Clinical trial results:
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)

Summary

EudraCT number	2015-001528-41
Trial protocol	GB ES BE AT LV HU PL IT
Global end of trial date	06 November 2020

Results information

Result version number	v1 (current)
This version publication date	29 November 2021
First version publication date	29 November 2021

Trial information

Trial identification

Sponsor protocol code	PG324-CS303

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03284853
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Aerie Pharmaceuticals Ireland Ltd.
Sponsor organisation address	Pembroke House, 28-32 Pembroke Street Upper, Dublin 2, Ireland, D02EK84
Public contact	Michelle Senchyna, PhD. Vice President, Clinical Development & Medical Affairs., Aerie Pharmaceuticals Inc., +1 908 947 3551, msenchyna@aeriepharma.com
Scientific contact	Finbar O'Neill, Aerie Pharmaceuticals Ireland Ltd., +353 87 632 8837, foneill@aeriepharma.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	13 October 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	06 November 2020
Global end of trial reached?	Yes
Global end of trial date	06 November 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate:
- The ocular hypotensive efficacy of PG324 Ophthalmic Solution relative to GANFORT® Ophthalmic solution over a 3-month period
- The ocular and systemic safety of PG324 Ophthalmic Solution relative to GANFORT® Ophthalmic solution over a 6-month period

Protection of trial subjects:

Potential study subjects were given all relevant study information and adequate time to consider participation as part of the Informed Consent process.

The study visit schedule and assessments performed were designed with consideration to minimise study burden for the subjects. All study visits were conducted at a clinic site, and by the investigator team, familiar to the subject.

Study medication was a single eye drop, self-administered to both eyes by the subject (or by a guardian/alternative person where appropriate), once daily in their own home.

Background therapy:

No background therapy was used in this study.

Evidence for comparator:

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 two pivotal studies, this study was conducted to compare PG324 to an existing fixed dose combination therapy containing a prostaglandin analogue. Following review of the study through scientific advice procedure with the EMA, GANFORT® (bimatoprost 0.03% and timolol maleate 0.5% ophthalmic solution) was confirmed as the comparator.

Actual start date of recruitment	05 September 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 6
Country: Number of subjects enrolled	Spain: 127
Country: Number of subjects enrolled	United Kingdom: 35
Country: Number of subjects enrolled	Austria: 34
Country: Number of subjects enrolled	Belgium: 10
Country: Number of subjects enrolled	Czechia: 61
Country: Number of subjects enrolled	France: 6

Country: Number of subjects enrolled	Germany: 74
Country: Number of subjects enrolled	Hungary: 19
Country: Number of subjects enrolled	Italy: 42
Country: Number of subjects enrolled	Latvia: 16
Worldwide total number of subjects	430
EEA total number of subjects	395

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	150
From 65 to 84 years	270
85 years and over	10

Subject disposition

Recruitment

Recruitment details:

Recruitment took place in 11 European countries between September 2017 and May 2020.

Pre-assignment

Screening details:

All participants underwent a period of washout for their pre-study ocular hypotensive medication for a prescribed period (up to 4 weeks or longer), depending on the medication, before receiving study medication.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

All subjects (and carers/guardians or alternatives, where relevant) and the site clinical study team remained blinded for the duration of the study.

Blinding was maintained using appropriate packaging and labelling, and separate user-specific access for all electronic study systems used for randomization, medication allocation and data collection.

Arms

Are arms mutually exclusive?	Yes
Arm title	Netarsudil/Latanoprost 0.02%/0.005%

Arm description:

PG324 Ophthalmic Solution (netarsudil 0.02% / latanoprost 0.005%) one drop daily to each eye for 180 days.

Arm type	Experimental
Investigational medicinal product name	Netarsudil/Latanoprost 0.02%/0.005%: Topical sterile ophthalmic solution
Investigational medicinal product code	PG324
Other name	
Pharmaceutical forms	Eye drops, solution
Routes of administration	Ocular use

Dosage and administration details:

One drop daily to each eye for 180 days.

Arm title	GANFORT®

Arm description:

GANFORT® (bimatoprost 0.03%/timolol 0.5%) Ophthalmic solution one drop daily to each eye for 180 days.

Arm type	Active comparator
Investigational medicinal product name	GANFORT®: Topical sterile ophthalmic solution
Investigational medicinal product code	GANFORT
Other name	
Pharmaceutical forms	Eye drops, solution
Routes of administration	Ocular use

Dosage and administration details:

One drop daily to each eye for 180 days.

