chloride, sodium phosphate dibasic heptahydrate, and citric acid monohydrate and preserved with benzalkonium chloride (0.005%). GANFORT® is a colorless to slightly yellow solution (GANFORT® SmPC).

5.2 Treatment of Subjects

Subjects will be randomized to receive IP (PG324 Q.D. or the active comparator (GANFORT® Q.D.). All treatments will be both eyes (OU). Subjects will instill 1 drop of study drug into each eye, one time per day in the evening between 20:00 and 22:00 hours (including days when the subject is scheduled to visit the study site). Doses will be administered by the study subjects. For subjects deemed unable to administer the doses, a guardian or alternative person will be asked to administer the medication. All subjects will administer study treatment for approximately 180 days.

5.3 Selection of Timing of Dose for Each Subject

The dose of PG324 selected for this study is based on the positive outcomes seen for PG324 in the PG324-CS201 clinical study. Each IP dose is being administered Q.D. OU in the evening (between 20:00 and 22:00 hours including days when the subject is scheduled to visit the study site) in this study to allow for estimated peak and trough levels of both netarsudil and latanoprost to be present in ocular tissue at the observation times selected in the clinic for the following morning and the subsequent afternoon. The treatment period is

selected on the basis of non-clinical safety studies and regulatory requirements for studies of ophthalmic glaucoma medications.

5.4 Method of Assigning Subjects to Treatment

A randomization code for allocating the treatments will be prepared by an independent biostatistician, who is not involved in the day-to-day conduct of the study. Subjects will be randomized in a 1:1 ratio to receive PG324 or GANFORT® stratified by Investigative site- and maximum baseline IOP < 25mmHg and ≥ 25mmHg.

5.5 Masking

The European Medicines Agency through the scientific advice procedure has agreed to the masking procedures documented in this section.

To minimize unmasking due to the differences in bottle closure cap color, clinical supplies will be packaged in identical outer containers labeled appropriately for clinical trial use as detailed in Section 5.9 of this document.

Differences in the physical characteristics of the PG324 and GANFORT® are minimal and should not pose a significant risk to the masking of the study. Both are essentially colorless liquids of equivalent viscosity which in individual eye drops are indistinguishable to subjects taking part in the study.

Treatment assignments will be masked to the Investigator, the clinical study team, Sponsor/ Sponsor representative working on behalf of the Sponsor, personnel involved in day to day study management, Monitors, Data Managers, and Statisticians), and the subjects for the duration of the study.

Masking of treatment assignment of study supplies is planned to be achieved via both IP packaging/labelling operations and as instructed in the study Pharmacy Manual.

5.5.1 Operational Measures at Study Sites

Study related site personnel will be instructed that the subject kits are not to be opened at the clinical site by staff involved in IOP measurements or safety assessments both at the time of IP dispensation as well as upon collection of the returned IP by the subjects at the defined visits. Study site staff member(s) not responsible for performing intraocular measurements and safety assessments will be assigned to accept and confirm receipt of IP shipments, to manage any temperature excursions, to dispense IP to the subjects at the defined visits and collect unused or returned IP, and to ensure the IP is stored as instructed by the label. The unmasked staff will also maintain the drug accountability records.

An unmasked monitor will be assigned to each site. During pre-study activities at each selected site it will be confirmed that unmasked staff is available to accept and document receipt of IP. The unmasked monitor will confirm IP storage and dispensing facilities are appropriate for the study and will ensure the unmasked site staff is adequately trained and the

training is documented. The unmasked monitor will confirm that unmasked site staff has the facilities to maintain study documentation that may unmask the masked site staff in a separate and limited access location. The unmasked monitor will be responsible for responding to study related questions from unmasked site staff for the duration of the study.

Throughout the course of the study and during unmasked monitoring visits, the unmasked monitor will check the integrity of the treatment masking and will communicate all unmasked monitoring activities in a separate monitoring report. The unmasked monitor will confirm access to the IP remains limited to unmasked site staff only (e.g. pharmacist) involved in the day to day management and storage of IP and dispensing and collection of returned/used or expired IP. The unmasked monitor will perform drug accountability of IP, storage of IP and dispensing and collection of returned/used IP.

Treatment assignment(s) will be unmasked and made available to the Investigator and the Sponsor's Medical Monitor/Designee during the study only in case of medical emergency or occurrence of adverse events that in the opinion of the investigator warrant unmasking. In the absence of medical need, the randomization code/treatment assignment(s) will not be available to the above study personnel until after the study is completed and the database is locked. All medical management (including the Medical Director and Medical Scientist who will review the line listings and AE's for the study) will remain masked for the duration of the study.

If the Investigator feels it is necessary to unmask a subject's treatment assignment in the event of an emergency situation, the Investigator will perform the unmasking through the IWRS or other randomization system. The treatment assignment will be revealed on a subject-by-subject basis, thus leaving the masking on remaining subjects intact.

In the case of such unmasking in an emergency situation, the Investigator should contact the Sponsor/Sponsor representative immediately thereafter and document the unmasking in writing, recording the date, time, and reason for unmasking the study drug treatment in the source documentation.

Once the subject is unmasked there is no requirement for the Medical Monitor to be informed of the treatment assignment. Individual unmasking by the Investigator will result in withdrawal of the subject from the study and should only be performed for the specific subject requiring unmasking in their treatment group.

5.6 Concomitant Medications

As noted in Section 5.7.1, subjects are required to undergo a washout of their current ocular hypotensive medications. Intermittent use of over-the-counter (OTC) artificial tear lubricant products is acceptable, with a minimum of 10 minutes between OTC products and study medication. However, concurrent therapy with any form of ocular hypotensive medications (prescription or OTC) is not allowed during the study.

Disallowed ocular medications include:

- Miotics.
- Epinephrine-related compounds.
- Carbonic anhydrase inhibitors (ocular or systemic).
- α-adrenoceptor agonists.
- β adrenoceptor antagonists
- Muscarinic agonists (e.g., pilocarpine).
- Prostaglandin analogues.
- Routine (e.g. daily) and intermittent use if topical medication containing steroids on the face or topical eye drops containing steroids is NOT permitted at any time during the study.

Systemic therapy with agents including corticosteroids that could influence IOP is to be consistent in dose, regimen and agent within the 30 days prior to screening and throughout the study. For example, a subject can be treated with a systemic β-adrenoceptor antagonist as long as the particular agent and its dose and regimen had been consistent for the 30 days prior to screening, and there is no reason to believe that alteration would be necessary at some point later during the study. Subjects should be cautioned to avoid use of alcohol or the use of any drugs such as cannabis or marijuana during the study visit days.

Intermittent use of topical steroids for certain skin conditions (but not on the face) may be permitted following consultation with and approval from the Medical Monitor if dosing has been intermittent for 90 days prior to screening and no alteration to the dosing regimen is anticipated during the 6-month study participation.

Contact lens wear during the study is acceptable. However, subjects must remove their contact lenses at least 30 minutes before instillation of study medication, and not place them in their eye(s) until 30 minutes after instillation.

As detailed in the GANFORT® SmPC Section 4.5 (Appendix 3) there is a potential for additive effects resulting in hypotension, and/or marked bradycardia when ophthalmic solution containing beta-blockers (timolol) is administered concomitantly with oral calcium channel blockers, guanethidine, beta-adrenergic blocking agents, parasympathomimetics, anti-arrhythmics (including amiodarone) and digitalis glycosides.

Potentiated systemic beta-blockade (e.g., decreased heart rate, depression) has been reported during combined treatment with CYP2D6 inhibitors (e.g. quinidine, fluoxetine, paroxetine) and timolol.

Mydriasis resulting from concomitant use of ophthalmic beta-blockers and adrenaline (epinephrine which is prohibited) has been reported occasionally.

Epinephrine is not permitted to be used concomitantly during the subject's participation in the study. Concomitant use of the other medications is at the discretion of the investigator who must assess if the subject should participate in the study based on the potential interactions listed in Section 4.5 of the GANFORT® SmPC.

Use of all medications should be documented on the appropriate CRF. Investigators are encouraged to contact the Sponsor/Sponsor representative for any questions regarding allowed medications. Judgment of continued study participation by the subject, and inclusion of this subject's subsequent visits in the safety and efficacy analysis will be made by the Sponsor.

All medications which the subject has taken within 30 days prior to screening and during the study will be recorded in 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 in the CRF.

5.7 Restrictions

5.7.1 Prior Therapy Washout period

To qualify subjects must have been taking the same IOP lowering medication for 30 days prior to screening. Subjects must undergo a minimum washout period as specified in Table 1. For prostaglandins the minimum washout period should be not less than 4 weeks and it may be extended if deemed necessary in investigator opinion.

Washout should not extend beyond 8 weeks (56 days). If for logistical or other reasons, the washout period needs to be extended beyond 8 weeks (56 days), the Sponsor should be contacted. Washout period can start at any time following the screening visit but the period between the screening (Visit 1) and qualification 1 (Visit 2) MUST not exceed 56 days.

The main risk associated with a wash period is an increase in IOP requiring immediate intervention. Therefore, the investigator must monitor the subject regularly during the washout period, ideally every week.

Table 1 Ocular Hypotensive Medication Washout Period

Medication class	Minimum washout period
Prostaglandin analogues	4 weeks
β-adrenoceptor antagonists	4 weeks
Adrenergic agonists (including α-agonists such as brimonidine and apraclonidine)	2 weeks
Muscarinic agonists (e.g., pilocarpine), Carbonic anhydrase inhibitors (topical or oral)	5 days

Stewart 2001, Hughes 2005 and European Glaucoma Society November 2011.

5.7.2 Fluid and Food Intake

There are no general restrictions on fluid or food intake for subjects participating in this study.

5.7.3 Subject Activity Restrictions

On days which diurnal IOP measurements are made, subjects may not engage in strenuous activity. Otherwise, there are no restrictions on subject activities during their participation in this study.

5.8 Treatment Compliance

All subjects will be instructed on the importance of following the once-daily dosing regimen. Dosing should occur in the evening between 20:00 and 22:00 hours. As no commercially available method is readily available for direct, single-container monitoring of treatment adherence with multi-dose ophthalmic products, no formal measure of treatment compliance is planned. Subjects should be reminded at all visits to dose every evening. In addition, subjects will be provided with a paper and electronic dosing reminder.

If a dose of study medication is missed the subject should take the next dose as planned. The dose of study medication should not exceed one drop daily in both eyes.

5.9 Packaging and Labeling

The container-closure systems for the two products are both multi-dose ophthalmic dropper dose bottles. The commercial label from the comparator will be removed and replaced with an investigational label which will be similar in appearance for both treatment groups. The labeled bottles will be packaged in identical appearing subject kits to ensure adequate masking.

The container-closure systems for the IP are both multi-dose ophthalmic dropper dose bottle. All clinical trial material packers (containing subject kits) and subject kits containing the bottles will be identical in appearance. A clinical trial material packer, which contains subject kits sufficient for the intended dosing period(s), will be packaged and provided to the site for

dispensation to the subjects. Subject packers therefore contain sufficient kits for an individual subject that will be distributed during this study.

Clinical supplies of PG324 and GANFORT® will be in a dropper dose bottle containing a volume of no less than 2.5 mL. The container-closure system used for PG324 in this clinical study is a clear, multi-dose low density polyethylene (LDPE) dropper dose ophthalmic bottle with a white polypropylene cap. The container-closure system used for GANFORT® in this clinical study is a white, multi-dose LDPE dropper dose ophthalmic bottle with a blue polystyrene cap (which is the presentation of the commercial product). Each packaged unit will be labeled with an investigational label with the minimal information required per the regulatory requirements of EU Guidelines to Good Manufacturing Practice. Once open, IP may only be used for 28 days.

5.10 Handling and Storage of Investigational Product

Investigational Product must be dispensed or administered according to the procedures prescribed in this protocol. Only subjects enrolled in the study may receive IP, in accordance with all the applicable regulatory requirements. Only authorized staff is allowed to dispense these medications.

Under normal conditions of handling and administration, IP is not expected to pose significant safety risk to site staff. Adequate precautions must be taken to avoid direct contact with IP.

Investigational Product will be stored in a secure area under the appropriate physical conditions for the product. Access to the IP will be limited to authorized site staff only. The IP will be stored as directed on the drug label (2°C to 8°C/ 36°F to 46°F). Temperature of the IP storage location at the site is to be monitored using a calibrated monitoring device and documented.

At time of dispensing, the subject will be instructed to store the bottle(s) as directed on the drug label (2°C to 8°C/ 36°F to 46°F). The bottle(s) must be protected from light, and is recommended to be stored in the carton provided at all times; further, the bottle must be used for no longer than 28 days once opened.

5.11 Investigational Product Retention at Study Site

5.11.1 Receipt and Disposition of Study Medication

Investigational Product will be shipped to the Investigator's site from a central depot. The unmasked study site personnel at the Investigator's site (see Section 5.5.1) will verify study medication shipment records by comparing the shipping documentation accompanying the study medication to the study medication actually received at the Investigator's site. If a discrepancy is noted, the appropriate individual at the Sponsor or designee must be notified immediately. The responsible person (e.g., unmasked pharmacist)

at the Investigator's institution has to account for all used, partially used and unused IP. The unmasked staff will also maintain the drug accountability records.

5.11.2 Return of Study Medication

When the site is closed, the study is completed or is terminated by the Sponsor; all study material including used and unused study IP will be returned to the Sponsor's designee. All IP medication accounting procedures must be completed before the study is considered to be concluded. The responsible person at the Investigator's institution has to account for all used, partially used and unused IP. The unmasked monitor will complete a study drug returns form or equivalent that will be signed by the Investigator or designee prior to returning the used and unused IP to the Sponsor's designee.

5.11.3 Completed subject

A completed subject is defined as one who completes all 6 months (180 days) of planned participation.

5.11.4 Non-completing subject

A non-completing subject is defined as one who exits the study by their own volition or at the discretion of the Investigator and/or the Sponsor Safety Officer/designee. Any subject may decide to voluntarily withdraw from the study at any time without prejudice. In the event that discontinuation of treatment is necessary, the Investigator will make every attempt to complete all subsequent safety assessments listed for Visit 9.0 (Day 180) as well as dilated ophthalmoscopy.

Per Section 5.5.1, unmasking of a subject by the investigator will result in withdrawal of the subject from the study.

The subject may also be discontinued from the study for the following reasons:

- **Lack of efficacy** (as demonstrated by IOP measurements and investigator decision that there is a risk of additional glaucomatous damage if the subject continues in the study).
- **Adverse Events** (adverse events including, in the opinion of the investigator, clinically relevant laboratory abnormalities and intercurrent diseases reported by the subject or observed by the investigator with documentation on the case report form [CRF]).
- **Withdrawal of consent**.
- **Non-compliance** (e.g., non-adherence to scheduled follow-up visits or non-compliance with dosing of medication and/or scheduled follow-up visits).
- **Lost to Follow-up**.
- **Disallowed concurrent medication**.

- **Investigator Decision**.
- **Protocol Deviation**.
- **Death**.
- **Other**.

5.11.5 Actions After Discontinuation

All subjects who discontinue IP due to a report of an AE must be followed-up and provided appropriate medical care until their signs and symptoms have remitted or stabilized or until abnormal laboratory findings have returned to acceptable or pre-study limits. At any time after completion of study treatment, the investigator may report any AE that they believe possibly related to study treatment or important for the clinical understanding of an AE.

For the subject who chooses to withdraw consent or who is non-compliant, every possible effort should be made by the Investigator to assure there is a final visit that includes all examinations listed for Visit 9.0 (Exit) and dilated ophthalmoscopy.

Subjects should not take part in another clinical trial within 30 days of withdrawing or completing the study.

5.11.6 Study and Site Closure Discontinuation of the Entire Study

The entire study may be discontinued at a given site (by the Investigator or the Sponsor/ Sponsor representative or at all sites (by the Sponsor). Aerie reserves the right to temporarily or permanently terminate the study at any time for reasons including but not limited to safety issues, ethical issues, or severe non-compliance. If Aerie determines that such action is required, Aerie or its representative will discuss the reasons for taking such action with the investigator or head of the medical institution (where applicable). When feasible, Aerie will provide advance notice to the investigator or head of the medical institution of the impending action. If a study is terminated or suspended for any reasons, Aerie or its representative will promptly inform all investigators, heads of institutions (where applicable and /or the institutions conducting the study. Aerie or Sponsor representative on behalf of Aerie will also promptly inform the relevant regulatory authorities/ IEC/ CECs of the suspension/termination with the reasons for such actions where required.

5.11.7 Completed study

The study is completed when the last visit of the last subject has completed at the last site of all the countries taking part in the study. The Sponsor representative will be in communication with investigational sites regarding study completion.

5.11.8 Procedure After the Completion of the Study

When the study is completed, the Investigator will provide the governing IEC/ CEC with a brief report.

5.12 Method and timing for Assessing, Recording, and Analyzing of Efficacy parameters

As detailed in subsequent sections and Appendix 1 describing each visit, IOP will be measured at a screening visit, at 2 qualification visits after washout of ocular hypotensive medications as required, and frequently throughout the study.

6. STUDY PROCEDURES

Please see Appendix 1 for schedule of visits and examinations and Appendix 2 for detailed description of study procedures

6.1 Informed Consent

Prior to any study procedures, the study will be discussed with each subject and subjects wishing to participate must give written informed consent. The verbal explanation of the study will cover all the elements specified in the written information provided for the subject. The Investigator will inform the subject of the aims, methods, anticipated benefits and potential hazards of the study, including any discomfort it may entail. The subject must be given every opportunity to clarify any points he/she does not understand and, if necessary, may ask for more information. At the end of the interview, the subject should be given time to reflect. Subjects then will be required to sign and date the informed consent form.