Number of subjects in period 1	Netarsudil/Latanoprost 0.02%/0.005%	GANFORT®
Started	218	212
Completed	163	199
Not completed	55	13
Adverse event, serious fatal	-	1
Consent withdrawn by subject	5	1
Disallowed concurrent medication	1	1
Adverse event, non-fatal	40	4
Reason not reported in CSR	4	3
Lost to follow-up	1	-
Lack of efficacy	1	-
Protocol deviation	3	3

Baseline characteristics

Reporting groups	
Reporting group title	Netarsudil/Latanoprost 0.02%/0.005%
Reporting group description:	
PG324 Ophthalmic Solution (netarsudil 0.02% / latanoprost 0.005%) one drop daily to each eye for 180 days.	

Reporting group title	GANFORT®
Reporting group description:	
GANFORT® (bimatoprost 0.03%/timolol 0.5%) Ophthalmic solution one drop daily to each eye for 180 days.	

Reporting group values	Netarsudil/Latanoprost 0.02%/0.005%	GANFORT®	Total
Number of subjects	218	212	430
Age categorical			
Participants were randomized on a 1:1 ratio to either arm. Age was not a consideration for arm assignment.			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	71	79	150
From 65-84 years	140	130	270
85 years and over	7	3	10
Age continuous			
Participants were randomized on a 1:1 ratio to either arm. Age was not a consideration for arm assignment.			
Units: years			
arithmetic mean	67.3	67.0	
full range (min-max)	25 to 91	22 to 91	-
Gender categorical			
Participants were randomized on a 1:1 ratio to either arm. Gender was not a consideration for arm assignment.			
Units: Subjects			
Female	131	92	223
Male	87	120	207

End points

End points reporting groups

Reporting group title	Netarsudil/Latanoprost 0.02%/0.005%

Reporting group description:

PG324 Ophthalmic Solution (netarsudil 0.02% / latanoprost 0.005%) one drop daily to each eye for 180 days.

Reporting group title	GANFORT®

Reporting group description:

GANFORT® (bimatoprost 0.03%/timolol 0.5%) Ophthalmic solution one drop daily to each eye for 180 days.

Primary: Comparison of PG324 to Ganfort for mean intraocular pressure at specified timepoints

End point title	Comparison of PG324 to Ganfort for mean intraocular pressure at specified timepoints

End point description:

Least squares mean diurnal intraocular pressure (IOP) measured by Goldmann Applanation Tonometry at the specified timepoints.

End point type	Primary

End point timeframe:

Specified timepoints: Week 2, Week 6 and Month 3

End point values	Netarsudil/Latanoprost 0.02%/0.005%	GANFORT®		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	218	212		
Units: mmHg				
least squares mean (full range (min-max))				
Mean IOP at Week 2	15.39 (15.09 to 15.84)	15.56 (15.42 to 15.67)		
Mean IOP at Week 6	15.64 (15.18 to 16.20)	15.25 (15.16 to 15.32)		
Mean IOP at Month 3	15.61 (15.28 to 15.93)	15.19 (15.09 to 15.27)		

Statistical analyses

Statistical analysis title	Statistical Analysis Overview

Statistical analysis description:

The primary analysis was performed on the per protocol population with imputation by Markov Chain Monte Carlo method.

Linear model with IOP at the given visit and time point as the response, baseline IOP as a covariate, and treatment as a main effect factor at each time point (08:00, 10:00, and 16:00 hours at the Week 2,

Week 6, and Month 3 Visits).

Comparison groups	Netarsudil/Latanoprost 0.02%/0.005% v GANFORT®
Number of subjects included in analysis	430
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
P-value	< 0.05
Method	Regression, Linear

Notes:

[1] - Non-inferiority for PG324 was concluded if the UL of the 95% CI was ≤ l.5 mmHg at all 9 time points and ≤ l.0 mmHg at the majority of time points.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse event data was collected from the first participant Screening visit until the last study visit of the last participant. This was a period of approximately 3 years and 3 months.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Netarsudil/Latanoprost 0.02%/0.005%

Reporting group description:

PG324 Ophthalmic Solution (netarsudil 0.02% / latanoprost 0.005%) one drop daily to each eye for 180 days.

Reporting group title	GANFORT®

Reporting group description:

GANFORT® (bimatoprost 0.03%/timolol 0.5%) Ophthalmic solution one drop daily to each eye for 180 days.