The informed consent form must have received approval/favorable review by a properly constituted IRB/IEC/CEC prior to use. A copy of the signed and dated consent document will be given to each subject. The original signed and dated informed consent document must be maintained in the study files at the Investigator's site.

The Investigator or staff is responsible for ensuring that no subject is subject to any study-related examination or activity before the subject has given written informed consent. It should be emphasized that the subject is at liberty to withdraw consent to participate at any time, without penalty or loss of benefits to which the subject is otherwise entitled. Subjects who refuse to give, or withdraw, written informed consent may not be included or continued in this study, and should be notified that discontinuation from the study will not impact on their subsequent care.

6.2 Demographics and Medical History

Demographic data and any ongoing medication use will be collected and recorded. Any medications the subject took but discontinued within the 30 days prior to screening also will be recorded. Significant medical history will be collected and any current underlying medical

conditions, including those that began within the last 30 days and which may have resolved before screening, additionally must be recorded.

6.3 Dispensing Investigational Product

Study related personnel will be cautioned that any unused or unused subject kits are not to be opened at the clinical site by the site staff involved in the efficacy or safety measurements.

Study staff responsible for dispensing IP will be listed on the Delegation of Responsibilities Log. When a subject meets all criteria for selection and has completed all screening assessments, the subject will be assigned to a treatment group according to the IWRS. The responsible unmasked study staff will account for used and unused investigation product packers and their kit contents by maintaining an IP accountability log.

6.4 Appropriateness of Measurements

The ophthalmic and systemic measures used in this study are consistent with standard of care. In particular, IOP as measured by Goldmann applanation tonometry, the primary efficacy assessment in this study, is accepted worldwide as a standard for testing of pharmacologically active agents intended to reduce IOP.

6.5 Efficacy Assessments

6.5.1 Specification of the Efficacy and Safety Parameters

The primary efficacy outcome will be the comparison of PG324 Ophthalmic Solution relative to GANFORT® for mean IOP within a treatment group at the following time points: 08:00, 10:00, and 16:00 hours at the Week 2, Week 6, and Month 3 study visits.

Secondary efficacy outcomes will be comparison of PG324 Ophthalmic Solution relative 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 in diurnal IOP levels.

Assessment of Safety

The primary safety measures will be visual acuity, goniometry, pachymetry, objective biomicroscopic and ophthalmoscopic examination, and adverse events.

Other safety measures will be systemic safety as measured by pregnancy testing, heartrate, blood pressure, and clinical laboratory evaluations.

Change in Self-Administered NEI Visual Functioning Questionnaire-25 (VFQ-25), and Short Form Health Survey Questionnaire (SF-36 v.2) scores from baseline to study exit.

Other secondary efficacy analyses, including those for the entire subject population, will be carried out as described in the study Statistical Analysis Plan.

7. STUDY ACTIVITIES

The schedule of study visits and procedures is shown in Appendix 1.

7.1 Study Visits

7.1.1 Visit 1 (Screening Visit)

This visit may occur at any time of the day.

A member of the Investigator's staff will interview the individual as to their qualifications for participation in the study.

Individuals will be asked to review the informed consent, discuss issues as needed, and to sign the form. A signed written informed consent must be obtained from the subject prior to any study specific procedures or assessments.

Significant medical and ophthalmic history including systemic and ocular medication use will be taken, and demographic measures recorded (see Section 6.2).

The following procedures will be performed:

- Confirm eligibility per inclusion and exclusion criteria.
- Heart rate and blood pressure.
- Pregnancy test: women of childbearing potential must have a negative urine pregnancy test prior to commencement of washout period.
- Best corrected visual acuity.
- Central corneal thickness will be measured by ultrasound pachymetry (taken at Screening or within 1 week prior to the Screening visit).

- Intraocular pressure (before pupil dilation).
- Biomicroscopy
- Dilated ophthalmoscopy (including cup:disc ratio): Medicated IOP must be ≥ 17mmHg in at least one eye and < 28mmHg in both eyes at screening visit.
- Visual fields and gonioscopy may be taken up to 3 months prior to randomization.
- Symptomatology: Individuals will be asked "How are you feeling?"
- The subject will complete both the Self-Administered NEI Visual Functioning Questionnaire-25 (VFQ-25) and the Self-Administered Health Survey Questionnaire (SF-36 v.2).

Blood samples will be taken for clinical chemistry and hematology (Appendix 2). The results of blood work should be reviewed after this study visit (if available) in order to determine eligibility of the subject prior to undertaking the examination at Visit 2 (Qualification Visit #1).

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).

The investigator will evaluate the results of these examinations for possible enrollment of the individual into the study.

All individuals who are qualified for enrollment should undergo a washout period as noted in Section 5.7.1.

7.1.1.1 Evaluation of eye-drop instillation performance

Subjects (or guardian or carer for subjects deemed unable to administer) will be provided a bottle of commercially available, multi-dose, non-medicated artificial tears in a room with access to water and soap. Medication instiller will be asked to instill a drop of the artificial tear in each eye under the observation of a member of the investigator's staff. The staff will observe the subject, guardian or alternative person to assure that they instill 1 drop of the artificial tear into each eye, without touching the tip of the bottle to their eye or face (Stone 2009). The staff member may work with the individual to improve their delivery technique to meet this standard. If the subject (guardian or alternative person) cannot demonstrate proper delivery of the eye drop, or if staff member feels that the individual will be unable to do so consistently, then the subject will be excluded from further study participation.

7.1.1.2 Washout Period

As noted in Section 5.7.1, as current use of at least one ocular hypotensive medication is an inclusion criterion, a washout period is required for those who meet other qualifications for enrollment. The investigator must perform interim visits, ideally at weekly intervals, during the washout period for IOP measurement.

In addition, all women of childbearing potential will have a pregnancy test performed during the washout period if the washout period extends beyond 4 weeks.

7.1.2 Visit 2 (Qualifying Visit #1, for 08:00 hours IOP and safety measurements)

After the washout, individuals will return to the Investigator's office in the early morning. The subject will be questioned regarding any changes in their health or concomitant medication use. Any change should be recorded on the Adverse Event page of the CRF.

Inclusion/exclusion criteria will be reviewed again for the qualified individual. Results of the clinical laboratory tests from Visit 1 need to be available and reviewed by the Investigator.

For subjects who were unable or unwilling to have blood drawn for clinical labs at Visit 1, 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).

The following procedures will be performed:

- Heart rate and blood pressure.
- Symptomatology: Individuals will be asked "How are you feeling?"
- Recording of any AEs.
- Best corrected visual acuity.
- A non-dilated eye examination will be performed, including IOP measurements and biomicroscopy. IOP must be measured within 60 minutes of the nominal time (i.e., 07:00 to 09:00 hours).
- Urine Pregnancy test: women of childbearing potential (who have a washout period that extends beyond 4 weeks).

For further evaluation in the study, at this time, unmedicated (post-washout) IOP must be > 20mmHg in at least one eye and < 36mmHg in both eyes. **This is the first of the four qualifying IOPs for randomization.** Individuals who do NOT meet this requirement may return for up to 2 additional qualification visits within 1 week of failing this qualification visit.

Individuals who screen fail due to IOP being ≥ 36mmHg in either eye (exclusion criterion) may not return for additional qualification visits.

Qualified individuals will be scheduled to return 2-7 days later for the second qualification visit.

7.1.3 Visit 3.0 (Qualifying Visit #2, Day 1, for IOP and safety measurement at 08:00 hours)

Within 2 to 7 days after Visit 2, individuals will return to the Investigator's office for the next 08:00 hour IOP measurement. The results of the clinical laboratory tests need to be available, and reviewed by the Investigator. In order for the individual to be enrolled, the tests cannot be indicative of any clinically significant disease in the opinion of the investigator. The subject will be questioned regarding any changes in their health or concomitant medication use. Any change should be recorded on the Adverse Event of the CRF. Inclusion/exclusion criteria will be reviewed again for the qualified individual.

The following procedures will be performed:

- Heart rate and blood pressure.
- Urine pregnancy test: women of childbearing potential must have a negative urine pregnancy test result within 7 days prior to randomization.
- Symptomatology: Individuals will be asked "How are you feeling?"
- Recording of any AEs.
- Best Corrected Visual Acuity.
- A non-dilated eye examination will be performed, including IOP measurements and biomicroscopy. IOP must be measured within 60 minutes of the nominal time (i.e., 07:00 to 09:00 hours).

For further evaluation in the study, at this time (08:00 hours) unmedicated IOP must be > 20mmHg in at least one eye and < 36mmHg in both eyes. **This is the second of the four qualifying IOPs for randomization. If one eye qualifies at the second qualification visit, it MUST be the same eye as in previous qualification visit (Visit 2 qualifying visit# 1) and this will be the study eye for the duration of the study.**''

Qualified individuals will continue with the measurements of IOP at 10:00 hours and 16:00 hours.

Individuals who do not meet this requirement may return for up to 2 additional qualification visits within 1 week of failing this qualification visit. Individuals returning at an unscheduled visit within 1 week are required to only re-measure IOP in both eyes.

Upon return for an unscheduled qualification visit, such individuals' IOP measurements would need to qualify at 08:00, 10:00 and 16:00 hours. Individuals who screen fail due to IOP being ≥ 36mmHg in either eye (exclusion criterion) may not return for additional qualification visits.

Individuals are allowed to leave the investigator's office between assessments, and eat and drink with no restrictions. However, individuals are not to consume alcohol or engage in strenuous exercise.

7.1.4 Visit 3.1 (Day 1, for IOP and safety measurement at 10:00 hours)

Inclusion/exclusion criteria will be reviewed again for the qualified individual. Qualified individuals will be examined. Each examination will include:

- Symptomatology: Individuals will be asked "How are you feeling?"

- A non-dilated eye examination will be performed, including IOP measurements and bio microscopy. IOP must be measured within 30 minutes of the nominal time (i.e., 09:30 to 10:30 hours). Please note, the minimum time between IOP measurements is 60 minutes. For example if the previous IOP measurement was taken at 09:00, the IOP at this visit should not be measured before 10:00.

At this and any other in-office visit, any subject complaining of visual function issues will have visual function assessed as judged appropriate by the investigator.

For further evaluation in the study, at this time (10:00 hours, Day 1) unmedicated IOP must be > 17mmHg in at least one eye and < 36mmHg in both eyes. **This is the third of the four qualifying IOPs for randomization. If one eye qualifies it must be the same eye as Visit 2.0 and Visit 3.0.**

Qualified individuals will continue with the qualification visit. Individuals who do not meet this requirement may return for up to 2 additional qualification visits within 1 week of failing this qualification visit. 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. Individuals who screen fail due to IOP being ≥ 36mmHg in either eye (exclusion criterion) may not return for additional qualification visits.

Individuals are allowed to leave the investigator's office between assessments, and eat and drink with no restrictions. However, individuals are not to consume alcohol or engage in strenuous exercise.

7.1.5 Visit 3.2 (Day 1, for IOP and safety measurements at 16:00 hours)

Inclusion/exclusion criteria will be reviewed again for the qualified individual. Qualified individuals will be examined. Each examination will include:

- Symptomatology: Individuals will be asked "How are you feeling?"

- A non-dilated eye examination will be performed, including IOP measurements and biomicroscopy. IOP must be measured within 30 minutes of the nominal time (i.e., 15:30 to 16:30 hours).

For further evaluation in the study, at this time (16:00 hours, Day 1) unmedicated IOP must be > 17mmHg in at least one eye and < 36mmHg in both eyes. **This is the fourth of the four qualifying IOPs for randomization. If one eye qualifies it must be the same eye as Visit 2.0, Visit 3.0. and Visit 3.1.**

Individuals who do NOT meet this requirement may return for up to 2 additional qualification visits within 1 week of failing the first qualification visit. 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. Individuals who screen fail due to IOP being ≥ 36mmHg in either eye (exclusion criterion) may not return for additional qualification visits.

For subjects that qualify in both eyes based upon 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 all subjects, both eyes will be treated.

At this point, eligible subjects will be randomized. The first IP kit(s) containing 1 bottle from the assigned subject packer will be dispensed within 48 hours of the randomization visit to the subject, along with dosing and storage instructions by unmasked site staff.

Subjects will be:

- Instructed to administer their masked medication in both eyes (OU) at home between 20:00 – 22:00 hours beginning with the first dose on the evening of this study visit or no later than within 48 hours of randomization.

- Instructed to return to the office with their study medication on Week 2 (Day 15).

For post randomization assessments a window of ±3 days for scheduled visits up to Month 5 is permitted. A window of ±7 days for Month 6 is permitted.

7.1.6 Visit 4.0 (Week 2 [Day 15], for IOP and safety measurements at 08:00 hours)

Subjects will return to the Investigator's office. The subject will be questioned about any missed doses any changes in their health or concomitant medication use. Subjects will be examined and each examination will include:

- Heart rate and blood pressure.

- Urine pregnancy test for women of childbearing potential.
- Symptomatology: Individuals will be asked "How are you feeling"?
- Recording of any AEs. At the investigator's discretion photography of any ocular events.
- Best Corrected Visual Acuity.
- A non-dilated eye examination will be performed, including IOP measurements and biomicroscopy. IOP must be measured within 60 minutes of the nominal time (i.e., 07:00 to 09:00 hours).
- All used/returned IP kits will be collected for destruction by the unmasked site staff.

After randomization, any new or worsening of symptoms beyond those collected at baseline are to be entered as adverse events.

Subjects are allowed to leave the investigator's office between assessments, and eat and drink without restrictions. However, individuals are not to consume alcohol or engage in strenuous exercise.

7.1.7 Visit 4.1 (Week 2 [Day 15], for IOP and safety measurements at 10:00 hours)

Subjects will be examined and each examination will include:

- Symptomatology: Individuals will be asked "How are you feeling?"
- Recording of any AEs. At the investigator's discretion photography of any ocular events.
- A non-dilated eye examination will be performed, including IOP measurements and biomicroscopy. IOP must be measured within 30 minutes of the nominal time (i.e., 09:30 to 10:30 hours). Please note, the minimum time between IOP measurements is 60 minutes. For example, if the previous IOP measurement was taken at 09:00, the IOP at this visit should not be measured before 10:00.

Subjects are allowed to leave the investigator's office between assessments, and eat and drink without restrictions. However, individuals are not to consume alcohol or engage in strenuous exercise.

7.1.8 Visit 4.2 (Week 2 [Day 15], for IOP and safety measurements at 16:00 hours)

Subjects will be examined and each examination will include:

- Symptomatology: Individuals will be asked "How are you feeling?"
- Recording of any AEs. At the investigator's discretion photography of any ocular events.

- A non-dilated eye examination will be performed, including IOP measurements and biomicroscopy. IOP must be measured within 30 minutes of the nominal time (i.e., 15:30 to 16:30 hours).

- Two new subject kits, each containing 1 bottle from the originally assigned subject packer, will be dispensed to the subject by the unmasked site staff, along with dosing and storage instructions.

Subjects will be:

- Instructed to continue to administer their masked medication in both eyes (OU) at home between 20:00 - 22:00 hours (taking the daily evening dose on that day).

- Instructed to return to the office with their used study medication on Week 6 (Day 43).

7.1.9 Visit 5.0 (Week 6 [Day 43], for IOP and safety measurements at 08:00 hours)

Subjects will return to the Investigator's office. The subject will be questioned regarding any missed doses and any changes in their health or concomitant medication use.

Subjects will be examined and each examination will include:

- Heart rate and blood pressure.

- Urine pregnancy test for women of childbearing potential.

- Symptomatology: Individuals will be asked "How are you feeling?"

- Recording of any AEs. At the investigator's discretion photography of any ocular events.

- Best Corrected Visual Acuity.

- A non-dilated eye examination will be performed, including IOP measurements and biomicroscopy. IOP must be measured within 60 minutes of the nominal time (i.e., 07:00 to 09:00 hours).

All used/returned IP kits will be collected for destruction by the unmasked site staff.

Any new or worsening of symptoms beyond those collected at baseline are to be entered as adverse events.

Subjects are allowed to leave the investigator's office, and eat and drink without restrictions. However, individuals are not to consume alcohol or engage in strenuous exercise.

7.1.10 Visit 5.1 (Week 6 [Day 43], for IOP and safety measurements at 10:00 hours)

Subjects will be examined and each examination will include:

Symptomatology: Individuals will be asked "How are you feeling" Recording of any AEs. At the investigator's discretion photography of any ocular events.

- A non-dilated eye examination will be performed, including IOP measurements and biomicroscopy. IOP must be measured within 30 minutes of the nominal time (i.e. 09:30 to 10:30 hours). Please note, the minimum time between IOP measurements is 60 minutes. For example if the previous IOP measurement was taken at 09:00, the IOP at this visit should not be measured before 10:00.

Subjects are allowed to leave the investigator's office, and eat and drink without restrictions. However, individuals are not to consume alcohol or engage in strenuous exercise.

7.1.11 Visit 5.2 (Week 6 [Day 43], for IOP and safety measurements at 16:00 hours)

Subjects will be examined and each examination will include:

- Symptomatology: Individuals will be asked "How are you feeling?"

- Recording of any AEs. At the investigator's discretion photography of any ocular events.

- A non-dilated eye examination will be performed, including IOP measurements and biomicroscopy. IOP must be measured within 30 minutes of the nominal time (i.e., 15:30 to 16:30 hours).

Three new subject kits, each containing 1 bottle from the originally assigned subject packer, will be dispensed to the subject by the unmasked site staff, along with dosing and storage instructions.

Subjects will be:

- Instructed to continue to administer their masked medication in both eyes (OU) at home between 20:00 - 22:00 hours (taking the daily evening dose on that day).

- Instructed to return to the office with their study medication on Month 3 (Day 90).

7.1.12 Visit 6.0 (Month 3 [Day 90], for IOP and safety measurements at 08:00 hours)

Subjects will return to the Investigator's office. The subject will be questioned about any missed doses and any changes in their health or concomitant medication use.

Subjects will be examined and each examination will include:

- Heart rate and blood pressure.

- Urine pregnancy test for women of childbearing potential.

- Symptomatology: Individuals will be asked "How are you feeling?"
- Recording of any AEs. At the investigator's discretion photography of any ocular events.
- Best corrected visual acuity.
- A non-dilated eye examination will be performed, including IOP and biomicroscopy. IOP must be measured within 60 minutes of the nominal time (i.e., 07:00 to 09:00 hours).
- Pachymetry at the study visit or within one week of the study visit.
- Visual fields (may be assessed up to one week prior to this visit, or later in the morning or afternoon of this series of Day 90 visits so long as it occurs after the 08:00 hour IOP measurement at that visit). See Appendix 2 for further details when dilation is required due to subject small pupils.
- All used/returned IP kits will be collected for destruction by the unmasked site staff.

Any new or worsening of symptoms beyond those collected at baseline are to be entered as adverse events.

Subjects are allowed to leave the investigator's office, and eat and drink without restrictions. However, individuals are not to consume alcohol or engage in strenuous exercise.

7.1.13 Visit 6.1 (Month 3 [Day 90], for IOP and safety measurements at 10:00 hours)

Subjects will be examined and each examination will include:

- Symptomatology: Individuals will be asked "How are you feeling?"
- Recording of any AEs. At the investigator's discretion photography of any ocular events.
- A non-dilated eye examination will be performed, including IOP measurements and biomicroscopy. IOP must be measured within 30 minutes of the nominal time (i.e., 09:30 to 10:30 hours). Please note, the minimum time between IOP measurements is 60 minutes. For example if the previous IOP measurement was taken at 09:00, the IOP at this visit should not be measured before 10:00.

Subjects are allowed to leave the investigator's office, and eat and drink without restrictions. However, individuals are not to consume alcohol or engage in strenuous exercise.

7.1.14 Visit 6.2 (Month 3 [Day 90], for IOP and safety measurements at 16:00 hours)

Subjects will be examined and each examination will include:

- Symptomatology: Individuals will be asked “How are you feeling?”
- Recording of any AEs. At the investigator’s discretion photography of any ocular events.
- A non-dilated eye examination will be performed, including IOP measurements and biomicroscopy. IOP must be measured within 30 minutes of the nominal time (i.e., 15:30 to 16:30 hours).
- A dilated ophthalmoscopy examination (including cup:disc ratio).

Two new subject kits, from the assigned safety extension subject packer, each containing 1 bottle will be dispensed to the subject by the unmasked site staff, along with dosing and storage instructions.

Subjects will be:

- Instructed to continue to administer their masked medication in both eyes (OU) at home between 20:00 - 22:00 hours (taking the daily evening dose on that day).
- Instructed to return to the office with their study medication on Month 4 (Day 120).

7.1.15 Visit 7.0 (Month 4 [Day 120], for IOP and safety measurements at 10:00 hours)

Subjects will return to the Investigator’s office. The subject will be questioned about any missed doses and any changes in their health or concomitant medication use.

Subjects will be examined and each examination will include:

- Heart rate and blood pressure.
- Urine pregnancy test for women of childbearing potential.
- Symptomatology: Individuals will be asked “How are you feeling?”
- Recording of any AEs. At the investigator’s discretion photography of any ocular events.
- Best corrected visual acuity.

- A non-dilated eye examination will be performed, including IOP measurements and biomicroscopy. IOP must be measured within 30 minutes of the nominal time (i.e., 09:30 to 10:30 hours).

- All used/returned IP kits will be collected for destruction by the unmasked site staff.

Any new or worsening of symptoms beyond those collected at baseline are to be entered as adverse events.

Two new subject kits, from the assigned safety extension subject packer, each containing 1 bottle will be dispensed to the subject by the unmasked site staff, along with dosing and storage instructions. Subjects will be:

- Instructed to continue to administer their masked medication in both eyes (OU) at home between 20:00 – 22:00 hours (taking the daily evening dose on that day).

- Instructed to return to the office with their study medication on Month 5 (Day 150).

7.1.16 Visit 8.0 (Month 5 [Day 150], for IOP and safety measurements at 10:00 hours)

Subjects will return to the Investigator's office. The subject will be questioned about any missed doses and any changes in their health or concomitant medication use.

Subjects will be examined and each examination will include:

- Heart rate and blood pressure.

- Urine pregnancy test for women of childbearing potential.

- Symptomatology: Individuals will be asked "How are you feeling?"

- Recording of any AEs. At the investigator's discretion photography of any ocular events.

- Best corrected visual acuity.

- A non-dilated eye examination will be performed, IOP measurements and biomicroscopy. IOP must be measured within 30 minutes of the nominal time (i.e., 09:30 to 10:30 hours).

- All used/returned IP kits will be collected for destruction by the unmasked site staff.

Any new or worsening of symptoms beyond those collected at baseline are to be entered as adverse events.

Two new subject kits, from the assigned safety extension subject packer, each containing 1 bottle will be dispensed to the subject by the unmasked site staff, along with dosing and storage instructions. Subjects will be:

- Instructed to continue to administer their masked medication in both eyes (OU) at home between 20:00 – 22:00 hours (taking the daily evening dose on that day).
- Instructed to return to the office with their study medication on Month 6 (Day 180).

7.1.17 Visit 9.0 (Month 6 [Day 180] for IOP and safety measurements at 10:00 hours)

Subjects will return to the Investigator's office. The subject will be questioned about any missed doses and any changes in their health or concomitant medication use.

Subjects will be examined and each examination will include:

- Heart rate and blood pressure.
- Symptomatology: Individuals will be asked "How are you feeling?"
- Blood samples will be taken for clinical chemistry and hematology (samples may be taken at any time point throughout Visit 9).
- Recording of any AEs. At the investigator's discretion photography of any ocular events.
- Best corrected visual acuity.
- A non-dilated eye examination will be performed, including IOP and biomicroscopy. IOP must be measured within 30 minutes of the nominal time (i.e., 09:30 to 10.30 hours).
- Central corneal thickness will be measured by ultrasound Pachymetry.
- Visual fields (may be assessed up to one week prior to this visit, or later in the morning or afternoon of this series of Day 180 visit so long as it occurs after the IOP measurement at that visit). See Appendix 2 for further details when dilation is required due to subject small pupils.
- The subject will complete both the Self-Administered VFQ-25 Questionnaire and the Self-Administered Health Survey Questionnaire (SF-36 v.2).
- Urine pregnancy test for women of childbearing potential.
- A dilated ophthalmoscopy examination (including cup:disc ratio).

- All used/returned IP kits will be collected for destruction by the unmasked site staff. Any new or worsening of symptoms beyond those collected at baseline are to be entered as adverse events.

Subjects will be thanked for their participation, will exit the study and are released to the normal care of their Physician.

7.1.18 Unscheduled Visits

An unscheduled visit may be any visit to the Investigator other than the specific visits requested in the protocol as possibly required for the subject's ophthalmic condition.

The Investigator will perform all procedures necessary to evaluate the study participant at these visits and record any adverse events in the CRF.

As noted in Section 5.11.5, every possible effort should be made by investigators to ensure that non-completing subjects have a final visit that includes all examinations listed for Visit 9.0 / Exit (Day 180) as well as dilated ophthalmoscopy.

7.1.19 Instructions for Completion of Case Report Forms

The initial point of entry of study data should be the subject record source documentation. Then, data should be transcribed to the CRF as follows:

At each subject visit, the appropriate CRFs must be completed. Whenever a CRF is used, be sure to provide all information requested including subject identification number and name or number of Investigator, date(s), etc. All applicable questions should be answered and all data requested should be provided. Those areas that require a response but are not filled in correctly are considered incomplete or erroneous entries, and will have to be corrected. Providing all the necessary data the first time saves office time for the Investigator during subsequent audits.

For this study, electronic CRFs will be used. Security and authorization procedures consistent with the system must be used.

7.2 Adverse Events Assessments and Ocular Safety

Performing Adverse Events Assessments

Qualified study staff responsible for assessing adverse events (AEs) will be listed on the Site Signature/Delegation of Responsibilities Log. This includes assessment of AE severity and relationship to investigational product. AE information may be volunteered by the subject or solicited by study personnel through non-leading questions.

All adverse events (AEs) occurring during the study, regardless of the assumption of causal relationship, must be documented on the respective eCRF. 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 an ongoing AE at the time of study completion, the ongoing AE must be followed-up and provided appropriate medical care until the event has resolved or stabilized.

Documentation of adverse events/adverse reactions includes start date and stop date, severity, action(s) taken, seriousness and outcome. Investigators at their discretion may also take photographs of ocular events to provide additional documentation of adverse events. These images can only be shared with the sponsor if the subject has provided permission to do so by signing the appropriate consent documentation.

7.2.1 Adverse Event Definitions

The following definitions of terms apply to this section:

- *Adverse event.* Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

- *Life-threatening adverse event or life-threatening suspected adverse reaction*. An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the Investigator or Sponsor, its occurrence places the patient at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

- *Serious adverse event (SAE) or serious suspected adverse reaction (SSAR)*. An adverse event or suspected adverse reaction 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. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in patient hospitalization, or the development of drug dependency or drug abuse.

- *Suspected adverse reaction* means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, ''reasonable possibility'' means there is evidence to suggest a causal relationship between the drug and the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

- *Unexpected adverse event or unexpected suspected adverse reaction*. An adverse event or suspected adverse reaction is considered ‘‘unexpected’’ if it is not listed in Section 8.4 of the Investigator’s Brochure ‘Reference Safety Information’ or is not listed at the specificity or severity that has been observed. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the Investigator’s Brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the Investigator’s Brochure listed only cerebral vascular accidents. “Unexpected,” as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the Investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

Note: Any medical condition present prior to administration of the masked study medication which remains unchanged or improved should not be recorded as an adverse event at subsequent visits.

Note: If an event occurs during the washout period (prior to subject enrollment and the commencement of study medication), it should be recorded as an adverse event.

Note: In the present study, Investigators are asked to use the verbatim term “conjunctival hyperemia” on the study AE form to describe observations of conjunctival redness if the ocular redness observation is increased from Visit 1 (screening) observations and clinically meaningful. Investigators are also asked to note all observations of conjunctival hyperemia on the biomicroscopy eCRF as well as on the study AE form.

7.2.2 Timing for Reporting of Adverse Events

The AEs occurring during the study must be documented, regardless of the assumption of a causal relationship. AEs should be documented from the time the subject signs and dates the patient consent form until subject participation in the study has been completed. If a subject has one or more ongoing AEs at the time of study completion, the subject must be followed and provided appropriate medical care until the sign(s) and/or symptoms(s) of the AE have remitted or stabilized in the opinion of the Investigator.

When recording an AE, the following information should be provided on the study AE eCRF:

1. Action Taken with Study Drug:

- None
- Investigational Product Discontinued
- Investigational Product Interrupted

2. Other Action Taken:

- None
- Non-Drug Therapy
- New OTC or Rx Drug Added
- Hospitalized less than 24 hours
- Hospitalized greater than or equal to 24 hours

3. Outcome of an adverse event is coded as:

- Fatal
- Not Recovered/Not Resolved
- Recovered/Resolved
- Recovered/Resolved with sequelae
- Recovering/Resolving
- Unknown/Lost to follow-up

7.2.3 Severity

Severity of an adverse event is defined as a qualitative assessment of the level of discomfort or the degree of intensity of an adverse event as determined by the Investigator or reported to him/her by the subject. The assessment of severity is made irrespective of study medication relationship or seriousness of the event and should be evaluated according to the following scale:

- 1 = Mild: present and noticeable, but not distressing, and no disruption of normal daily activities.
- 2 = Moderate: bothersome, discomfort sufficient to possibly reduce or affect normal daily activity.
- 3 = Severe: incapacitating, with inability to work or perform normal daily activity.

A change in severity for a reported AE will require a stop date for the previous severity and a new start and stop date for the new severity. For example, a change in severity may go from mild to severe or from severe to moderate. In both cases, the start and stop dates should be recorded.

Please note: a severe AE is not the same as a serious AE. Seriousness of an AE (NOT severity) serves as a guide for defining regulatory reporting obligations (see Section 7.2.6 for further information on serious AEs [SAEs]).

7.2.4 Relationship

The study medication relationship for each adverse event/adverse reaction should be determined by the Investigator using these explanations:

- **Not Related**: The event is clearly related to other factors such as subject's clinical condition; therapeutic interventions, concomitant disease or therapy administered to the subject and does not follow a known response pattern to the product.

- **Unlikely Related**: The event is most probably caused by other etiologies such as participant's underlying condition, therapeutic intervention, or concomitant therapy; or the delay between administration and the onset of the AE is incompatible with a causal relationship. Therefore, there is not a reasonable possibility that the AE was caused by the study medication.

- **Possibly Related**: The event follows a reasonable, temporal sequence from the time of study medication administration and/or follows a known response pattern to the study medication, but could have been produced by other factors such as the subject's clinical state, therapeutic interventions or concomitant therapy administered to the subject.

- **Related**: The event follows a reasonable, temporal sequence from the time of study medication administration and/or follows a known response pattern to the study medication and cannot be reasonably explained by other factors such as subject's clinical state, therapeutic interventions or concomitant therapy administered to the subject, and either occurs immediately following study medication administration, or improves on stopping the study medication, or reappears on repeat exposure, or there is a positive reaction at the application site.

7.2.5 Expectedness

For netarsudil, the most frequently reported AE in 3 Phase 2 and one Phase 3 studies (Clinical Study Reports AR-13324-CS201, AR-13324-CS202, PG324-CS201, AR-13324-CS301, and AR-13324-CS302, AR-13324-CS304) has been conjunctival hyperemia. Other AEs seen in significantly greater frequency with netarsudil than in active control treatment arms in these studies include instillation site erythema or pain, eyelid erythema, conjunctival hemorrhage, conjunctival vascular disorder, blurred vision, corneal deposits, eye irritation, increased lacrimation, and foreign body sensation.

The very common ocular AE's seen with GANFORT® in clinical trials as reported in the GANFORT® prescribing information has been conjunctival hyperemia (Appendix 3). Common systemic effects are headache and dizziness. Common Ocular side effects seen with GANFORT® are superficial punctuate keratitis, corneal erosion, burning sensation, eye

pruritus, stinging sensation in the eye, foreign body sensation, eye dryness, eyelid erythema, eye pain, photophobia, eye discharge, visual disturbance, eyelid pruritus, visual acuity worsened, blepharitis, eyelid oedema, eye irritation, epiphora, growth of eyelashes.

An AE or suspected adverse reaction is considered "unexpected" if it is not listed in the Section 8.4 of the Investigator's Brochure 'Reference Safety Information' or is not listed at the specificity or severity that has been observed. "Unexpected," as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the Investigator's Brochure as occurring with this class of drugs or as anticipated from the pharmacological properties of PG324 or GANFORT®, and are not specifically mentioned as occurring with the IP. The AEs that are both unexpected and serious should be reported in an expedited fashion to the Sponsor (see Section 7.2.6 for further details).

7.2.6 Serious Adverse Events (SAEs) or Serious Unexpected Suspected Adverse Reaction Safety Reports (SUSARs)

An investigator must immediately report to the Sponsor representative any SAE or serious unexpected suspected adverse reactions within 24 hours of occurrence or being informed of the event, whether or not considered drug related including those listed in the protocol or investigator brochure and must include an assessment of whether there is a reasonable possibility that the drug caused the event. A reaction will be considered unexpected if it is not listed in the Reference Safety Information Section 8.4 in the AR-13324 Ophthalmic Solution (Netarsudil Ophthalmic Solution)/PG324 Ophthalmic Solution Investigator Brochure and /or in Section 4.8 of the GANFORT® SmPC. Study endpoints that are serious adverse events (e.g., all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the drug and the event (e.g., death from anaphylaxis). In that case, the Investigator must immediately report the event to the Sponsor. The investigator must record non-serious adverse events and report them to the Sponsor. In case of incomplete information, the Investigator must provide follow-up information as soon as possible, again using the SAE report form.

This requirement applies to occurrences observed during the course of the study and within 30 days of last administration of the study medication. In addition, in the case of immediately life-threatening AEs or AEs with fatal outcome, or adverse events that are serious, unexpected (i.e., not in the Clinical Investigator's Brochure and/or in Section 4.8 of the GANFORT® SmPC [see Appendix 3]) and judged related to the IP, the Investigator must inform the Sponsor or Sponsor representative by phone within 24 hours of observation or occurrence of the SAE.

SAEs must be reported to the IEC/ CEC according to the IEC/ CEC requirements. Prompt notification of SAE's by the investigator to Sponsor/ Sponsor representative is essential so that legal obligations and ethical responsibilities towards the safety of the subjects are met.

Sponsor/ Sponsor representative has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. The Sponsor or Sponsor representative will comply with country specific

regulatory requirements relating the safety reporting to the regulatory authority, Independent Ethics Committee (IEC/ CEC) and Investigators.

Investigator safety reports are prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and Sponsor /Sponsor representative and are forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing an SAE(s) or other specific safety information (e.g. summary or listing of SAEs) from Sponsor/ Sponsor representative will file it with the IB and will notify the IEC/ CEC, if appropriate according to local requirements.

Procedurally, for this study, the Investigator will report the event to [redacted] Drug Safety. An SAE report should be completed and faxed or emailed directly to [redacted]lth Drug Safety, using the study-specific SAE fax coversheet. The SAE fax/email cover page is included in attachment 1 of the Safety Management Plan (SMP) together with all relevant fax numbers and email addresses. The SAE report should include the essential elements. The investigator should not wait to receive additional information to document fully the event before notification of a SAE, though additional information may be requested. Where applicable, information from relevant laboratory results, hospital case records, and autopsy reports should be obtained.

Instances of death, congenital abnormality, or an event that is of such clinical concern as to influence the overall assessment of safety, if brought to the attention of the investigator at any time after cessation of study drug administration and linked by the investigator to this study, should be reported to the study monitor.

The sponsor and/or [redacted] will promptly notify all relevant investigators and the regulatory authorities of findings that could adversely affect the safety of subjects, impact on the conduct of the study or alter the Institutional Review Board/Independent Ethics Committee (IEC/ CEC) approval/favourable opinion of the study. In addition, [redacted], on behalf of the sponsor, will expedite the reporting to all concerned investigators, to the IEC/ CECs where required, and to the regulatory authorities of all adverse reactions that are both serious and unexpected.

Pregnancy, Testing Prevention and Reporting

For Female Subjects

The need for a screening pregnancy test depends on whether a woman is of childbearing potential or non-childbearing potential.

A woman of non-childbearing potential (i.e. physiologically incapable of becoming pregnant) is defined as any woman who has had a hysterectomy, bilateral oophorectomy (ovariectomy) or bilateral tubal ligation, or is post-menopausal.

A practical definition accepts menopause after 1 year without menses with an appropriate clinical profile, e.g., age appropriate, > 45 years in the absence of hormone replacement therapy (HRT). In questionable cases the subject must have follicle stimulating hormone (FSH) value > 40mIU/mL and an estradiol value < 40pg/mL (< 140 pmol/L)

A woman of childbearing potential is defined as any woman who does not meet the criteria of the non-childbearing potential as described in the previous paragraph.

If a woman is of childbearing potential, she must have a urine pregnancy test performed within 7 days prior to the first dose of study treatment. Subjects with positive pregnancy test result must be excluded from the study. Subjects with negative pregnancy test must agree to use a highly effective contraception method described below from time of randomization and for 3 months following the last dose of study medication.

Highly acceptable contraceptive methods when used consistently and in accordance with both the product label and the instructions of the physician, are as follows (Clinical Trials Facilitation Group 2014):

- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation. Due to lack of systemic absorption of netarsudil and no systemic effects seen with latanoprost, PG324 is not expected to lower the effectiveness of hormonal contraception:
    - oral
    - intravaginal
    - transdermal
- progestogen-only hormonal contraception associated with inhibition of ovulation. Due to lack of systemic absorption of netarsudil and no systemic effects seen with latanoprost, PG324 is not expected to lower the effectiveness of hormonal contraception:
    - oral
    - injectable
    - implantable (considered to have low user dependency)
- intrauterine device (IUD).
- intrauterine hormone-releasing system (IUS) (considered to have low user dependency).
- bilateral tubal occlusion (considered to have low user dependency).
- vasectomised partner (is considered as having lower user dependency and highly effective birth control method providing that the partner is the sole sexual partner of the

women of childbearing potential and that the vasectomized partner has received a medical assessment of the surgical success).

- sexual abstinence: sexual abstinence is only considered to be an acceptable method of contraception when defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the trial and the preferred and usual lifestyle of the subject. Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception.

Female subjects who are lactating must discontinue nursing prior to the first dose of IP and must refrain from nursing throughout the treatment period and for 30 days following the last dose of IP.

Male subjects

Men with a female partner of childbearing potential must have either had a prior vasectomy or agree to use a condom as an effective method of contraception from time of randomization and for 3 months following the last dose of study medication. A combination of male condom with either cap, diaphragm or sponge with spermicide (double barrier methods) are also considered acceptable, but not highly effective, birth control methods.

Pregnancy Reporting

Pregnancies occurring in subjects enrolled in the study or in their partners must be reported and followed to outcome. While pregnancy itself is not considered to be an AE or SAE, pregnancy reports are tracked by [redacted] Drug Safety. Premature terminations including miscarriage, spontaneous abortion, or elective termination of a pregnancy for medical reasons will be reported as an SAE. Other pregnancy complications should be reported as SAE's, if they meet the serious criteria. Should the pregnancy result in a congenital anomaly or birth defect, a separate SAE must be submitted. Furthermore, all neonatal deaths that occur within 30 days of the birth should be reported as SAE's without regard to causality.

The investigator must complete the Pregnancy Report Form and fax or email the form to [redacted] Drug Safety within one business day of the pregnancy. Following delivery or termination of the pregnancy, the Pregnancy Report Form is to be completed and sent by fax or email to [redacted] Drug Safety.

7.2.7 Follow-up of Subjects After Adverse Events

If an adverse event/adverse reaction occurs, the Investigator will institute support and/or treatment as deemed appropriate. If a serious or non-serious adverse event/adverse reaction is unresolved at the time of the last visit, efforts will be made to follow up until the adverse

event/adverse reaction is resolved or stabilized, the subject is lost to follow-up, or there is other resolution to the event.

8. STATISTICAL METHODS

8.1 Primary Hypotheses

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

- H_1: The difference between study eyes treated with PG324 Ophthalmic Solution Q.D. and study eyes treated with GANFORT® Q.D., 0.5% (PG324 Q.D. - GANFORT® Q.D.), in the mean IOP at the following time points: 08:00, 10:00, and 16:00 hours at Week 2, Week 6, and Month 3 Visits, is ≤ 1.5mmHg for all time points over all visits and ≤ 1.0 mmHg at 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 Q.D. - GANFORT® Q.D.) is ≤ 1.5mmHg at all time points and ≤ 1.0 mmHg at the majority of time points through Month 3.

The non-inferiority (NI) margin specified in the protocol was based on advice received from EMA through the scientific advice procedure (EMA/CHMP/SAWP/588765/2016) on 15 September 2016. In addition to the 1.5 mmHg margin at all time points specified in the draft protocol submitted to EMA for comment, advice was given that in accordance with the European Glaucoma Society's (EGS) Glaucoma Guideline a difference of 1 mmHg in IOP was considered to also be clinically relevant and therefore a NI margin no larger than this at the majority of time points should be included in the protocol.

As agreed with the USA FDA at the End of Phase 2 meeting for netarsudil (AR-13324) in accordance with the agency's draft guidance paragraph 16 (recommended Sep 2008; Revised Feb 2014, Dec 2014, Mar 2015).

8.2 Sample Size Considerations

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, approximately up to 220 subjects per arm will be randomized.

8.3 Analysis Populations

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.

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.

Per-protocol population: 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.

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.

8.4 Statistical Methods to be Employed

8.4.1 General Considerations

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

Hypothesis testing, unless otherwise indicated, will be performed at a 2-sided 0.05 significance level. Where applicable, 2-sided 95% CIs 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'. Difference between PG324 and GANFORT® will be calculated as PG324 - GANFORT®.

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

For diurnally-adjusted IOP, baseline will refer to the time-relevant measure at Visit 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 Visit 4.0, Visits 5.0 and 6.0, IOP at 10:00 hours at Visit 3.1 will be the baseline for 10:00 hours at Visit 4.1, Visits 5.1 and 6.1, etc.). For all other variables, baseline is defined as the last measurement prior to the first dose of study medication.

The unit of analysis for efficacy will be the study eye. If the Subject qualifies in both eyes, 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.

Statistical methods will be more fully described in a separate Statistical Analysis Plan.

8.5 Interim analyses

When all subjects have completed 3 months of treatment, select individuals from the Sponsor/Designee will unmask the study to analyze the 3-month efficacy and safety data. This is the time for primary analysis of the study. Efforts will be made to keep the investigators masked as to individual subject assignments as the subjects continue to be evaluated for safety and efficacy for the following 3 months.

8.5.1 Analysis of Baseline Data

Demographic and baseline characteristics such as age, gender, or disease status will be summarized and listed. Medical history, history of ocular surgery and procedures, glaucoma history and washout period will also be summarized and listed.

8.5.2 Subject Disposition

Subject enrollment, discontinuation of IP, and withdrawal from the study will be summarized and listed.

8.5.3 Analysis of Efficacy

The primary efficacy outcome will be comparison of PG324 Ophthalmic Solution relative to GANFORT® for:

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

Secondary efficacy outcomes will be comparison of PG324 Ophthalmic Solution relative 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 in diurnal IOP levels.

Note that each subject will have one eye designated as the study eye. Only the study eyes will be evaluated for the primary efficacy measure; however, both eyes will be treated.

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, using the intent-to-treat population with Monte Carlo Markov chain multiple imputation techniques used to impute missing data. Each time point within each visit will be modeled separately. The least squares mean differences (PG324 Q.D. – GANFORT® Q.D.) will be presented as well as 2-sided 95% confidence intervals (CIs) and p-values.

If the upper limits of the 95% confidence intervals are < 1.5mmHg at all time points and < 1.0mmHg at a majority of time points (at least 5 of 9), then the null hypothesis will be rejected in favour of the alternative hypothesis and PG324 Q.D. will be considered to be clinically non-inferior to GANFORT® Q.D. Results will be presented in both tabular and graphical form.

Analyses will be performed primarily on the ITT population using multiple imputation techniques to impute missing data and secondarily 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. Additional imputation techniques may be designated in the formal statistical analysis plan.

Secondary analyses of the primary endpoint will be completed using individual 2-sample t-tests and 95% t-distribution confidence intervals at each time point (08:00, 10:00, and 16:00 hours at Week 2, Week 6, and Month 3 Visits) using the ITT and PP populations.

Similar analyses will be completed on the secondary endpoints: change from baseline IOP measures at each time point and visit, mean diurnal IOP and change from baseline mean diurnal IOP measures. Note that the linear model analysis including baseline IOP as a covariate will only be completed for the IOP values at the given visit and time point and will not be presented for change from baseline as inference is identical between the mean IOP response variable and the mean change from baseline IOP response in such a model.

Additionally, for the individual 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 model 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.

Percent change from diurnally adjusted baseline IOP at each time point will be analyzed using 2-sample t-tests, between PG324 Q.D. and GANFORT® Q.D. at each time point and visit, including 95% t-distribution confidence intervals on the difference (PG324 Q.D. - GANFORT® Q.D.).

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

Sub-group analyses based upon pre-study characteristics such as site, demographics, or pre-study ocular hypotensive medications may be completed to further investigate the efficacy measures.

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 mmHg to ≤ 14 mmHg in 1mmHg 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. Additional sub-group analyses based upon pre-study characteristics such as site, demographics, or pre-study ocular hypotensive medications will be completed to further investigate efficacy measures.

8.5.4 Analysis of Safety

8.5.4.1 Ocular and Systemic Safety Assessments

Slit lamp biomicroscopy and dilated ophthalmoscopy measures will be summarized at each measured time point using discrete summary statistics.

Visual acuity data will be summarized at each time point using both continuous summaries (logMAR), including change from baseline, and discrete summaries, including change from baseline in the number of lines and the proportion of subjects with a worsening of ≥ 3 lines from baseline.

Vital signs will be summarized at each visit and for change from baseline to each visit using continuous summary statistics by treatment group and visit.

Clinical laboratory results will be summarized using both continuous summaries, including change from baseline, and discrete summaries, including frequency and percent of subjects with an abnormal value and shift tables from baseline. Additionally, laboratory data will be presented in data listings.

8.5.4.2 Adverse Events

Verbatim descriptions of AEs will be mapped to MedDRA 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 frequency and percent for each system organ class (SOC) and preferred term (PT) within each SOC. These summaries will also be presented for relation to IP and by severity. Fisher's exact test will be used to test the difference in proportions of subjects with each AE between treatment groups (SOC and PT).

8.5.4.3 NEI Visual Functioning Questionnaire-25 (VFQ-25)

The VFQ-25 measurements 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 for the total score, subscale scores, and each individual question score using observed data only. Imputation of missing individual question scores will be detailed in the formal statistical analysis plan and will follow methodology used in developing the instrument. One-sample 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.

8.5.4.4 Medical Outcome Short Form (36) Health Survey (SF-36 v.2)

The SF-36 measurements 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 for the total score, physical and mental health composite summary scores, domain scores, and each individual question score using observed data only. Imputation of missing individual question scores in calculating domain scores will be detailed in the formal statistical analysis plan and will follow methodology detailed in the instrument's manual. One-sample 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.

8.6 Procedure for Accounting for Missing, Unused or Spurious Data

Analyses will be performed primarily using multiple imputation techniques to impute missing data and secondarily 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.

Any missing, unused, or spurious data will be noted in the final statistical report.

8.7 Procedure for Reporting Deviations from the Statistical Plan

Any deviations from the statistical plan will be described and a justification given in the final statistical report.

8.8 Data Listings

Data listings will be prepared for all data on the database.

9. ACCESS TO SOURCE DOCUMENTATION

The Investigator will permit study-related monitoring visits, audits, IEC/ CEC review, and regulatory inspection(s) by providing direct access to source data and documents.

10. STUDY MONITORING

The progress of the study will be monitored by on-site, written, and telephone communications between personnel at the Investigator's site and the masked and unmasked Study Monitor. The Investigator will allow the Sponsor or designee to inspect all CRFs; subject records (source documents); signed consent forms; records of study medication receipt, storage, preparation, and disposition; and regulatory files related to this study.

The monitor and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents and to allocate their time and the time of their staff to monitor to discuss findings and any issues

Sponsor/designee will monitor the study to ensure:

- Data are authentic, accurate and complete.
- Safety and rights of the subjects are being protected.
- Study is conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP and all applicable regulatory requirements.

11. ETHICAL CONSIDERATIONS AND COMPLIANCE WITH GOOD CLINICAL PRACTICE

Publication and Disclosure Policy

Study information for this protocol will be posted on publicly available clinical trial registers before enrollment of Subjects begins. Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures and relevant reports and will have the opportunity to review the complete study results at a mutually-agreeable location. Aerie will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.

Aerie will provide the Investigator with the randomization codes for their site only after the completion of the full statistical analysis.

The results summary will be posted no later than 8 months after the final primary completion date, the date the final subject examined or received an intervention for the purposes of final collection of data for the primary outcome. In addition, a manuscript will be submitted to a peer reviewed journal for publication no later than 18 months after the last subject's last visit when manuscript publication in a peer reviewed journal is not feasible, a statement will be added to the register for not publishing.

11.1 GCP compliance

The proposed study is subject to all applicable governmental rules and regulations concerning the conduct of clinical trials on human subjects. This includes, but is not necessarily limited to: the approval of IEC/ CECs, the Helsinki Declaration (Appendix 6), US FDA Law, EU Clinical Trials Directive2001/20/EC and EC local laws and regulations, ICH E6 (GCP) R2 guidelines, obtaining prospective informed consent, monitoring of the conduct of the study and the completeness of the CRFs by the Sponsor or its designee(s); and appropriate record retention by the Investigator. Applicable IEC/ CEC, Investigator/Sponsor obligations, study monitoring and protocol change procedures are detailed in Appendix 4 and Appendix 5.

11.2 Subject Confidentiality

The Investigator and his/her staff will maintain all personal subject data collected and processed for the purposes of this study using adequate precautions to ensure confidentiality, in accordance with local, state and federal laws and regulations.

Monitors, auditors and other authorized representatives of Aerie, the IEC/ CEC approving this study, and government regulatory authorities (e.g., FDA and other EU regulatory agencies) may be granted direct access to the study subject's original medical and study records for verification of the data or clinical study procedures. Access to this information

will be permitted to representatives of the aforementioned organizations to the extent permitted by law.

A report of this study's results may be published or sent to the appropriate health authorities in any country in which the study drug may ultimately be marketed, but subject identities will not be disclosed in these documents.

11.3 Study Monitoring

Clinical research associates hired or contracted by the Sponsor will be responsible for monitoring the study sites and study activities. Clinical research associates will contact and visit the Investigator regularly. The actual frequency of monitoring visits depends on subject enrollment and on study site performance. Among others, the following items will be reviewed:

- Study progress
- Compliance with the protocol
- Completion of CRFs
- Dispensing, storage, and accountability of IP, including intentional or inadvertent unmasking of IP
- Source data verification
- AE and SAE reporting
- Essential documents contained within the regulatory binder

For source data verification (i.e., comparison of CRF entries with subject records), data will be 80% source verified and will include as a minimum:

- Subject identification
- Informed consent (procedure, signature, and date)
- Selection criteria
- Primary efficacy and safety parameters (i.e., AEs)

Member(s) of the Sponsor or their designee will meet with the Investigator prior to the initiation of the study in order to assess the adequacy of the Investigator's subject population, facilities, and equipment, and to familiarize the Investigator with the protocol.

A member of the Sponsor or their designee in the role of Study Monitor will subsequently meet with the Investigator after several of the subjects have initiated the study in order to

ensure that the subjects are being properly selected, that adequate supplies for the study have been provided and that the assignment of medication is properly recorded. In addition, the Study Monitor will verify that the Investigator follows the approved protocol and all approved amendments, if any, by reviewing the Investigator's regulatory documents, source documents, Informed Consent Forms, and Case Report Forms of study subjects.

The Study Monitor will meet with the Investigator when all subjects have completed the Final Visit of the study, in order to collect, unused study medications, and unused supplies and materials.

Interim monitoring visits and telephone consultations will be done by the Study Monitor as necessary, to ensure the proper progression and documentation of the study.

11.4 Case Report Forms and Study Records

The initial point of entry of study data should be the subject source documentation.
The location and nature of the source documentation for all data collected in the study will be identified in the study files at the investigator's site. In cases where no source documents will be used (i.e., data will be recorded directly onto the CRF without first being recorded on another document, such as a flowsheet, laboratory report, or other typical form of data reporting for later transcription to the CRF), the original data will be included in the CRF.

Source document information should be legible. Recorded data should only be corrected by drawing a single line through the incorrect entry and writing the revision next to the corrected data. The person who has made the correction should place his or her initials as well as the date of the correction next to the correction. Data may not be obliterated by erasure, redaction, or with correction fluid.

Study data will be transcribed and recorded via an electronic data capture (EDC) system as electronic CRFs (eCRFs). Security and authorization procedures consistent with the EDC system must be used. At each subject visit, the appropriate eCRFs must be completed. Whenever an eCRF is used, be sure to provide all information requested including subject identification number and initials, name or number of Investigator, date(s), etc. All applicable questions should be answered and all data requested should be provided. Those areas that require a response but are not filled in correctly are considered incomplete or erroneous entries, and will have to be corrected.

Each authorized study staff member will receive a unique access account in order to use the EDC system. Access accounts will not be shared among study staff. Authorized users will make entries and/or changes to eCRFs via a secure internet access. Each completed set of eCRFs will be reviewed by the Investigator who will then electronically sign and date the eCRF confirming that data for the subjects are complete and accurate.

The study records must include a copy of each Investigator's CV and medical license, and statement of Investigator qualifications. The name of each sub-investigator working under the supervision of the investigator is also required to be filed in the study records. In addition,

each eCRF, subject charts/source documents, Investigator's Brochure, protocol, protocol amendments, correspondence with the Sponsor/designee and the IEC/ CEC, IP storage, receipts, returns and dispensing records, Delegation of Responsibilities Log, site training records, records of site monitoring, any unmasking documentation, AE and SAE reporting, IEC/ CEC approvals, advertisements, written information provided to subjects, and subject completed ICFs will be included in the study records.

If the Investigator moves, withdraws from an investigation, or retires, the responsibility for maintaining the records may be transferred to another person (e.g., Sponsor, other Investigator) who will accept the responsibility. Notice of this transfer, including written acceptance, must be made to and agreed upon by the Sponsor.

11.5 Independent Ethics Committee/Competent Ethics Committee (IEC/ CEC)

This protocol, materials used to recruit subjects, and materials used to document consent must be approved by the IEC/ CEC prior to initiation of the study. The name and address of each reviewing IEC/ CEC will be documented in the Trial Master File for each participating country. Written IEC/ CEC approval must adequately identify the protocol and informed consent. In addition to approving the protocol, the IEC/ CEC must also approve the Subject Information and Consent Form, as well as any advertising tools that will be used for the study.

Written approval also must indicate whether approval was granted based on full committee review or expedited review. Copies of all approved materials, all correspondence with the IEC/ CEC and written approval from the IEC/ CEC must be made available to the Sponsor, prior to the start of subject enrollment into the study. The investigator will report promptly to the IEC/ CEC any new information that may adversely affect the safety of the subjects or the conduct of the study. The investigator will submit written summaries of the study to the IEC/ CEC as required. On completion of the study the IEC/ CEC will be notified that the study has ended.

11.6 Protocol Deviations

Per ICH E6 (GCP) R2 Section 4.5.1 the investigator/institution should conduct the trial in compliance with the protocol agreed with the sponsor and, if required, by the Regulatory Authority(ies) and which was given approval/favorable opinion by IEC/CEC

Protocol waivers or deviations from the protocol inclusion and exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

The site will contact the Sponsor for clarification of inclusion /exclusion criteria as needed prior to enrollment of the study subject. The sponsor will document clarification requests and responses or their representative. If a subject does not meet all the inclusion and exclusion criteria during screening, that subject may not be enrolled into the study.

If a protocol deviation is identified by the investigator or through site monitoring activities an immediate submission to the IEC/ CEC may be required e.g. 24 or 48 hours. The Sponsor will assess any protocol deviation and decide whether any of these non-compliances should be reported to the relevant competent authority as a serious breach of GCP and the protocol. If per the relevant competent authorities' requirements, the protocol deviation is not required to be reported immediately but is still required to be notified to the IEC/ CEC, the specific protocol deviation will be added to the annual progress report.

The Sponsor will review, designate, and/or approve all protocol deviations prior to the data base lock.

11.7 Informed Consent Requirements

Written informed consent will be obtained from each subject before any subject specific procedures are initiated. A copy of the signed and dated consent document will be given to each subject. The original signed and dated informed consent document must be maintained in the study files at the Investigator's site.

The investigator is responsible for ensuring that no subject is subject to any study-related examination or activity before that subject has given informed consent. The subject must give written consent after the receipt of detailed information. The verbal explanation will cover all the elements specified in the written information provided for the subject.

It should be emphasized that the subject is at liberty to withdraw consent to participate at any time, without penalty or loss of benefits to which the subject is otherwise entitled.

Subjects who refuse to give, or withdraw, written informed consent may not be included or continued in this study, but this will not impact on their subsequent care.

The investigator will inform the subject of the aims, methods, anticipated benefits and potential hazards of the study, including any discomfort it may entail. The subject must be given every opportunity to clarify any points he/she does not understand and if necessary, ask for more information. At the end of the interview, the subject may be given time to reflect if this is required, or if the subject requests more time. All Subjects will be required to sign and date the informed consent form.

Signed informed consent must be attained prior to the conductance of any study procedures.

12. DATA HANDLING AND RECORD KEEPING

All procedures for the handling and analysis of data will be conducted using good computing practices meeting ICH and according to the requirements of the EU Clinical Trials Directive/2001/20/EC guidelines for the handling and analysis of data for clinical trials.

12.1 Data Generation and Analysis

After data have been entered into the study database, a system of computerized data validation checks will be implemented and applied to the database. Query reports pertaining to data omissions and discrepancies will be forwarded to the clinical Investigator and the Sponsor for resolution. The study database will be updated by the clinical investigator or their staff, in accordance with the resolved query reports. All changes to the study database will be documented.

12.2 Archiving of Data

Archived versions of the database will be saved by the Sponsor consistent with ICH Good Clinical Practices Guidelines E6 (R2) section 5.5.11 (see Appendix 4), complying with whichever of the requirements is longer. The Sponsor will notify the investigator when documents should be returned.

12.3 Records Retention

The Investigator's site and clinical laboratory will retain all records related to the study in compliance with ICH Good Clinical Practices Guidelines E6 (R2) Section 4.9.4 (see Appendix 5).

12.4 Amendments to the Protocol

Modifications of the signed protocol are only possible by approved protocol amendments and with the agreement of all responsible persons. The procedure for approval of a protocol amendment is identical to that for approval of the protocol. The ethics committee must be informed of all protocol amendments and should be asked for its opinion as to whether a full re-evaluation of the ethical aspects of the study is necessary by the committee. This should be fully documented.

The investigator must not implement any deviation from or change to the protocol, without discussion with, and agreement by the sponsor and prior review and documented approval/favourable opinion of the amendment from the relevant ethics committee or competent authority, except where it is necessary to eliminate an immediate hazard to study subjects, or where the change(s) involves only logistical or administrative aspects of the study (e.g., change in monitor(s), change of telephone number(s)).

Protocol amendments will be submitted to the appropriate authority(ies) as required by the applicable regulatory requirement(s).

13. REFERENCES

13.1 Published References

1. AGIS Investigators. The Advanced Glaucoma Intervention Study (AGIS): 7. The relationship between control of intraocular pressure and visual field deterioration. Am J Ophthalmol 2000; 130:429-40.
2. Bacharach J, Dubiner HB, Levy B, et al. Double-masked, randomized, dose-response study of AR-13324 versus latanoprost in patients with elevated intraocular pressure. Ophthalmology. 2015; 122:302-307.
3. Bailey IL, Lovie JE. New design principles for visual acuity letter charts. Am JOptom Physiol Opt 1976;53:740-5.
4. Chan RY, Smith JA, Richardson KT. Arch Ophthalmol. 1981 Arch Ophthalmol. 1981 Jan; 99(1):104-7. Anterior segment configuration correlated with Shaffer's grading of anterior chamber angle.
5. Chen J, Runyan SA, Robinson MR. Novel ocular antihypertensive compounds in clinical trials. Clin Ophthalmol 2011; 5:667-77.
6. Clinical Trials Facilitation Group; Recommendations related to contraception and pregnancy testing.
7. Collaborative Normal-Tension Glaucoma Study Group. The effectiveness of intraocular pressure reduction in the treatment of normal-tension glaucoma. Am J Ophthalmol 1998; 126:498-505.
8. European Glaucoma Society, Tip of the Month, November 2011, Ann Hoste, Antwerp.
9. FDA Draft Guidance on Brimonidine Tartrate recommended Sep2008: Revised 2014, Dec 2014, Mar 2015
10. Ferris FL, Freidlin V, Kassoff A, et al. Relative letter and position difficulty on visual acuity charts from the early Treatment Diabetic Retinopathy Study. Am JOphthalmol 1993; 116:735-40.
11. GANFORT® SmPC.
12. Heijl A, Leske MC, Bengtsson B, et al. Reduction of intraocular pressure and glaucoma progression: results from the Early Manifest Glaucoma Trial. Arch Ophthalmol 2002; 120: 1268-79.
13. Hughes BA, Bacharach J, Craven ER, et al. A three-month, multicenter, double-masked study of the safety and efficacy of travoprost 0.004%/timolol 0.5% ophthalmic solution compared to travoprost 0.004% ophthalmic solution and timolol 0.5% dosed concomitantly in subjects with open angle glaucoma or ocular hypertension. J Glaucoma 2005; 14:392-9.
14. Kass MA, Heuer DK, Higginbotham EJ, et al. The Ocular Hypertension Treatment Study. Arch Ophthalmol 2002; 120:701-13.

15. Kass MA, Gordon MO, Gao F, et al. Delaying Treatment of Ocular Hypertension: The Ocular Hypertension Treatment Study. Arch Ophthalmol 2010; 128:276-87.

16. Kiel JW, Kopczynski CC. Effect of AR-13324 on episcleral venous pressure in Dutch Belted rabbits. J Ocul Pharmacol Ther 2015; 31(3):146-51.

17. Kolker AE, Hetherington J Jr, eds, Becker and Shaffer's diagnosis and therapy of glaucomas 5th ed. St Louis: CV Mosby, 1976.

18. Kopczynski CC and Epstein DL. Emerging Trabecular Outflow Drugs. J Ocul Pharmacol Ther 2014; 30:85-7.

19. Lewis RA, Levy B, Ramirez N, et al. for the PG324-CS201 Study Group. Fixed-dose combination of AR-13324 and latanoprost: a double-masked, 28-day, randomised, controlled study in patients with open-angle glaucoma or ocular hypertension. Br J Ophthalmol 2015; doi: 10.1136/bjophthalmol-2015-306778.

20. Lichter PR, Musch DC, Gillespie BW, et al. Interim clinical outcomes in the Collaborative Initial Glaucoma Treatment Study comparing initial treatment randomized to medications or surgery. Ophthalmology 2001; 108:1943–53.

21. Mangione, C. M., Lee, P. P., Gutierrez, P. R., Spritzer, K., Berry, S., & Hays, R. D. Development of the 25-item National Eye Institute Visual Function Questionnaire (VFQ-25) (2001) Archives of Ophthalmology, 119, 1050-1058.

22. Sherwood MB, Craven ER, Chou C, et al. Twice-daily 0.2% brimonidine-0.5% timolol fixed-combination therapy vs. monotherapy with timolol or brimonidine in patients with glaucoma or ocular hypertension: a 12-month randomized trial. Arch Ophthalmol 2006; 124:1230-8.

23. Stewart WC, Holmes KT, Johnson MA. Washout periods for brimonidine 0.2% and latanoprost 0.05%. Am J Ophthalmol. 2001;798-9.

24. Stone JL, Robin AL, Novack GD, et al. An objective evaluation of eye-drop instillation in glaucoma patients. Arch Ophthalmol 2009; 127:732-6.

25. Wang R-F, Williamson JE, Kopczynski C, et al. Effect of 0.04% AR-13324, a ROCK and Norepinephrine Transporter Inhibitor, on Aqueous Humour Dynamics in Normotensive Monkey Eyes. J Glaucoma, 2015; 24:51-4.

26. Wang SK and Chang RT. An emerging treatment option for glaucoma: Rho kinase inhibitors. Clin Ophthalmol 2014; 8:883-90.

27. Ware, J.E., Jr., SF-36 Health Survey Update SPINE 2000; 25 (24): 3130-9.

13.2 Internal References

1. Aerie Pharmaceuticals, Inc., AR-13324 and PG324 Investigator's Brochure.

2. AR-13324-CS101 Clinical Study Report: An Open-Label Study Assessing the Ocular and Systemic Safety and Systemic Absorption of AR-13324 Ophthalmic Solution 0.02% in Healthy Volunteers (2014).

3. AR-13324-CS102 Clinical Study Report: A double masked, randomized, paired comparison, controlled study of the aqueous humor dynamics of AR-13324 Ophthalmic Solution 0.02% in healthy volunteers (2016).
4. AR-13324-CS201 Clinical Study Report: A Phase 2, double-masked, randomized, placebo-controlled, dose-response study assessing the safety and ocular hypotensive efficacy of three doses of AR-13324 Ophthalmic Solution in patients with elevated intraocular pressure (2012).
5. AR-13324-CS202 Clinical Study Report: A phase 2, double-masked, randomized, multi-center, active-controlled, dose-response parallel-group study comparing the safety and ocular hypotensive efficacy of AR-13324 to latanoprost in patients with elevated intraocular pressure (2013).
6. AR-13324-CS301 Clinical Study Report: A double-masked, randomized, multi-center, active-controlled, parallel, 3-month study assessing the safety and ocular hypotensive efficacy of AR-13324 Ophthalmic Solution, 0.02% compared to timolol maleate ophthalmic solution, 0.5% in patients with elevated intraocular pressure (2015).
7. AR-13324-CS302 Clinical Study Report: A double masked, randomized, multi-center, active controlled, parallel 12-month study assessing the safety and efficacy of AR-13324 Ophthalmic Solution, 0.02% q.d. and b.i.d compared to Timolol Maleate Ophthalmic Solution, 0.5% b.i.d in patients with elevated intraocular pressure (2016).
8. AR-13324-CS304 Clinical Study Report: A double masked, randomized, multi-center, active controlled, parallel 6-month study with a 3-month interim analysis assessing the ocular hypotensive efficacy and safety of AR-13324 Ophthalmic Solution, 0.02% QD compared to Timolol Maleate Ophthalmic Solution, 0.5% BID in patients with elevated intraocular pressure (2017)
9. PG324-CS201 Clinical Study Report: A double-masked, randomized, controlled study assessing the safety and ocular hypotensive efficacy of PG324 Ophthalmic Solution, 0.01% and PG324 Ophthalmic Solution 0.02%, compared to AR-13324 Ophthalmic Solution 0.02% and Latanoprost Ophthalmic Solution 0.005% in patients with elevated intraocular pressure (2014).
10. PG324-CS301 Clinical Study Report: A prospective, double-masked, randomized, multi-center, active-controlled, parallel-group 12-month study assessing the safety and ocular hypotensive efficacy of PG324 Ophthalmic Solution compared to AR-13324 Ophthalmic Solution, 0.02% and Latanoprost Ophthalmic Solution, 0.005% in subjects with elevated intraocular pressure (2018)
11. PG324-CS302 Clinical Study Report: A prospective, double-masked, randomized, multi-center, active-controlled, parallel-group, 3-month study assessing the safety and ocular hypotensive efficacy of PG324 Ophthalmic Solution compared to AR-13324 Ophthalmic Solution, 0.02% and Latanoprost Ophthalmic Solution, 0.005% in subjects with elevated intraocular pressure (2018)

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[10]	X	X[10]	X			X			X			X			X	X
Clinical Labs (Chem/ Hem)[2]	X[2]															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[4]	X[4]	X[4]	X[4]	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[8]			X[8]			X[8]			X[8]	X[8]
Study Completed																X

Abbreviations: D=Day; W = Week; M = Month; HR/BP = heart rate/blood pressure; Chem/ Hem = Chemistry/Hematology; AE = adverse event; ETDRS = 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. **For women of childbearing 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.**

Note: **At the investigator's discretion photography of ocular events, such as cornea verticillata, conjunctival hemorrhage, may be taken**.

Appendix 2 Procedures

Procedures: Best Corrected Visual Acuity

Introduction: Best corrected visual acuity (Distance) will be measured at baseline and at each follow-up visit. Visual acuity will be measured using Bailey Lovie charts, ETDRS charts, or their equivalents. Accepted charts are those designed according to the following principles described by Bailey and Lovie (1976) and the National Academy of Science-National Research Council (NAS-NRC) Committee on Vision 1980 (1980): 1) letters of equal legibility; 2) combine the letters so that each line is of approximately equal difficulty (as described by Ferris 1993); 3) present five letters at each acuity level; 4) space rows by the height of the smaller letter 5) space letters by the width of same-sized letters and 6) use a logarithmic progression of letter size from logMAR (Minimum Angle of Resolution to base 10) -0.3 (20/10) to 1.0 (20/200).

Rationale: Best corrected acuity taken at follow-up visits as a measure of ocular function. Best corrected visual acuity will be measured at screening and frequently throughout the study.

Procedure: Distance visual acuity must be assessed using an Early Treatment of Diabetic Retinopathy Study (ETDRS) or equivalent chart. Visual acuity testing should precede intraocular pressure measurement, the administration of topical anesthetic agents, or any examination requiring contact with the anterior segment.

Distance visual acuity will be measured with best correction.

The visual acuity chart may be either retro-illuminated ("back-lit"), or reflectance illuminated. If the latter, then the illumination must be checked at regular intervals to be consistent with ETDRS guidelines. Standard charts for a distance from subject to chart of 3 meters to 6 meters must be used. Ideally, the subject should be seated. The right eye should be tested first. Sites are directed to refer to the instructions on the commercial ETDRS charts. If there is any question, contact the Sponsor's monitor.

The subject should attempt to read each letter, line by line, left to right, beginning with line 1 at the top of the chart (20/200 line). The subjects should be told that the chart has letters only, no numbers. If the subject reads a number, he or she should be reminded that the chart contains no numbers, and the examiner should then request a letter in lieu of the number.

The subjects should be asked to read slowly, about one letter per second, so as to achieve the best identification of each letter. He/she is not to proceed to the next letter until he/she has given a definite response.

A maximum effort should be made to identify each letter on the chart. When the subject says he/she cannot read a letter, he/she should be encouraged to guess. If the subject identifies two letters (e.g. A or B), he/she should be asked to choose one letter and, if necessary, to guess. When it becomes evident that no further meaningful readings can be made despite encouragement to read or guess, the examiner should stop the testing for that eye. However,

all letters on the last line should be attempted as letter difficulties vary and the last letter may be the only one read correctly. The number of letters missed or read incorrectly should be noted. Repeat with left eye.

In order to provide standardized and well-controlled assessment of visual acuity during the study, all visual acuity assessments for a subject must be performed consistently (e.g., the same lighting conditions, viewing distance, etc.) during the entire study.

The number of letters missed is multiplied by 0.02 and added to the baseline value to determine the logMAR visual acuity. Baseline is defined as the last line for which the subject reads at least one letter.

logMAR units VA = Baseline value + (n x 0.02).

If refraction was used at the screening or baseline, then this refraction should be used in the phoropter or trial frame for subsequent examinations. A repeated refraction is not required at these subsequent examinations.

A priori, a change of three lines (visual acuity in either eye is considered clinically significant.

For comparison with Snellen, a chart of the Snellen ratio that best corresponds with logMAR is provided in Table 2. This is provided for convenience only. Visual Acuity is not to be measured by Snellen Acuity charts in this study.

Table 2 Comparison of Snellen ration and logMAR units

Snellen ratio	logMAR
20/200	+1.0
20/160	+0.9
20/125	+0.8
20/100	+0.7
20/80	+0.6
20/62.5	+0.5
20/50	+0.4
20/40	+0.3
20/32	+0.2
20/25	+0.1
20/20	+0.0
20/16	-0.1
20/12.5	-0.2
20/10	-0.3

Procedures: Visual field examination

Visual fields must be automated threshold visual fields (e.g., 30-2 or 24-2 Humphrey or Octopus Perimetry).

C-24 SITA Standard preferred, SITA fast also allowed. Visual fields must be reliable, defined as those with a) fixation losses less than or equal to 33%, b) false positives less than

or equal to 33%, and c) false negatives less than or equal to 33%. Both eyes must have fixation losses ≤ 33% to qualify for the study. Visual fields fixation losses should not be rounded up to the next whole number value. **The gaze track and blind spot should be turned on for all visual fields assessments in order to calculate the fixation losses.**

For the visual field required at study entry:

- In order for an individual to enter the study, unreliable entry visual fields (excessive fixation losses, false negatives or false positives) must be repeated until they meet above criteria.

- They may have been performed **within three months prior to randomization**, given that they meet the above requirements.

- Visual fields are to be performed with a non-dilated pupil unless, in the opinion of the Investigator, the pupil is so miotic that dilation is required (e.g., < 3mm). If dilation was performed at baseline, it should be performed at all subsequent visual field examinations.

- If the individual is unreliable on two visual fields, the Investigator should consider that this individual is not appropriate for study entry.

Procedures: Biomicroscopy and measurement of Intraocular pressure (IOP)

The subject will be seated while being examined.

External examination and biomicroscopy will be performed using a slit lamp. Magnification will be consistent with standard clinical practice.

The clinician will examine and grade the eyelid. Observations will be documented on the appropriate CRF. The clinician will examine the conjunctiva, cornea, anterior chamber, iris, pupil and lens of the eye with the aid of a slit lamp, which is a table-mounted binocular microscope. Fluorescein dye will be instilled into the ocular cul-de-sac to facilitate this examination.

Local anesthetic will also be applied in order to facilitate IOP measurements with the Goldmann Applanation Tonometer. Tonometer validation on at least a monthly basis must be documented.

Two consecutive IOP measurements of each eye must be obtained. If the 2 measurements differ by more than 2 mmHg, a third measurement must be obtained. IOP will be analyzed as the mean of 2 measurements or as the median of 3 measurements (Sherwood 2006).

Each Goldmann tonometry value is read as an integer. When calculating the mean or median, it is possible to have a fractional value. For purposes of qualification, the number should not be rounded up to the nearest complete IOP number. For example, a mean or median value of 20.5mmHg should not be rounded up 21. Any non –integral mean IOP values obtained should be documented for the duration of study.

IOP should be measured by qualified individuals using a calibrated Goldmann applanation tonometer.

The Sponsor recommends that the same examiner should conduct all biomicroscopy examinations at each time point and at each visit for a given subject.

Biomicroscopic grading will be done as follows:

LID

Erythema

None (0) =	Normal, without any redness, or less than mild
Mild (+1) =	A low grade flushed reddish color
Moderate (+2) =	Diffused redness encompassing the entire lid margin
Severe (+3) =	Deep diffused reddish color of lid margins and superior or inferior eyelid

Edema

None (0) =	Normal, no swelling of the lid tissue, or less than mild
Mild (+1) =	Slight diffuse swelling above normal
Moderate (+2) =	General swelling
Severe (+3) =	Extensive swelling of the eyelid(s), with or without eversion of upper and/or lower lids.

CONJUNCTIVA

Hyperemia

None (0) =	Normal. Appears white with a small number of conjunctival blood vessels easily observed.
Mild (+1) =	Prominent, pinkish-red color of both the bulbar and palpebral conjunctiva;
Moderate (+2) =	Bright, scarlet red color of the bulbar and palpebral conjunctiva
Severe (+3) =	“Beefy Red” with petechiae --- Dark red bulbar and palpebral conjunctiva with evidence of subconjunctival hemorrhage

Edema

None (0) =	Normal, no swelling of the conjunctiva or less than mild
Mild (+1) =	Slight diffuse or regional swelling of the conjunctiva
Moderate (+2) =	General swelling of the conjunctiva
Severe (+3) =	Extensive swelling of the conjunctiva

CORNEA

Edema

None (0) =	Transparent and clear or less than mild
Mild (+1) =	Dull glassy appearance
Moderate (+2) =	Dull glassy appearance of epithelium with large number of vacuoles
Severe (+3) =	Stromal edema, localized or diffuse, with stromal striae

Staining

None (0) =	No fluorescein staining of epithelium, OR less than mild
Mild (+1) =	Slight punctate fluorescein staining
Moderate (+2) =	Regionally dense coalescent fluorescein staining
Severe (+3) =	Marked fluorescein staining with immediate stromal leakage as a result of epithelial loss

ANTERIOR CHAMBER

Cells

None (0) =	No cells seen or less than mild
Mild (+1) =	+ cells
Moderate (+2) =	++ cells
Severe (+3) =	+++ cells
Hypopyon (+4) =	++++ cells, Hypopyon Formation (indicate size of hypopyon)

Flare

None (0) =	No Tyndall effect or less than mild
Mild (+1) =	Tyndall beam in the anterior chamber has a mild intensity
Moderate (+2) =	Tyndall beam in the anterior chamber is of strong intensity
Severe (+3) =	Tyndall beam is very intense. The aqueous has a white, milky appearance

LENS PATHOLOGY

Lens status

- Phakic
- Pseudophakic
- Aphakic

Lens Opacity (Phakic only)

None (0) =	None present or less than mild
Mild (+1) =	Subtle
Moderate (+2) =	Moderate
Severe (+3) =	Dense

IRIS/PUPIL PATHOLOGY

Procedures: Ophthalmoscopy

The Sponsor recommends that the same masked examiner should conduct all ophthalmoscopy exams for a given subject.

RETINA, VITREOUS, MACULA, CHOROID, OPTIC NERVE

0= Normal
1= Abnormal

CUP-DISC RATIO (Vertical)

Score from 0.1 to 1.0 in 0.1 increments

A priori, a change of 0.2 units in either eye is considered clinically significant.

Procedures: Pachymetry - Central corneal thickness

Central corneal thickness will be measured by ultrasound pachymetry in both eyes (mean of two readings per eye). The mean value will be used for enrollment criteria. An additional pachymetry reading will be collected at the Month 3 and Month 6 visit.

For individuals with mean central corneal thickness greater than 620μm, they may return either the same day, or within 7 days for another pachymetry measurement. If the mean of two readings on that second pachymetry is ≤ 620μm, then the individual may be considered for the study.

Procedures: Gonioscopy

The purpose of this examination is to confirm that the iridocorneal angle is open, and that the subject does not have narrow angle glaucoma, which is an exclusion criteria for study participation. Gonioscopy may be taken up to three months prior to randomization. Gonioscopy will be performed at the slit lamp, bilaterally, using a goniolens.

Procedures: Photography

At the investigator's discretion images of treatment emergent events may be taken. Such events such as corneal verticillata or conjunctival hemorrhage can be imaged using a slit lamp mounted camera system using the investigator's normal practice. Subjects must confirm by checking the relevant section on the patient information and consent form that images can be taken and shared with the sponsor.

Images should be stored electronically ideally in an uncompressed JPEG format identifying the subject by site and patient number only and date image acquired.

Procedures: Symptomatology

Subjects will be queried "How are you feeling?" and any treatment emergent adverse events will be documented on the adverse event form.

Procedures: Heart Rate

Heart rate will be measured after the subject has been seated quietly for at least five minutes. Pulse will be detected at the wrist, and will be counted for 30 seconds, and multiplied by 2.

If an electronic measurement device is used, it must be documented.

Procedures: Blood pressure

Blood pressure will be measured after heart rate (and thus the subject will already be in a resting state). Blood pressure will be measured using a sphygmomanometer with appropriate size cuff and a stethoscope. If an electronic measurement device is used, it must be documented.

Procedures: Clinical laboratories

Central laboratories should be used for clinical chemistries as mandated by the protocol. A copy of the certification for the reference laboratory conducting any clinical laboratory tests required by this protocol will be provided. Laboratory requisition forms must be completed and samples must be clearly labelled with the subject number, protocol number, site/center number and visit date. Details for the preparation and shipment of samples and reference ranges will be provided in the laboratory manual.

A Chemistry panel and complete blood count (hematology and differential) will be performed as follows. Note that fasting is NOT required and specific values may be out of the typical fasting range.

- **Clinical chemistry:**
  - Alanine aminotransferase
  - Albumin
  - Alkaline phosphatase
  - Aspartate aminotransferase
  - Calcium
  - Creatinine
  - Glucose, Random
  - Potassium (K)
  - Sodium (Na)
  - Triglycerides
- Hematology:
  - White blood cells

- Differential Including:
  - Absolute and Percent Neutrophil Count
  - Absolute and Percent Lymphocyte Count
  - Absolute and Percent Monocyte Count
  - Absolute and Percent Eosinophil Count
  - Absolute and Percent Basophil Count
- Platelets:
  - Mean Platelet Volume
  - Platelet count
- Red blood cells
  - Hemoglobin
  - Hematocrit
  - Mean corpuscular volume
  - Mean corpuscular hemoglobin
  - Mean corpuscular hemoglobin concentration
  - Red Cell Distribution Width

- **Procedures**: Urine Pregnancy Test.
- Urine Pregnancy test for women of childbearing potential will be performed.

Procedures: Self-Administered NEI Visual Functioning Questionnaire-25 (VFQ-25)

The purpose is to evaluate the change in glaucoma quality of life score from baseline to study exit. The NEI Visual Functioning Questionnaire-25 (VFQ-25) will be completed using self-administered format at baseline and final study visit. Responses from the instrument will be coded according to developer recommendations. Further detail on the analyses of this data will be addressed in the Study Analysis Plan.

Translations of the NEI Visual Functioning Questionnaire-25 (VFQ-25), if available, will be provided for participating centers in non-English-speaking countries.

The NEI Visual Functioning Questionnaire-25 (VFQ-25) is a validated VFQ-25 and reliable 25-item version of the 51-item National Eye Institute Visual Function Questionnaire (NEI-VFQ). It is especially useful in settings such as clinical trials. (Mangione 2001).

Procedures: Self-Administered Short Form Health Survey Questionnaire-36 (SF-36 v.2)

The purpose is to evaluate the change in overall quality of life score from baseline to study exit. The survey taps eight health concepts: physical functioning, bodily pain, role limitations due to physical health problems, role limitations due to personal or emotional problems, emotional well-being, social functioning, energy/fatigue and general health perceptions. The Short Form Health Survey Questionnaire-36 (SF-36 v.2) will be completed using a self-administered format at baseline and final study visit. Responses from the instrument will be coded according to developer recommendations. Further detail on the analyses of this data will be addressed in the Study Analysis Plan.

Translations of the SF-36 v.2, if available, will be provided for participating centers in non-English-speaking countries.

Appendix 3 Marketed Product Medication Information – GANFORT®

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

GANFORT 0.3 mg/ml + 5 mg/ml eye drops, solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml of solution contains 0.3 mg of bimatoprost and 5 mg of timolol (as 6.8 mg of timolol maleate).

Excipient with known effect
Each ml of solution contains 0.05 mg of benzalkonium chloride.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Eye drops, solution.

Colourless to slightly yellow solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Reduction of intraocular pressure (IOP) in adult patients with open-angle glaucoma or ocular hypertension who are insufficiently responsive to topical beta-blockers or prostaglandin analogues.

4.2 Posology and method of administration

Posology
Recommended dosage in adults (including older people)
The recommended dose is one drop of GANFORT in the affected eye(s) once daily, administered either in the morning or in the evening. It should be administered at the same time each day.

Existing literature data for GANFORT suggest that evening dosing may be more effective in IOP lowering than morning dosing. However, consideration should be given to the likelihood of compliance when considering either morning or evening dosing (see section 5.1).

If one dose is missed, treatment should continue with the next dose as planned. The dose should not exceed one drop in the affected eye(s) daily.

Renal and hepatic impairment
GANFORT has not been studied in patients with hepatic or renal impairment. Therefore caution should be used in treating such patients.

Paediatric population
The safety and efficacy of GANFORT in children aged 0 to 18 years has not been established. No data are available.

Method of administration
If more than one topical ophthalmic medicinal product is to be used, each one should be instilled at least 5 minutes apart.

When using nasolacrimal occlusion or closing the eyelids for 2 minutes, the systemic absorption is reduced. This may result in a decrease in systemic side effects and an increase in local activity.

4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

- Reactive airway disease including bronchial asthma or a history of bronchial asthma, severe chronic obstructive pulmonary disease.

- Sinus bradycardia, sick sinus syndrome, sino-atrial block, second or third degree atrioventricular block, not controlled with pace-maker. Overt cardiac failure, cardiogenic shock.

4.4 Special warnings and precautions for use

Like other topically applied ophthalmic medicinal products, the active substances (timolol/ bimatoprost) in GANFORT may be absorbed systemically. No enhancement of the systemic absorption of the individual active substances has been observed. Due to the beta-adrenergic component, timolol, the same types of cardiovascular, pulmonary and other adverse reactions as seen with systemic beta-blockers may occur. Incidence of systemic ADRs after topical ophthalmic administration is lower than for systemic administration. To reduce the systemic absorption, see section 4.2.

Cardiac disorders
Patients with cardiovascular diseases (e.g. coronary heart disease, Prinzmetal's angina and cardiac failure) and hypotension therapy with beta-blockers should be critically assessed and therapy with other active substances should be considered. Patients with cardiovascular diseases should be watched for signs of deterioration of these diseases and of adverse reactions.

Due to its negative effect on conduction time, beta-blockers should only be given with caution to patients with first degree heart block.

Vascular disorders
Patients with severe peripheral circulatory disturbance/disorders (i.e. severe forms of Raynaud's disease or Raynaud's syndrome) should be treated with caution.

Respiratory disorders
Respiratory reactions, including death due to bronchospasm in patients with asthma have been reported following administration of some ophthalmic beta-blockers.

GANFORT should be used with caution, in patients with mild/moderate chronic obstructive pulmonary disease (COPD) and only if the potential benefit outweighs the potential risk.

Endocrine disorders
Beta-adrenergic blocking medicinal products should be administered with caution in patients subject to spontaneous hypoglycemia or to patients with labile diabetes as beta-blockers may mask the signs and symptoms of acute hypoglycemia.

Beta-blockers may also mask the signs of hyperthyroidism.

Corneal diseases
Ophthalmic β-blockers may induce dryness of eyes. Patients with corneal diseases should be treated with caution.

Other beta-blocking agents
The effect on intra-ocular pressure or the known effects of systemic beta-blockade may be potentiated when timolol is given to the patients already receiving a systemic beta-blocking agent. The response of these patients should be closely observed. The use of two topical beta-adrenergic blocking agents is not recommended (see section 4.5).

Anaphylactic reactions
While taking beta-blockers, patients with a history of atopy or a history of severe anaphylactic reaction to a variety of allergens may be more reactive to repeated challenge with such allergens and unresponsive to the usual dose of adrenaline used to treat anaphylactic reactions.

Choroidal detachment
Choroidal detachment has been reported with administration of aqueous suppressant therapy (e.g. timolol, acetazolamide) after filtration procedures.

Surgical anaesthesia
β-blocking ophthalmological preparations may block systemic β-agonist effects e.g. of adrenaline. The anaesthesiologist should be informed when the patient is receiving timolol.

Hepatic
In patients with a history of mild liver disease or abnormal alanine aminotransferase (ALT), aspartate aminotransferase (AST) and/or bilirubin at baseline, bimatoprost had no adverse reactions on liver function over 24 months. There are no known adverse reactions of ocular timolol on liver function.

Ocular
Before treatment is initiated, patients should be informed of the possibility of eyelash growth, darkening of the eyelid or periocular skin and increased brown iris pigmentation since these have been observed during treatment with bimatoprost and GANFORT. Increased iris pigmentation is likely to be permanent, and may lead to differences in appearance between the eyes if only one eye is treated. After discontinuation of GANFORT, pigmentation of iris may be permanent. After 12 months treatment with GANFORT, the incidence of iris pigmentation was 0.2%. After 12 months treatment with bimatoprost eye drops alone, the incidence was 1.5% and did not increase following 3 years treatment. The pigmentation change is due to increased melanin content in the melanocytes rather than to an increase in the number of melanocytes. The long term effects of increased iridial pigmentation are not known. Iris colour changes seen with ophthalmic administration of bimatoprost may not be noticeable for several months to years. Neither nevi nor freckles of the iris appear to be affected by treatment. Periorbital tissue pigmentation has been reported to be reversible in some patients.

Macular oedema, including cystoid macular oedema, has been reported with GANFORT. Therefore, GANFORT should be used with caution in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular oedema (e.g. intraocular surgery, retinal vein occlusions, ocular inflammatory disease and diabetic retinopathy).
GANFORT should be used with caution in patients with active intraocular inflammation (e.g. uveitis) because the inflammation may be exacerbated.

Skin
There is a potential for hair growth to occur in areas where GANFORT solution comes repeatedly in contact with the skin surface. Thus, it is important to apply GANFORT as instructed and avoid it running onto the cheek or other skin areas.

Excipients
The preservative in GANFORT, benzalkonium chloride, may cause eye irritation. Contact lenses must be removed prior to application, with at least a 15-minute wait before reinsertion. Benzalkonium chloride is known to discolour soft contact lenses. Contact with soft contact lenses must be avoided.

Benzalkonium chloride has been reported to cause punctate keratopathy and/or toxic ulcerative keratopathy. Therefore monitoring is required with frequent or prolonged use of GANFORT in dry eye patients or where the cornea is compromised.

Other conditions
GANFORT has not been studied in patients with inflammatory ocular conditions, neovascular, inflammatory, angle-closure glaucoma, congenital glaucoma or narrow-angle glaucoma.

In studies of bimatoprost 0.3 mg/ml in patients with glaucoma or ocular hypertension, it has been shown that more frequent exposure of the eye to more than 1 dose of bimatoprost daily

may decrease the IOP-lowering effect. Patients using GANFORT with other prostaglandin analogues should be monitored for changes to their intraocular pressure.

4.5 Interaction with other medicinal products and other forms of interaction

No specific interaction studies have been performed with the bimatoprost / timolol fixed combination.

There is a potential for additive effects resulting in hypotension, and/or marked bradycardia when ophthalmic beta-blockers solution is administered concomitantly with oral calcium channel blockers, guanethidine, beta-adrenergic blocking agents, parasympathomimetics, anti-arrhythmics (including amiodarone) and digitalis glycosides.

Potentiated systemic beta-blockade (e.g., decreased heart rate, depression) has been reported during combined treatment with CYP2D6 inhibitors (e.g. quinidine, fluoxetine, paroxetine) and timolol.

Mydriasis resulting from concomitant use of ophthalmic beta-blockers and adrenaline (epinephrine) has been reported occasionally.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate data from the use of the bimatoprost / timolol fixed combination in pregnant women. GANFORT should not be used during pregnancy unless clearly necessary. To reduce the systemic absorption, see section 4.2.

Bimatoprost
No adequate clinical data in exposed pregnancies are available. Animal studies have shown reproductive toxicity at high maternotoxic doses (see section 5.3).

Timolol
Epidemiological studies have not revealed malformative effects but shown a risk for intra uterine growth retardation when beta-blockers are administered by the oral route. In addition, signs and symptoms of beta-blockade (e.g. bradycardia, hypotension, respiratory distress and hypoglycaemia) have been observed in the neonate when beta-blockers have been administered until delivery. If GANFORT is administered until delivery, the neonate should be carefully monitored during the first days of life. Animal studies with timolol have shown reproductive toxicity at doses significantly higher than would be used in clinical practice (see section 5.3).

Breast-feeding

Timolol
Beta-blockers are excreted in breast milk. However, at therapeutic doses of timolol in eye drops it is not likely that sufficient amounts would be present in breast milk to produce

clinical symptoms of beta-blockade in the infant. To reduce the systemic absorption, see section 4.2.

Bimatoprost
It is not known if bimatoprost is excreted in human breast milk but it is excreted in the milk of the lactating rat. GANFORT should not be used by breast-feeding women.

Fertility
There are no data on the effects of GANFORT on human fertility.

4.7 Effects on ability to drive and use machines

GANFORT has negligible influence on the ability to drive and use machines. As with any ocular treatment, if transient blurred vision occurs at instillation, the patient should wait until the vision clears before driving or using machines.

4.8 Undesirable effects

GANFORT
Summary of the safety profile
The adverse reactions reported in clinical studies using GANFORT were limited to those earlier reported for either of the single active substances bimatoprost and timolol. No new adverse reactions specific for GANFORT have been observed in clinical studies.

The majority of adverse reactions reported in clinical studies using GANFORT were ocular, mild in severity and none were serious. Based on 12-month clinical data, the most commonly reported adverse reaction was conjunctival hyperaemia (mostly trace to mild and thought to be of a non-inflammatory nature) in approximately 26% of patients and led to discontinuation in 1.5% of patients.

Tabulated list of adverse reactions
Table 1 presents the adverse reactions that have been reported during clinical studies with all GANFORT formulations (multi-dose and single-dose) (within each frequency grouping, adverse reactions are presented in order of decreasing seriousness) or in the post-marketing period.

The frequency of possible adverse reactions listed below is defined using the following convention:

Very common	≥1/10
Common	≥1/100 to <1/10
Uncommon	≥1/1,000 to <1/100
Rare	≥1/10,000 to <1/1,000
Very rare	<1/10,000
Not known	Frequency cannot be estimated from available data

Table 1

System Organ Class	Frequency	Adverse reaction
Immune system disorders	Not known	hypersensitivity reactions including signs or symptoms of allergic dermatitis, angioedema, eye allergy
Psychiatric disorders	Not known	Insomnia[2], nightmare[2]
Nervous system disorders	Common	headache
	Not known	Dysgeusia[2], dizziness
Eye disorders	Very common	conjunctival hyperaemia.
	Common	punctuate keratitis, corneal erosion[2], burning sensation[2], conjunctival irritation[1], eye pruritus, stinging sensation in the eye[2], foreign body sensation, dry eye, erythema of eyelid, eye pain, photophobia, eye discharge, visual disturbance[2], eyelid pruritus, visual acuity worsened[2], blepharitis[2], eyelid oedema, eye irritation, lacrimation increased, growth of eyelashes.
	Uncommon	iritis[2], conjunctival oedema[2], eyelid pain[2], abnormal sensation in the eye[1], asthenopia, trichiasis[2], iris hyperpigmentation[2], deepening of eyelid sulcus, eyelid retraction[2], eyelash discolouration (darkening)[1].
	Not known	cystoid macular oedema[2], eye swelling, vision blurred[2], ocular discomfort
Cardiac disorders	Not known	Bradycardia
Vascular disorders	Not known	Hypertension
Respiratory, thoracic and mediastinal disorders	Common	Rhinitis[2]
	Uncommon	dyspnoea
	Not known	bronchospasm (predominantly in patients with pre-existing bronchospastic disease)[2], asthma

Skin and subcutaneous tissue disorders	Common	blepharal pigmentation[2], hirsutism[2], skin hyperpigmentation (periocular).
	Not known	Alopecia, skin discolouration (periocular)
General disorders and administration site conditions	Not known	fatigue

[1]adverse reactions only observed with Ganfort single-dose formulation
[2]adverse reactions only observed with Ganfort multi-dose formulation

Like other topically applied ophthalmic drugs, GANFORT (bimatoprost/timolol) is absorbed into the systemic circulation. Absorption of timolol may cause similar undesirable effects as seen with systemic beta-blocking agents. The incidence of systemic ADRs after topical ophthalmic administration is lower than for systemic administration. To reduce the systemic absorption, see section 4.2.

Additional adverse reactions that have been seen with either of the active substances (bimatoprost or timolol), and may potentially occur also with GANFORT are listed below in Table 2:

Table 2

System Organ Class	**Adverse reaction**
Immune system disorders	systemic allergic reactions including anaphylaxis[1]
Metabolism and nutrition disorders	hypoglycaemia[1]
Psychiatric disorders	depression[1], memory loss[1], hallucination[1]
Nervous system disorders	syncope[1], cerebrovascular accident[1], increase in signs and symptoms of myasthenia gravis[1], paraesthesia[1], cerebral ischaemia[1]
Eye disorders	decreased corneal sensitivity[1], diplopia[1], ptosis[1], choroidal detachment following filtration surgery (see section 4.4)[1], keratitis[1], blepharospasm[2], retinal haemorrhage[2], uveitis[2],
Cardiac disorder	atrioventricular block[1], cardiac arrest[1], arrhythmia[1], cardiac failure[1], congestive heart failure[1], chest pain[1], palpitations[1], oedema[1]
Vascular disorders	hypotension[1], Raynaud's phenomenon[1], cold hands and feet[1]
Respiratory, thoracic and mediastinal disorders	Asthma exacerbation[2], COPD exacerbation[2], cough[1]
Gastrointestinal disorders	nausea[1,2], diarrhoea[1], dyspepsia[1], dry mouth[1], abdominal pain[1], vomiting[1]
Skin and subcutaneous tissue disorders	psoriasiform rash[1] or exacerbation of psoriasis[1], skin rash[1]

Musculoskeletal and connective tissue disorders	myalgia[1]
Reproductive system and breast disorders	sexual dysfunction[1], decreased libido[1]
General disorders and administration site conditions	asthenia[1,2]
Investigations	liver function tests (LFT) abnormal[2]

[1] adverse reactions observed with Timolol
[2] adverse reactions observed with Bimatoprost

Adverse reactions reported in phosphate containing eye drops

Cases of corneal calcification have been reported very rarely in association with the use of phosphate containing eye drops in some patients with significantly damaged corneas.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V*.

4.9 Overdose

A topical overdose with GANFORT is not likely to occur or to be associated with toxicity.

Bimatoprost
If GANFORT is accidentally ingested, the following information may be useful: in two-week oral rat and mouse studies, doses of bimatoprost up to 100 mg/kg/day did not produce any toxicity. This dose expressed as mg/m2 is at least 70-times higher than the accidental dose of one bottle of GANFORT in a 10 kg child.

Timolol
Symptoms of systemic timolol overdose include: bradycardia, hypotension, bronchospasm, headache, dizziness, shortness of breath, and cardiac arrest. A study of patients with renal failure showed that timolol did not dialyse readily.

If overdose occurs treatment should be symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Ophthalmological,– beta-blocking agents – ATC code: S01ED51.

Mechanism of action
GANFORT consists of two active substances: bimatoprost and timolol. These two components decrease elevated intraocular pressure (IOP) by complementary mechanisms of action and the combined effect results in additional IOP reduction compared to either compound administered alone. GANFORT has a rapid onset of action.

Bimatoprost is a potent ocular hypotensive active substance . It is a synthetic prostamide, structurally related to prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) that does not act through any known prostaglandin receptors.
Bimatoprost selectively mimics the effects of newly discovered biosynthesised substances called prostamides. The prostamide receptor, however, has not yet been structurally identified. The mechanism of action by which bimatoprost reduces intraocular pressure in man is by increasing aqueous humour outflow through the trabecular meshwork and enhancing uveoscleral outflow.

Timolol is a $beta_1$ and $beta_2$ non-selective adrenergic receptor blocking agent that does not have significant intrinsic sympathomimetic, direct myocardial depressant, or local anaesthetic (membrane-stabilising) activity. Timolol lowers IOP by reducing aqueous humour formation. The precise mechanism of action is not clearly established, but inhibition of the increased cyclic AMP synthesis caused by endogenous beta-adrenergic stimulation is probable.

Clinical effects
The IOP-lowering effect of GANFORT is non-inferior to that achieved by adjunctive therapy of bimatoprost (once daily) and timolol (twice daily).

Existing literature data for GANFORT suggest that evening dosing may be more effective in IOP lowering than morning dosing. However, consideration should be given to the likelihood of compliance when considering either morning or evening dosing.

Paediatric population
The safety and efficacy of GANFORT in children aged 0 to 18 years has not been established.

5.2 Pharmacokinetic properties

GANFORT medicinal product
Plasma bimatoprost and timolol concentrations were determined in a crossover study comparing the monotherapy treatments to GANFORT treatment in healthy subjects. Systemic absorption of the individual components was minimal and not affected by co-administration in a single formulation.

In two 12-month studies where systemic absorption was measured, no accumulation was observed with either of the individual components.

Bimatoprost
Bimatoprost penetrates the human cornea and sclera well *in vitro*. After ocular administration, the systemic exposure of bimatoprost is very low with no accumulation over

time. After once daily ocular administration of one drop of 0.03% bimatoprost to both eyes for two weeks, blood concentrations peaked within 10 minutes after dosing and declined to below the lower limit of detection (0.025 ng/ml) within 1.5 hours after dosing. Mean C_{max} and $AUC_{0\text{-}24hrs}$ values were similar on days 7 and 14 at approximately 0.08 ng/ml and 0.09 ng•hr/ml respectively, indicating that a steady drug concentration was reached during the first week of ocular dosing.

Bimatoprost is moderately distributed into body tissues and the systemic volume of distribution in humans at steady-state was 0.67 1/kg. In human blood, bimatoprost resides mainly in the plasma. The plasma protein binding of bimatoprost is approximately 88%.

Bimatoprost is the major circulating species in the blood once it reaches the systemic circulation following ocular dosing. Bimatoprost then undergoes oxidation, N-deethylation and glucuronidation to form a diverse variety of metabolites.

Bimatoprost is eliminated primarily by renal excretion, up to 67% of an intravenous dose administered to healthy volunteers was excreted in the urine, 25% of the dose was excreted via the faeces. The elimination half-life, determined after intravenous administration, was approximately 45 minutes; the total blood clearance was 1.5 1/hr/kg.

Characteristics in older people
After twice daily dosing, the mean $AUC_{0\text{-}24hrs}$ value of 0.0634 ng•hr/ml bimatoprost in the elderly (subjects 65 years or older) were significantly higher than 0.0218 ng•hr/ml in young healthy adults. However, this finding is not clinically relevant as systemic exposure for both elderly and young subjects remained very low from ocular dosing. There was no accumulation of bimatoprost in the blood over time and the safety profile was similar in elderly and young patients.

Timolol
After ocular administration of a 0.5% eye drops solution in humans undergoing cataract surgery, peak timolol concentration was 898 ng/ml in the aqueous humour at one hour post-dose. Part of the dose is absorbed systemically where it is extensively metabolised in the liver. The half-life of timolol in plasma is about 4 to 6 hours. Timolol is partially metabolised by the liver with timolol and its metabolites excreted by the kidney. Timolol is not extensively bound to plasma.

5.3 Preclinical safety data

GANFORT medicinal product
Repeated dose ocular toxicity studies on GANFORT showed no special hazard for humans. The ocular and systemic safety profile of the individual components is well established.

Bimatoprost
Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity, carcinogenic potential. Studies in rodents produced species-specific abortion at systemic exposure levels 33- to 97-times that achieved in humans after ocular administration.

Monkeys administered ocular bimatoprost concentrations of ≥0.03% daily for 1 year had an increase in iris pigmentation and reversible dose-related periocular effects characterised by a prominent upper and/or lower sulcus and widening of the palpebral fissure. The increased iris pigmentation appears to be caused by increased stimulation of melanin production in melanocytes and not by an increase in melanocyte number. No functional or microscopic changes related to the periocular effects have been observed, and the mechanism of action for the periocular changes is unknown.

Timolol
Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzalkonium chloride
Sodium chloride
Sodium phosphate dibasic heptahydrate
Citric acid monohydrate
Hydrochloric acid or sodium hydroxide (to adjust pH)
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

Chemical and physical in-use stability has been demonstrated for 28 days at 25°C.

From a microbiological point of view, the in-use storage times and conditions are the responsibility of the user and would normally not be longer than 28 days at 25°C.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

White opaque low-density polyethylene bottles with polystyrene screw cap. Each bottle has a fill volume of 3 ml.

The following pack sizes are available: cartons containing 1 or 3 bottles of 3 ml. Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Allergan Pharmaceuticals Ireland
Castlebar Road
Westport
Co. Mayo
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/340/001-002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation 19 May 2006
Date of latest renewal 23 June 2011

10. DATE OF REVISION OF THE TEXT

<{MM/YYYY}>
<{DD/MM/YYYY}>
<{DD month YYYY}>

Detailed information on this medicinal product is available on the website of the European Medicines Agency: http://www.ema.europa.eu/.

GANFORT® Product Information obtained from www.ema.europa.eu, date of last update 26 February 2020

Investigators should review the above website for the current version of the Summary of Product Characteristics for GANFORT® eye drops.

Appendix 4 Sponsor's Obligations

Aerie Pharmaceuticals Ireland Ltd. is committed to:

A. Complying with the local health authority regulations for the conduct of clinical research studies.

B. Informing the Investigator of any new information about the investigational product that may affect the subject's welfare or may influence the subject's decision to continue participation in the study.

C. In the event of a serious adverse experience, whether related to the use of the study medication or device or not, or the death of a subject, the Sponsor is responsible for notifying the regulatory authority(ies) immediately (see Section 7.2, Adverse events Assessments and Ocular safety).

D. When the study is terminated the Sponsor should promptly inform the regulatory authority(ies) of the termination and the reason(s) for it. The IEC/CEC should also be informed promptly and provide the reason(s) for the termination by the Sponsor as specified by the applicable regulatory requirement(s).

E. Providing to the Investigator the most up-to-date editions of the Clinical Investigator's Brochure (for the investigational product), the protocol, Serious Adverse Experience forms, and a full set of Case Report Forms for each subject entered into the study to document the study evaluation parameters.

F. Providing study medications suitably masked/blinded, coded and packaged for use with subjects entered into the study.

G. Providing statistical and report writing resources to complete appropriate reporting of study results.

H. Ensuring equity considerations among all Investigators in multicenter studies, including all matters of publications and meeting presentations, etc. (where applicable).

I. Prepare an FDA Form No. 3454 (Certification: Financial Interests and Arrangements of Clinical Investigators) or 3455 (Disclosure: Financial Interests and Arrangements of Clinical Investigators) or Sponsor's equivalent.

Appendix 5 Investigator's Obligations

An Investigator for the PG324-CS303 study must be a physician duly qualified to practice medicine. The Investigator is obligated to:

A. Questioning (evaluation of) examination regarding, as well as collection and documentation of, adverse events and efficacy parameters. In the event of a serious adverse experience, whether related to the use of the study medication or device or not, or the death of a subject, the Investigator is responsible for notifying the Sponsor Safety Officer immediately (see Section 7.2 Adverse Events Assessment and Ocular Safety). The Investigator must also notify the Sponsor Representative and the Institutional Review Board (IEC/ CEC) to which he/she is responsible.

B. Under 21 CFR 54 and according to the EU Clinical Trials Directive 2001/20/EC the Investigator/Sub investigator is required to provide the sponsor with sufficient accurate financial information to allow for complete disclosure or certification and to update this information if any relevant changes occur during the study and for one year following its completion

C. Obtain and submit to the Sponsor a copy of his/her IEC/ CEC approval of the protocol prior to initiating the study.

D. Obtain signed informed consent from each subject or his/her legal guardian prior to acceptance of the subject into the study.

E. Read, and agree to adhere to the study protocol prior to the initiation of the study. Deviations from the study protocol are not to be implemented without the prior written approval of the Sponsor and IEC/ CEC, unless protection of the safety and welfare of study subjects requires prompt action. During the study, if the Investigator feels that in his/her clinical judgment, it is necessary to promptly terminate one or more subjects from the study, or to promptly implement reasonable alternatives to, or deviations from the protocol in consideration of the safety of study subjects, the Sponsor is to be notified of these terminations, alternatives, and deviations, and the reasons for such changes are to be documented in the study records. The Investigator is to also notify his/her IEC/ CEC of any such changes.

F. Accurately record, at the Investigator's site, all required data on each subject's CRF.

G. Replace subjects consistent with the directions in Section 4.1

H. Keep accurate records of the number of study medication or device units received from the Sponsor and dispensed or administered to each subject during the study, and return any unused study medication or devices to the Sponsor at the completion of the study. Before returning the study medications or devices to the Sponsor, a detailed inventory should be recorded and placed in the Investigator's file.

I. Assure that Investigational Products will be dispensed or administered only to subjects under his/her personal supervision, or under the supervision of authorized sub-Investigators responsible to him/her.

J. Allow a representative of the Sponsor and/or representatives of health regulatory agencies to inspect all CRFs and corresponding portions of each study subject's original office, hospital, and laboratory records at mutually convenient times at regular intervals during the study and upon request after the study has been completed. The purpose of these on-site monitoring visits is to provide the Sponsor the opportunity to evaluate the progress of the study, document compliance with the protocol and with regulatory requirements, verify the accuracy and completeness of subject CRFs, resolve any apparent discrepancies or inconsistencies in the study records, and account for all investigational supplies.

K. Provide the governing IEC/CEC with a brief (i.e., 1 to 3 pages) Investigator's summary within 90 working days of the study completion.

L. Complete the study within the time limits agreed upon with the Sponsor prior to the initiation of the study.

M. Maintenance of records

a. Disposition of drug. An investigator is required to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects. If the investigation is terminated, suspended, discontinued, or completed, the investigator shall return the unused supplies of the drug to the Sponsor, or otherwise provide for disposition of the unused supplies of the drug according to Clinical Trial Directive 2001/20/EC

b. Case histories. An investigator is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation. Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. The case history for each individual shall document that informed consent was obtained prior to participation in the study.

c. Record retention. An investigator shall retain records required to be maintained under this part for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and the IEC/ CEC and the country specific Competent Authority is notified.

These documents should be retained for a longer period however if required by the applicable regulatory requirements or by an agreement with the Sponsor.

If for any reason the Investigator withdraws from the responsibility of maintaining the study records for the required period of time, custody of the records may be transferred to any other person who will accept responsibility for the records. The Sponsor is to be notified in writing of any such transfer.

Appendix 6 Declaration of Helsinki

Recommendations Guiding Medical Doctors in Biomedical Research Involving Human Subjects.

I. BASIC PRINCIPLES

1. Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.

2. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted to a specially appointed independent committee for consideration, comment and guidance.

3. Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest with the subject of the research, even though the subject has given his or her consent.

4. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.

5. Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.

6. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

7. Doctors should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Doctors should cease any investigation if the hazards are found to outweigh the potential benefits.

8. In publication of the results of his or her research, the doctor is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

9. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her

consent to participation at any time. The doctor should then obtain the subject's given informed consent, preferably in writing.

10. When obtaining informed consent for the research project the doctor should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case, the informed consent should be obtained by a doctor who is not engaged in the investigation and who is completely independent of this official relationship.

11. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation.

12. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

II. MEDICAL RESEARCH COMBINED WITH PROFESSIONAL CARE (CLINICAL RESEARCH)

1. In the treatment of the sick person, the doctor must be free to use a new diagnostic and therapeutic measure, if in his or her judgment it offers hope of saving life, reestablishing health or alleviating suffering.

2. The potential benefits, hazards and discomforts of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.

3. In any medical study, all subjects - including those of a control group, if any, should be assured of the best proven diagnostic and therapeutic methods.

4. The refusal of the patient to participate in a study must never interfere with the doctor-patient relationship.

5. If the doctor considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee.

6. The doctor can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

III. NON-THERAPEUTIC BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECT (NONCLINICAL BIOMEDICAL RESEARCH)

1. In the purely scientific application of medical research carried out on a human being, it is the duty of the doctor to remain the protector of the life and health of that person on whom biomedical research is being carried out.

2. The subjects should be volunteers - either healthy person or subjects for whom the experimental design is not related to the patient's illness.

3. The Investigator or the team should discontinue the research if in his/her or their judgment it may, if continued, be harmful to the individual.

4. In research on man, the interest of science and society should never take precedence over consideration related to the well-being of the subject.

Appendix 7 Self-Administered National Eye Institute Visual Functioning Questionnaire-25 (VFQ-25)

PB/SA

National Eye Institute Visual Functioning Questionnaire-25 (VFQ-25)

Version 2000

(SELF-ADMINISTERED FORMAT)

January 2000

NEI-VFQ25 (Self Administered) - UK/English – Version of 26 Aug 04 - Mapi.
ID2285_item16a:2980

The following is a survey with statements about problems which involve your eyesight or feelings that you have about your eye condition. After each question please choose the response that best describes your situation.

Please answer all the questions as if you were wearing your glasses or contact lenses (if any).

Please take as much time as you need to answer each question. All your answers are confidential. As the purpose of this survey is to improve our knowledge about eyesight problems and how they affect your quality of life, your answers must be as accurate as possible. Remember, if you wear glasses or contact lenses, please answer all of the following questions as if you were wearing them.

INSTRUCTIONS:

1. **In general, we would like to have people try to complete these forms on their own. If you find that you need assistance, please feel free to ask the project staff and they will assist you.**

2. **Please answer every question (unless you are asked to skip questions because they do not apply to you).**

3. **Answer the questions by circling the appropriate number.**

4. **If you are unsure of how to answer a question, please give the best answer you can and make a comment in the left margin.**

5. **Please complete the questionnaire before leaving the centre and give it to a member of the project staff. Do not take it home.**

6. **If you have any questions, please feel free to ask a member of the project staff, and they will be glad to help you.**

STATEMENT OF CONFIDENTIALITY:

All information that would permit identification of any person who completed this questionnaire will be regarded as strictly confidential. Such information will be used only for the purposes of this study and will not be disclosed or released for any other purposes without prior consent, except as required by law.

NEI-VFQ25 (Self Administered) - UK/English – Version of 26 Aug 04 - Mapi.
ID2285_item16a:2980

Visual Functioning Questionnaire-25

PART 1 - GENERAL HEALTH AND VISION

1. In general, would you say your health is:

	(Circle One)
Excellent	1
Very Good	2
Good	3
Fair	4
Poor	5

2. At the present time, would you say your eyesight in both eyes (with glasses or contact lenses, if you wear them) is excellent, good, fair, poor, or very poor, or are you completely blind?

	(Circle One)
Excellent	1
Good	2
Fair	3
Poor	4
Very Poor	5
Completely Blind	6

NEI-VFQ25 (Self Administered) - UK/English – Version of 26 Aug 04 - Mapi.
ID2285_item16a:2980

3. How often are you concerned about your eyesight?

	(Circle One)
None of the time	1
A little of the time	2
Some of the time	3
Most of the time	4
All of the time?	5

4. How much pain or discomfort have you had in and around your eyes (for example, burning, itching, or aching)?

	(Circle One)
None	1
Mild	2
Moderate	3
Severe	4
Very severe?	5

PART 2 - DIFFICULTY WITH ACTIVITIES

The next questions are about how much difficulty, if any, you have doing certain activities wearing your glasses or contact lenses if you use them for those activities.

5. How much difficulty do you have reading ordinary print in newspapers?

	(Circle One)
No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

NEI-VFQ25 (Self Administered) - UK/English – Version of 26 Aug 04 - Mapi.
ID2285_item16a:2980

6. How much difficulty do you have doing work or hobbies that require you to see well close up, such as cooking, sewing, fixing things around the house, or using hand tools?

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

7. Because of your eyesight, how much difficulty do you have finding something on a crowded shelf?

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

8. How much difficulty do you have reading street signs or the names of shops?

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

NEI-VFQ25 (Self Administered) - UK/English – Version of 26 Aug 04 - Mapi.
ID2285_item16a:2980

9. Because of your eyesight, how much difficulty do you have going down steps, stairs, or curbs in dim light or at night?

	(Circle One)
No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

10. Because of your eyesight, how much difficulty do you have noticing objects on the side while you are walking straight ahead?

	(Circle One)
No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

11. Because of your eyesight, how much difficulty do you have seeing how people react to things you say?

	(Circle One)
No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

NEI-VFQ25 (Self Administered) - UK/English – Version of 26 Aug 04 - Mapi.
ID2285_item16a:2980

12. Because of your eyesight, how much difficulty do you have picking out and matching your own clothes?

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

13. Because of your eyesight, how much difficulty do you have visiting with people in their homes, at parties, or in restaurants?

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

14. Because of your eyesight, how much difficulty do you have going out to see films, plays or sports events?

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

NEI-VFQ25 (Self Administered) - UK/English – Version of 26 Aug 04 - Mapi.
ID2285_item16a:2980

15. Are you currently driving, at least once in a while?

(Circle One)

Yes ..... 1 ***Skip To Q 15c***

15a. IF NO: Have you never driven or have you given up driving?

(Circle One)

Never drove..... 1 ***Skip To Part 3, Q 17***

Gave up 2

15b. IF YOU HAVE GIVEN UP DRIVING: Was that mainly because of your eyesight, for some other reason, or because of your eyesight and other reasons?

(Circle One)

Mainly eyesight..... 1 ***Skip To Part 3, Q 17***

Mainly other reasons..... 2 ***Skip To Part 3, Q 17***

Eyesight and other reasons..... 3 ***Skip To Part 3, Q 17***

15c. IF CURRENTLY DRIVING: How much difficulty do you have driving during the daytime in familiar places? Would you say you have:

(Circle One)

No difficulty at all..... 1
A little difficulty 2
Moderate difficulty 3
Extreme difficulty 4

NEI-VFQ25 (Self Administered) - UK/English – Version of 26 Aug 04 - Mapi.
ID2285_item16a:2980

16. How much difficulty do you have driving at night?

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Have you stopped doing this because of your eyesight	5
Have you stopped doing this for other reasons or not interested in doing this	6

16a. How much difficulty do you have driving in difficult conditions, such as in bad weather, during the rush hour, on the motorway, or in city traffic?

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Have you stopped doing this because of your eyesight?	5
Have you stopped doing this for other reasons or are you not interested in doing this?	6

NEI-VFQ25 (Self Administered) - UK/English – Version of 26 Aug 04 - Mapi.
ID2285_item16a:2980

PART 3 - RESPONSES TO VISION PROBLEMS

The next questions are about things you may do because of your vision. For each one, please circle the number to indicate whether for you the statement is true for you all, most, some, a little, or none of the time.

READ CATEGORIES:	All of the time	Most of the time	Some of the time	A little of the time	None of the time
	(Circle One On Each Line)				
17. Do you accomplish less than you would like to because of your eyesight?	1	2	3	4	5
18. Are you limited in how long you can work or do your activities because of your eyesight?.....	1	2	3	4	5
19. How often does pain or discomfort in or around your eyes, for example, burning, itching, or aching, keep you from doing what you'd like to be doing?	1	2	3	4	5

NEI-VFQ25 (Self Administered) - UK/English – Version of 26 Aug 04 - Mapi.
ID2285_item16a:2980

For each of the following statements, please circle the number to indicate whether for you the statement is definitely true, mostly true, mostly false, or definitely false, or you are not sure.

(Circle One On Each Line)

	Definitely True	Mostly True	Not sure	Mostly False	Definitely False
20. I stay at home most of the time because of my eyesight	1	2	3	4	5
21. I feel frustrated a lot of the time because of my eyesight	1	2	3	4	5
22. I have much less control over what I do, because of my eyesight	1	2	3	4	5
23. Because of my eyesight, I have to rely too much on what other people tell me	1	2	3	4	5
24. I need a lot of help from others because of my eyesight	1	2	3	4	5
25. I am concerned about doing things that might embarrass myself or others, because of my eyesight	1	2	3	4	5
eyesight					

NEI-VFQ25 (Self Administered) - UK/English – Version of 26 Aug 04 - Mapi.
ID2285_item16a:2980

Appendix 8 Health Survey Questionnaire Short Form 36 Questions (SF-36)

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. ***Thank you for completing this survey!***

For each of the following questions, please tick the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. <u>Compared to one year ago</u>, how would you rate your health in general <u>now</u>?

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

3. The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	☐ 1	☐ 2	☐ 3
b Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
c Lifting or carrying groceries	☐ 1	☐ 2	☐ 3
d Climbing several flights of stairs	☐ 1	☐ 2	☐ 3
e Climbing one flight of stairs	☐ 1	☐ 2	☐ 3
f Bending, kneeling, or stooping	☐ 1	☐ 2	☐ 3
g Walking more than a mile	☐ 1	☐ 2	☐ 3
h Walking several hundred yards	☐ 1	☐ 2	☐ 3
i Walking one hundred yards	☐ 1	☐ 2	☐ 3
j Bathing or dressing yourself	☐ 1	☐ 2	☐ 3

4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Were limited in the kind of work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Had difficulty performing the work or other activities (for example, it took extra effort)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

5. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Did work or other activities less carefully than usual	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

6. During the <u>past 4 weeks</u>, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours, or groups?

Not at all	Slightly	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

7. How much <u>bodily</u> pain have you had during the <u>past 4 weeks</u>?

None	Very mild	Mild	Moderate	Severe	Very severe
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

8. During the <u>past 4 weeks</u>, how much did <u>pain</u> interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks…

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Did you feel full of life?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Have you been very nervous?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Have you felt so down in the dumps that nothing could cheer you up?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
e Did you have a lot of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
f Have you felt downhearted and low?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
g Did you feel worn out?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
h Have you been happy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
i Did you feel tired?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

11. How TRUE or FALSE is <u>each</u> of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a I seem to get ill more easily than other people	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b I am as healthy as anybody I know	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c I expect my health to get worse	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d My health is excellent	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Thank you for completing these questions!