Serious adverse events	Netarsudil/Latanoprost 0.02%/0.005%	GANFORT®	
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 218 (3.21%)	7 / 212 (3.30%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastases to lung			
subjects affected / exposed	0 / 218 (0.00%)	1 / 212 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transitional cell carcinoma			
subjects affected / exposed	1 / 218 (0.46%)	0 / 212 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Accidental poisoning			

subjects affected / exposed	0 / 218 (0.00%)	1 / 212 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	0 / 218 (0.00%)	1 / 212 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Congenital, familial and genetic disorders			
Dermoid cyst			
subjects affected / exposed	0 / 218 (0.00%)	1 / 212 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	0 / 218 (0.00%)	1 / 212 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Umbilical hernia repair			
subjects affected / exposed	1 / 218 (0.46%)	0 / 212 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Facial paralysis			
subjects affected / exposed	0 / 218 (0.00%)	1 / 212 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	0 / 218 (0.00%)	1 / 212 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Enteritis			

subjects affected / exposed	1 / 218 (0.46%)	0 / 212 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	1 / 218 (0.46%)	0 / 212 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	2 / 218 (0.92%)	0 / 212 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	1 / 218 (0.46%)	0 / 212 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	0 / 218 (0.00%)	1 / 212 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Inappropriate antidiuretic hormone secretion			
subjects affected / exposed	1 / 218 (0.46%)	0 / 212 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Lower respiratory tract infection			
subjects affected / exposed	0 / 218 (0.00%)	1 / 212 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			

subjects affected / exposed	0 / 218 (0.00%)	1 / 212 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Netarsudil/Latanoprost 0.02%/0.005%	GANFORT®	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	117 / 218 (53.67%)	53 / 212 (25.00%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	10 / 218 (4.59%)	17 / 212 (8.02%)	
occurrences (all)	10	17	
Eye disorders			
Conjunctival haemorrhage			
subjects affected / exposed	18 / 218 (8.26%)	5 / 212 (2.36%)	
occurrences (all)	18	5	
Conjunctival hyperaemia			
subjects affected / exposed	72 / 218 (33.03%)	23 / 212 (10.85%)	
occurrences (all)	72	23	
Conjunctivitis allergic			
subjects affected / exposed	12 / 218 (5.50%)	1 / 212 (0.47%)	
occurrences (all)	12	1	
Cornea verticillata			
subjects affected / exposed	24 / 218 (11.01%)	0 / 212 (0.00%)	
occurrences (all)	24	0	
Eye pruritus			
subjects affected / exposed	17 / 218 (7.80%)	4 / 212 (1.89%)	
occurrences (all)	17	4	
Punctate keratitis			
subjects affected / exposed	12 / 218 (5.50%)	5 / 212 (2.36%)	
occurrences (all)	12	5	
Infections and infestations			
Viral upper respiratory tract infection			
subjects affected / exposed	11 / 218 (5.05%)	10 / 212 (4.72%)	
occurrences (all)	11	10	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 January 2017	Amendment #1: 27 January 2017 Changes made included 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.
07 April 2017	Amendment #2: 07 April 2017 (Country Specific - UK) Changes made to the Protocol include: • 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.
05 June 2017	Amendment #3: 05 June 2017 Changes to the protocol have been made in accordance with observations made by the following Competent Authorities and/or Ethics Committees in participating countries. These changes included the following: • Clarification of eligibility criteria • Guidance on use of the NEI VFQ-25 questionnaire • Details on contraception use • Instructions for the washout period (duration, monitoring of subjects, etc.) • Clarification on subjects capable of giving consent to participate • Addition of a pregnancy test type and timepoints • Justification for the 30-day period post-study to refrain from breast feeding • Introduction of drug interactions indicated in the GANFORT SmPC • Various administrative changes and updates

19 March 2018	Amendment #4: 19 March 2018 1. Changes to inclusion and exclusion criteria were 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) to 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 would 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 were made: 1. From the time that the subject gives written consent events that occur to 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. INC Research has changed name to Syneos Health. INC research has been updated to the new company name Syneos Health throughout. Other changes were made to correct typographical errors and inconsistencies.
06 August 2018	Amendment #5: 06 August 2018 (Country Specific – Hungary) Changes to the protocol were made in accordance with observations made by the Hungary Medical Research Council Ethics Committee for Clinical Pharmacology (MRC ECCP) 23 July 2018. The changes were to amend the study title to clarify that PG324 is a fixed dose combination of netarsudil and latanoprost.
27 May 2020	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.
27 May 2020	Amendment #7: 27 May 2020 (Country Specific Hungary) 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.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

None

Notes: