19 September 2019
EMA/545191/2019
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Rhokiinsa

International non-proprietary name: netarsudil

Procedure No. EMEA/H/C/004583/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AM	Morning
AST	Aspartate aminotransferase
AUC	Area under the curve
BAK	Benzalkonium chloride
BID	Twice daily
BP	Blood pressure
BPM	Beats per minute
C_{max}	Maximum concentration
CAD	cationic amphiphilic drug
CNS	Central nervous system
CPP	Critical Process Parameters
CQA	Critical Quality Attributes
CSR	Clinical study report
CV	Cardiovascular
CYP	Cytochrome
DBMPP	(S)-3-amino-2-(4-(((2,4- dimethylbenzoyl)oxy)methyl)phenyl)propanoic acid
DBP	Diastolic blood pressure
DE	Diastereomeric Excess
DVS	Dynamic Vapor Sorption
ECD	Endothelial cell density
EU	European Union
F	Female
FDA	Food and drug administration
hERG	human Ether-à-go-go-Related Gene
HR	Heart rate
HTM	human trabecular meshwork
ICH	International Council for Harmonization
IOP	Intraocular pressure

ISS	Integrated summary of safety
M	Male
MAA	Marketing Authorization Application
MedDRA	Medical Dictionary for Regulatory activities
NDA	New drug application
NET	norepinephrine transporter
NTG	Normal Tension Glaucoma
OAG	Open-angle glaucoma
OD	Oculus dexter (Right eye)
OHT	Ocular hypertension
OS	Oculus sinister (Left eye)
OU	Both eyes
PG324	Fixed combination netarsudil/latanoprost ophthalmic solution
PKN2	protein kinase N2
PM	Evening
POAG	Primary Open-angle glaucoma
PT	Preferred term
PTM	porcine trabecular meshwork
QD	Once daily
ROCK	Rho kinase
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SITA	Swedish interactive threshold algorithm
SBP	Systolic blood pressure
SOC	System organ class
TEAE	Treatment emergent adverse event
USA	United States of America
VA	Visual acuity
VF	Visual field
YRS	Years

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Aerie Pharmaceuticals Ireland Ltd submitted on 12 September 2018 an application for marketing authorisation to the European Medicines Agency (EMA) for Rhokiinsa, through the centralised procedure under Article 3 (2) (a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 21 July 2016.

The applicant applied for the following indication Rhokiinsa is indicated for the reduction of elevated intraocular pressure (IOP) in adult patients with open-angle glaucoma or ocular hypertension.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0368/2016 on the granting of a product-specific waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

New active Substance status

The applicant requested the active substance netarsudil contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

Scientific advice

The applicant received Scientific Advice on the development relevant for the approved indication from the CHMP on 18 May 2017, 20 July 2017; and 22 February 2018. Also the applicant requested clarification on 09 August 2017. The Scientific Advice pertained to the following quality, and clinical aspects of the dossier.

To summarise, in the advices on Netarsudil intended for the reduction of elevated intra-ocular pressure in open angle glaucoma or ocular hypertension, the applicant asked for advice concerning:

- The concentration of benzalkonium chloride (BAK) in the proposed formulation
- Plans for additional pharmaceutical development studies to further evaluate the level of benzalkonium chloride, whether the proposed pharmaceutical development and stability study plans were acceptable, the proposals to assess stability of any new formulation, and

specifications for passing antimicrobial effectiveness testing.

- The bridging strategy to preserve the validity of studies conducted with the current formulation in the event that additional pharmaceutical development indicated a new formulation was needed, and the possible timing and strategy for implementation of a new formulation.
- Clarification of the applicant's understanding of the advice provided in terms of the range of benzalkonium chloride concentrations on which to focus, the success criteria in the proposed bridging study, and the timing and strategy for additional formulation development and possible clinical bridging work in order to potentially change the formulation post-approval.
- The proposal for the primary endpoint and study design in any non-inferiority bridging study.

EMA/CHMP/SAWP/284155/2017; On 17 March 2017 the applicant Aerie Pharmaceuticals Ireland Ltd requested scientific advice for their product Netarsudil intended for the reduction of elevated intra-ocular pressure in open angle glaucoma or ocular hypertension with the questions concerning quality development. Advice was adopted on the 18 May 2017.

EMA/CHMP/SAWP/432861/2017; On 19 May 2017 the applicant Aerie Pharmaceuticals Ireland Ltd requested scientific advice for their product Netarsudil as a follow-up to advice provided by CHMP in May 2017 with the questions concerning quality development. Advice was adopted on the 20 July 2017;

EMA/CHMP/SAWP/432860/2017; On 19 May 2017 the applicant Aerie Pharmaceuticals Ireland Ltd requested scientific advice for their product Netarsudil with the questions concerning clinical development for the same indication as earlier advices. Advice was adopted on the 20 July 2017.

EMA/520545/2017; 09 August 2017 Aerie Pharmaceuticals Ireland Ltd requested clarification from the SAWP on the CHMP response to Quality and Clinical questions in the Scientific Advice letters (EMA/CHMP/SAWP/432860/2017 and EMA/CHMP/SAWP/432861/2017) adopted by the CHMP on 20 July 2017.

EMA/CHMP/SAWP/87800/2018; On 06 November 2017 the applicant Aerie Pharmaceuticals Ireland Ltd requested scientific advice for their product Netarsudil as a follow-up to the advice provided by CHMP in July 2017 with questions concerning clinical development; advice was adopted on the 22 February 2018.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Jayne Crowe Co-Rapporteur: Ewa Balkowiec Iskra

The application was received by the EMA on	12 September 2018
The procedure started on	4 October 2018
The Rapporteur's first Assessment Report was circulated to all CHMP members on	20 December 2018
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	21 December 2018
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	10 January 2019
The CHMP agreed on the consolidated List of Questions to be sent to	31 January 2019

the applicant during the meeting on	
The applicant submitted the responses to the CHMP consolidated List of Questions on	24 April 2019
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	31 May 2019
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	14 June 2019
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	27 June 2019
The applicant submitted the responses to the CHMP List of Outstanding Issues on	16 August 2019
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	04 September 2019
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Rhokiinsa on	19 September 2019

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Open-angle glaucoma are chronic, progressive optic neuropathies that have in common characteristic morphological changes of the optic nerve head and retinal nerve fibre layer in the absence of other ocular disease or congenital anomalies. Progressive retinal ganglion cells death and visual field loss are associated with these changes and can eventually lead to blindness (EGS 2014).

A number of schemes for classifying glaucoma have been proposed based on age, site to obstruction to aqueous outflow and aetiology. The most widely used is the separation between open angle and angle closure.

In open angle glaucoma, which is applied for in this application, the anterior chamber angle is open upon gonioscopic observation, and frequently there is elevated intraocular pressure (IOP).

Glaucoma is not a homogenous disease which includes a spectrum of optic neuropathies such as:

Primary open angle glaucoma (POAG) – optic disc damage and visual field loss associated with elevated IOP.

Normal tension glaucoma (NTG) – optic nerve damage and visual field loss associated with normal IOP. NTG is a form of Primary open angle glaucoma.

Ocular hypertension (OHT) – normal optic disc and visual field associated with elevated IOP

Secondary open-angle glaucoma – increased resistance to trabecular meshwork outflow associated with other condition (pseudoexfoliation or pigment dispersion syndrom,steroid-induced glaucoma, facolitic, infectious, neovascular glaucoma).

A major risk factor for glaucomatous visual field loss is elevated intraocular pressure (The AGIS Investigators, 2000).

Normal IOP has been defined as two standard deviations above normality, i.e. 21 mmHg, and any IOP above this level is considered to be elevated.

2.1.2. Epidemiology and risk factors

Glaucoma is the second leading cause of blindness in the world. Primary open angle glaucoma accounts for approximately 74% of all glaucoma cases worldwide. In Europe the population prevalence of primary open angle glaucoma was estimated to be 2% in the population aged over 40 years in 2015.

Risk factors include increasing age, family history, elevated intraocular pressure and ethnicity, with persons of African origin having a higher risk of developing open angle glaucoma.

Elevated intraocular pressure is the most important known risk factor for primary open angle glaucoma. Studies such as the Early Manifest Glaucoma Trial (Heijl 2011), the Ocular Hypertension Treatment Study (Kass 2002, Kass 2010), and the Collaborative Normal Tension Glaucoma Study (CNTGS Study Group 1998, Anderson 2003) support the role of lowering intraocular pressure (IOP) as the only modifiable risk factor for glaucomatous visual field loss.

2.1.3. Aetiology and pathogenesis

Glaucoma is a progressive optic neuropathy that causes characteristic loss of visual fields and can eventually lead to blindness due to progressive degeneration of retinal ganglion cells and resulting changes in the head of the optic nerve. The pathophysiology of open angle glaucoma is not fully understood. Multiple genetic factors and the influence of co-morbidities are likely to play a role. Elevated intraocular pressure is a major risk factor for glaucomatous visual field loss though ocular hypertension is not a feature in all cases of glaucoma.

The intraocular pressure is influenced by the balance between the aqueous humour secreted by the ciliary body and drainage through two independent pathways, the trabecular meshwork and the uvoscleral outflow pathway. Patients with raised intraocular pressure and open angle glaucoma have increased resistance to aqueous outflow through the trabecular meshwork.

2.1.4. Clinical presentation, diagnosis and stage / prognosis

The early stages of the condition are asymptomatic and patients may not realise until they have significant visual field loss. The condition is often detected during routine eye examinations on the basis of raised intraocular pressure or fundal changes. Visual acuity is unaffected as long as central vision is preserved.

Glaucoma is diagnosed in patients with characteristic nerve damage on fundus examination and visual field testing, usually in the presence of elevated intraocular pressure.

2.1.5. Management

The aim of open angle glaucoma treatment is to lower intraocular pressure. There is evidence that lowering intraocular pressure in case of intraocular hypertension or open angle glaucoma (even when the patient has normal intraocular pressure) can delay progression and reduce the risk of developing visual field loss or delay exacerbation of visual field loss. IOP lowering therapy can be pharmacological (mainly topical) or surgical (including laser therapy). First line therapy is usually a topical product e.g. prostaglandins, beta blockers and less frequently alpha adrenergic agonists. Topical prostaglandins are more frequently used in Europe as initial therapy, in particular latanoprost.

About the product

Netarsudil is a potent Rho kinase inhibitor and a norepinephrine transporter inhibitor. Both of these biochemical activities likely contribute to the multiple mechanisms by which topical netarsudil influences aqueous humour dynamics and lowers IOP. The main effect on IOP appears to be due to increased aqueous outflow.

Type of Application and aspects on development

The applicant has submitted a number of pharmacokinetic, pharmacodynamics and efficacy and safety studies to support the application. Two studies allowed for the recruitment of children aged under two. Of these one recruited only 2 children and the other none.

The five efficacy and safety studies and one stand-alone safety study were conducted in North America mainly in the US in patients with a diagnosis of ocular hypertension or open angle glaucoma between 2012 and 2016. Almost 1,400 patients with intraocular hypertension or open angle glaucoma have been exposed to netarsudil in efficacy and safety studies submitted to support this application. The majority of participants were female (at least 60% across all of the studies). Most participants were White

approximately 75% with approximately 22% Black or African American and under 2% Asian. The median age of study participants ranged for 62 to 69 years. (See first Table in the Efficacy section for further detail on these studies).

Since 2015 the applicant has obtained scientific advice from the MPA, the MHRA and the EMA. The advice has only focused specifically on this application in a limited fashion. All of the studies apart from the pivotal studies had already been concluded prior to seeking scientific advice.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as a topical, multidose, sterile aqueous ophthalmic solution containing 200 micrograms/ml of netarsudil (as mesylate salt) as active substance.

Other ingredients are benzalkonium chloride, mannitol, boric acid, sodium hydroxide (pH-adjustment) and water for injections.

The product is available in opaque white low density polyethylene bottles and tips with white polypropylene caps and anti-tamper seals, containing 2.5 ml of solution.

2.2.2. Active Substance

General information

The chemical name of netarsudil mesylate is {4-[(1*S*)-2-amino-1-[(isoquinolin-6-yl) carbamoyl]ethyl]phenyl} methyl 2,4-dimethylbenzoate, methanesulfonate (1:2). It corresponds to the molecular formula $C_{30}H_{35}N_3O_9S_2$ (dimesilate salt) ($C_{28}H_{27}N_3O_3$ (free base)), its relative molecular mass is 645.74 g/mol (dimesilate salt) (453.53 g/mol (free base)) and it has the structure shown in Figure 1.

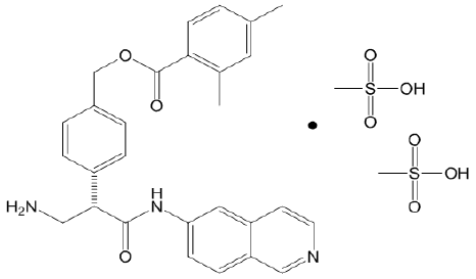


Figure 1. Structure of netarsudil mesylate.

The structure of the active substance (AS) was elucidated by a combination of elemental analysis (EA), mass spectrometry (MS), infrared spectroscopy (IR), nuclear magnetic resonance spectroscopy (NMR) and X-ray powder diffraction. Single-crystal X-ray diffractometric (XRD) analysis was performed to confirm the absolute stereochemistry.

Netarsudil mesylate appears as a light yellow to white moderately hygroscopic crystalline powder. It is freely soluble in water and soluble in methanol. Its partition coefficient (LogP) was determined to be 4.44 and two pKa values were determined to be pKa1: 5.43 and pKa2: 7.91.

It has a single stereocenter and is produced selectively as a single enantiomer of the (*S*)-configuration. The absolute stereochemistry was established from single-crystal X-ray analysis of the penultimate intermediate.

Netarsudil mesylate exhibits polymorphism. Two polymorphs of the drug substance have been identified by X-ray powder diffraction – A and B. The final isolated product of the manufacturing process is a mixture of the identified forms A and B. Stability of the two forms has been studied with no significant difference seen between them. Furthermore, no difference was seen in the processing characteristics. However, due to the type of the finished product formulation (solution), the physical form of the active substance has not been classified as critical.

Based on the information provided by the applicant, netarsudil is considered to be a New Active Substance (NAS).

Manufacture, characterisation and process controls

The active substance is synthesized in six steps from three starting materials. One of the starting material (SM) was redefined as requested by the CHMP and the revised process is now described in the dossier. As a result the supplier of the redefined SM is included in the dossier together with batch analysis data have been presented and demonstrated compliance of the active substance with the specification. Updated stability data are available and also met specification limits. The redefined starting material has been adequately justified. Purging of impurities has been demonstrated. The quality of the obtained netarsudil was equivalent to netarsudil manufactured using the originally applied route of synthesis. All other proposed starting materials have been justified, along with their specifications, and are considered acceptable.

Acceptable specifications analytical methods and batch information were provided for the control of the intermediates. The optimization of the manufacturing process during development has been described in sufficient detail. Critical steps were identified and a suitable control strategy has been defined. Critical and key process parameters have been identified for each manufacturing step and normal operating ranges (NORs) proposed.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised. The selection of the dimesylate salt form has been justified sufficiently based on solubility considerations and assessment of the risk of formation of alkyl methanesulfonate impurities during the active substance manufacturing process and on storage. The control limit for the three methanesulfonates (methyl, ethyl, isopropyl) is well below the ICH M7 accepted TTC of 1.5 µg/day and well below the published PDEs of the individual methanesulfonate esters (PDE_{methyl} = 75 µg/day; PDE_{ethyl} = 125 µg/day; PDE_{iPr} = 2.5 µg/day).

The packaging material of netarsudil mesylate has been clearly described and the suppliers and the specifications have been listed in the dossier. The packaging material comply with the relevant requirements of Ph. Eur. and with the applicable with EU Regulation No. 10/2011 as amended, and EU Regulation No. 202/2014.

Specification

Netarsudil mesylate active substance specification includes appropriate tests and limits for description (visual), identification (IR and HPLC), assay (HPLC), chromatographic purity (HPLC), chiral impurity ((*R*)-enantiomer - chiral HPLC), residual solvents (GC), elemental impurities (ICP-MS), methanesulfonates (GC), residual solvents (HS-GC), methanesulfonic acid content (IC), water content (KF), and microbiological examination (Ph. Eur.).

The mesylate salt content of netarsudil (counter-ion) is determined from the assay for methanesulfonic acid using ICP. Methanesulfonates are controlled with limit, which is consistent with obtained results and complies with ICH M7.

Considering the route of synthesis, the risk for class 1 solvents to be present in the active substance is deemed to be insignificant, and therefore the inclusion of tests for Class 1 solvents in the specification is not considered necessary. Furthermore the risk assessment was supported by batch analysis data that showed no Class 1 solvents detected in three batches of the active substance with detection limits at or below 44% of the ICH limits. This could be accepted in view of the low dose of the finished product.

Limits for elemental impurities meet the requirements of ICH Q3D permitted daily intakes (PDEs). The elemental impurities lithium, used in the manufacture of netarsudil mesylate, and palladium, used in the manufacture of one of the starting materials, are also specified. To date, none of the elemental impurities have been observed above the specification limits.

The justification for not including certain parameters in the active substance specification is considered acceptable and was based on batch results. The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Full batch analysis data has been provided for 8 batches of drug substance. All batches fulfilled the proposed specifications. Additionally, batch data for 7 early development batches analysed according to specifications in effect at the time of testing have been included. The batch data provided is considered to be sufficient. Consistency and uniformity of the active substance quality have been demonstrated.

Stability

Stability data on three production scale and three pilot scale batches of active substance stored in the intended commercial packaging for up to 36 months under long term conditions (-20 ºC ±5 ºC), and for up to 12 months under accelerated conditions (5 °C ± 3 °C) was provided according to the ICH guidelines. Supportive data from two further pilot batches for up to 48 months under long-term conditions (-20°C ±5°C) and 12 months under accelerated conditions (5°C±3°C) was also provided. All batches of drug substance were manufactured using the commercial synthetic route at the proposed site.

Samples were tested for description, assay, chromatographic purity, water content, chiral purity (not tested for one of supportive batches), methanesulfonates (not tested for both supportive batches), microbial bioburden (not tested for both supportive batches. No significant changes were observed to any of the measured parameters in any of the tested batches. All samples met the specifications demonstrating the chemical stability of netarsudil mesylate.

In order to evaluate any potential impact on the stability profile of netarsudil mesylate due to the change in starting material supplier, data from two pilot scale batches of netarsudil mesylate manufactured using the redefined starting material supplied by the new supplier was presented. Three months' stability data was available also indicating that these two batches also meet the specification. The active substance manufacturer commits to provide updated stability data as the stability study proceeds as per the submitted stability protocol.

Stress studies were performed for the two supportive batches and one pilot batch at 25 °C ± 2 °C/60 ±5% RH for a period of 12, 6 and 3 months, respectively. After 6 months' storage, an increase in water content was observed. After 12 months' storage, significant growth in impurities was detected. The obtained results confirm the hygroscopic nature of the active substance and demonstrate that the active substance stability is maintained for an excursion period of up to 3 months only under the stressed conditions.

Freeze/Thaw studies
Samples of netarsudil mesylate were subjected to 5 freeze/thaw cycles between -20°C ± 5°C and controlled room temperature simulating the use of the material over time. Likewise, the desiccant and secondary packaging were replaced after each cycle. For all the tested parameters specifications were met.

Photostability
Photostability of netarsudil mesylate was studied on a pilot batch as per ICH Photostability Option 2 conditions in a clear glass bottle, an amber bottle, and an amber bottle wrapped in foil (control). For all the tested parameters specifications were met. The suitability of the proposed container was demonstrated.

Based on the provided data, the proposed retest period of 36 months for the active substance when stored at -20 °C protected from light and moisture, is considered acceptable.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

Rhokiinsa 200 micrograms/ml eye drops, solution is a clear, sterile, isotonic solution at approximately pH 5; it is multi-dose product and is preserved with benzalkonium chloride.

The composition of the finished product includes netarsudil along with the following excipients: mannitol, boric acid, benzalkonium chloride, sodium hydroxide and water for injections.

The finished product is designed as a multi-dose product for ophthalmic application and is intended to conform to the characteristics for topical ophthalmic solutions: clarity, pH, tonicity and the need for adequate preservation were of prime consideration in the selection of the formula composition.

The Quality Target Product Profile (QTPP) has been presented. The finished product Critical Quality Attributes (CQAs) have been presented and appropriately justified. The CQAs formed the basis for the specifications for the finished product.

The excipients used (boric acid, mannitol, benzalkonium chloride and sodium hydroxide) are compendial and their concentrations are consistent with those contained in other approved ophthalmic products in the EU.
The buffering agent used is boric acid which is present at a relatively low level. The use of boric acid in ophthalmic products is well established as detailed in EMA's Questions and answers on boric acid and borates used as excipients in medicinal products for human use (EMA/CHMP/619104/2013). For ocular comfort, the product is isotonic with its tonicity adjusted using mannitol.
This multi-dose product is preserved with benzalkonium chloride (BAK). The level of BAK used in this formulation is within the range of other topical ophthalmic products approved in the EU. The use of BAK in topical ophthalmic products at a similar concentration is well established as detailed in EMA's Questions and answers on benzalkonium chloride used as an excipient in medicinal products for human use (EMA/CHMP/495737/2013). Studies were performed to evaluate the ability of various preserved formulations of netarsudil to inhibit the growth of common microbes and conform to the Ph. Eur. antimicrobial effectiveness criteria for ophthalmic products demonstrating that the selected concentration of the preservative is appropriate for use in this formulation. In order to optimise the benefit-risk profile in the proposed indication, especially in the context of long term treatment of OAG/OHT, upon the request of the CHMP, the applicant confirmed that is actively exploring re-formulation of the product and relevant proposals for a revised bridging study have been submitted. The CHMP considers that since the current formulation fulfils the quality requirements necessary to maintain microbiological quality, the proposed

concentration of the BAK preservative is acceptable, based on the established safety and efficacy profile. Overall, the information regarding the preservative system is deemed sufficient.
Sodium hydroxide is used to adjust the pH of the final formulation. Water for Injection is used throughout the manufacturing process for the dissolution of excipients and adjustment of the product formulation to its final batch size. No novel excipients are used.
Early prototype formulations were routinely tested for ocular hypotensive efficacy and ocular irritation in rabbits to ensure compatibility between the excipients and the active substance. No compatibility issues have been observed between netarsudil mesylate, the selected excipients and the container closure system during development and stability.

Various strengths of netarsudil ophthalmic solution were evaluated throughout development, ranging in netarsudil concentration from 0.01 to 0.12%. A 0.02% concentration of netarsudil was selected as the definitive strength for Phase 3 clinical studies and commercialization. With the exception of the concentration of the active substance, all excipients remained the same and in comparable relative proportions though an overage of BAK was not applied at all stages.

During manufacturing process development, a process that meets the functional requirements of the formulation and the ophthalmic dosage form was selected. Ingredients are added in a specific sequential order to Water for Injections with mixing to ensure complete dissolution and a homogenous solution. A risk assessment was performed to determine the impact of key manufacturing process variables (i.e., raw material attributes, process parameters for the major manufacturing steps) on the quality attributes of the finished product. The conclusions of the risk assessment were confirmed through the process validation studies.
The sterilization method of the drug product solution is sterile filtration, followed by aseptic filling and was sufficiently justified based on the physicochemical properties of the active substance and the container closure system. The choice of sterilization method of container components has been justified considering the nature of the materials and the effect of other means of sterilisation (e.g. gamma radiation).
The site of manufacture of the pivotal Phase 3 clinical batches, registration stability batches, and commercial scale batches is the same as the proposed manufacturer.

The finished product is packaged in white, multi-dose, low-density polyethylene (LDPE) bottle fitted with linear low-density polyethylene dropper tip (LLDPE) and white polypropylene (PP) screw cap. The container-closure system is one which is routinely used for administration of multi-dose ophthalmic solutions as drops. Compliance of the packaging materials with relevant compendial monographs or directives has been stated. Product-specific leachables studies have demonstrated acceptable levels of leachables with this container closure system, when in contact with the product formulation.

A dose delivery performance study was conducted and the results demonstrate that Rhokiinsa can be reproducibly dosed with the selected container closure system.
Patient experience and suitability of the proposed commercial container closure was studied through use in two Phase 3 clinical trials. The age of the patients reflected the age range of the target population proposed for this product. There were no reported complaints about the usability of the product or container closure system. This indicates that the type, size, shape, and usability of the selected container closure system is adequate and provides evidence that the expected patient population for the product can effectively and reproducibly self-administer the eye drops according to the recommended instructions for administration.

Manufacture of the product and process controls

The finished product manufacturing process consists of dissolving the excipients and the active substance in water for injections. Following compounding of the formulation, sterile filtration of the bulk solution and aseptic filling into to a pre-sterilized container closure system takes place. The manufacturing process

involves aseptic processing with filtration as the method of sterilization and is classified as non-standard manufacturing process.
The critical steps have been defined and appropriate in process controls have been presented and are in place. Hold times have been established and clearly stated.

Process validation has been completed on six commercial scale batches of the finished product to confirm the ability of the manufacturing process to meet the in-process and finished product specifications. During validation the essential/critical steps were verified. The sterility assurance of the manufacturing process has been demonstrated through completion of media fills and is verified semi-annually through the on-going media fill program. Sterilization processes are validated for each designated piece of equipment. These sterilization processes are qualified on an annual basis. Sufficient details on the sterilisation of the container and on validation were presented. Process validation data suggest that the process is adequately controlled, reproducible and robust, and yields a product that complies with the specifications.

Product specification

The finished product release and shelf life specifications include appropriate tests and limits for description (visual), description of container (visual), pH (Ph. Eur.), osmolality (Ph. Eur.), identification of active substance (UV, HPLC), identification of BAK (HPLC), assay (HPLC), degradation products (HPLC), chiral impurity (chiral HPLC), BAK content (HPLC), particulate matter (Ph. Eur.), sterility (Ph. Eur.) and efficacy of antimicrobial preservation (Ph. Eur.).

The limits for any impurity exceeding the threshold for identification and qualification, according to ICH Guideline Q3B(R2) has been qualified in non-clinical studies. Additional known degradation products were also qualified via long term ocular toxicity studies using product formulations lots intentionally spiked with each impurity.

The potential presence of elemental impurities in the finished product in line with the new ICH Q3D Guideline for Elemental Impurities has been assessed using a risk-based approach. In general, the oral route limits were applied, since the oral route of exposure was considered the most relevant for topically administered ocular drugs with regards to systemic exposure. A literature search was performed to identify any toxicity information relevant to the topical ocular route of administration. For any evidence of local effects, the literature limits were compared to the ICH PDE. If a difference was observed, correction factors were applied when relevant exposure data were available. No specific risks in relation to the ocular administration were identified for Class 1 elements. For Class 2 and 3 elements the limits are considered acceptable and the performed risk assessment demonstrated the risk of elemental impurity introduction from the raw materials, container closure system and manufacturing process is very low and no further controls are warranted in the specification.

The analytical methods used have been adequately described and validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used in the routine analysis of finished product has been presented.

Batch analysis data was provided for 17 commercial scale batches from the proposed manufacturer and for twelve smaller batches from development sites used in pre-clinical and clinical studies. The data demonstrate that all parameters are well within their specifications and therefore indicate consistent manufacture of the finished product.

Stability of the product

Stability data on six commercial scale batches of finished product stored in inverted and upright positions for up to 36 months under long term conditions at 5 °C ± 3 °C and for six months under accelerated conditions at 25 °C ± 2°C/40% ± 5% RH and 30 °C ± 2 °C / 65% ± 5% RH according to the ICH

guidelines have been presented. The six commercial scale batches were manufactured and filled into the proposed container closure system.
Data from supportive stability studies for eight pilot and full scale batches having fill volumes ranging from 1 mL to 5 mL stored at 5 °C ± 3 °C and 25 °C ± 2 °C / 40% RH±5% RH conditions and 30 °C ± 2 °C / 65% RH ± 5% RH were also provided.
All batches were manufactured and packaged at the proposed commercial manufacturing and packaging site and evaluated in both upright and inverted position.
The following attributes were assessed: description, pH, osmolality, assay and degradation products, chiral impurity, benzalkonium chloride (preservative content), particulate matter, sterility, antimicrobial effectiveness and additionally for three commercial scale batches, leachables, and weight loss/gain. All results in the stability studies comply with the proposed specification.

Forced degradation studies
Finished product solution and placebo solution were exposed to predetermined severe acid, base, peroxide, heat, and light (UV and white, ICH Option 2), or conditions necessary to target 10-15% degradation if lower. Significant degradation occurred under basic, heat, oxidative and light conditions. Based upon the results of the forced degradation studies, the analytical methods for assay and degradation products are considered to be stability-indicating.

In-use Stability Studies
Several studies that simulated use of the product were conducted, according to the *Note for Guidance on In-use Stability Testing of Human Medicinal Products* (CPMP/QWP/2934/99). A total of three different lots of finished product were tested for a period of 28-days and 42-days stored at 25°C to simulate use at room temperature. At the beginning of the in-use stability study, the product samples had been stored for 18, 21, 24, or 36 months at 5 °C ± 3 °C. All results met specifications. This indicates that the product is stable when used and stored in the multi-dose container at temperatures up to 25 °C. This is reflected in section 6.3 of the SmPC where the following recommendation is included: "*Opened bottle: 4 weeks after first opening the bottle. Do not store above 25 °C*" (SmPC 6.3).

Temperature Excursion Studies and Freeze-Thaw Cycle Study
Multiple batches of finished product with different fill volumes were evaluated after storage at 30 °C ± 2 °C/65% ± 5% RH for up to 6 months and 40 °C ± 2 °C / 20% ± 5% RH for up to 1 month. All lots conformed to the proposed specifications after 1 month's storage under both sets of conditions. Unknown impurities were observed for different lots of product stored at 30 °C ± 2 °C / 65% ± 5% RH after 2, 3, and 6 months but no trends in the data were observed.
The finished product was evaluated using two different freeze-thaw conditions:
- #1: Product samples were stored at -20 °C followed by 30 °C / 65% RH on alternate days for 2 weeks.
- #2: Product samples were evaluated for 3 cycles of 2 days storage at -20 °C followed by 2 days storage at 30 °C / 65% RH. For both studies, the product was tested for description, assay and impurities, chiral impurity, pH, osmolality and particulate matter. All specifications were met for both freeze-thaw cycle studies.
The results of the freeze-thaw cycle study and the 30 °C ± 2 °C / 65 ± 5% RH stability storage condition indicate that the product is robust with regards to temperature fluctuations (excursions from the proposed long-term storage condition) that may be encountered during shipping and handling.

Photostability Study
A photostability study on the finished product was conducted as per ICH Q1B, Option 2. The samples were tested for description, pH, assay and impurities, and chiral impurity. All acceptance criteria for the attributes evaluated were met for all samples except for the unprotected exposed sample in the quartz tube. The results of this study confirmed that the primary package (white plastic bottle) provides sufficient protection from light for the finished product.

Based on the overall stability data, the claimed shelf life of 3 years and storage conditions “Store in a refrigerator (2 °C – 8 °C) until opened” is acceptable (SmPC sections 6.3 and 6.4).

Adventitious agents

No excipient or materials of animal or human origin are used.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The manufacturing process for the finished product is non-standard and the required validation data have been provided. This multi-dose product is preserved with benzalkonium chloride the proposed formulation fulfils the quality requirements necessary to maintain microbiological quality while adequate safety and efficacy profile has been shown from a clinical perspective. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that from a quality perspective the product should have a satisfactory and uniform clinical performance.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable and consistent. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendations for future quality development

None.

2.3. Non-clinical aspects

2.3.1. Introduction

Several substances are mentioned within non-clinical section. These include the active substance netarsudil mesylate (AR-13324), its active metabolite (AR 13503), the R-enantiomer of netarsudil mesylate (AR-13323) and the R-enantiomer of the metabolite of netarsudil mesylate (AR-13534).

2.3.2. Pharmacology

Primary pharmacodynamics

The potency and selectivity of netarsudil as an inhibitor of two isoforms of Rho kinase ROCK 1 and 2 was determined in enzyme inhibition assays with a panel of human protein kinases. Netarsudil (AR-13324) is a potent inhibitor of human ROCK 1 and 2 with Ki values of 1.1 and 1.2 nM, respectively. The metabolite, AR-13503, is about 5-fold more potent with Kis of 0.2 nM for both ROCK1 and ROCK2. In addition, netarsudil shows potent inhibition on other structurally or functionally related protein kinases including protein kinase N2 (PKN2; Kis 3.0/1.0 nM), protein kinase A (PKA; Kis 5.0/1.0 nM) and protein kinase MRCK alpha (MRCKα; Kis 129/7.0 nM). Based on these results, the selectivity of netarsudil and its metabolite is questioned.

Effects on cytoskeletal components were examined *in vitro* in cultured porcine and human trabecular meshwork cells. Netarsudil and its metabolite, AR-13503, disrupted actin stress fibers in porcine trabecular meshwork (PTM) cells and focal adhesions in human trabecular meshwork (HTM) cells, with

PTM/HTM IC50s of 504 nM/219 nM and 102 nM/64 nM, respectively. AR-13503 had approximately 4- to 5-fold greater activity than netarsudil in both assays.

The active metabolite AR 13503 was evaluated for its effects on trabecular outflow facility and tissue morphology in perfused human eye anterior segments. AR 13503 at 0.3 µM (92 ng/ml) caused significant increases in outflow facility compared to control eyes from 30 minutes through 3 hours post-treatment. Fluorescent imaging and histological analysis showed that AR 13503 increased the area of actively filtering tissue in the trabecular outflow pathway, expanded the trabecular meshwork tissue and caused dilation of episcleral veins.

The primary pharmacologic effect of netarsudil mesylate is lowering of IOP. A series of in vivo studies were performed in normotensive pigmented rabbits and monkeys to evaluate the pharmacodynamics and preliminary tolerability of netarsudil (clinical formulation) at various concentrations. These studies were typically performed over 3-4 or 10 days and compared treated eyes to fellow untreated eyes for ocular tolerability (based upon Draize scoring) and IOP response. In a 3-day rabbit study, IOP was measured following administration of AR-13324 to one eye at 0.005% (1.5 µg/eye), 0.01% (3 µg/eye), 0.02% (6 µg/eye) and 0.04% (12 µg/eye, clinical formulation). All four concentrations produced significant and dose-related reductions in IOP as compared to the contralateral control eye at all time points throughout the study and displayed progressively larger reductions over 3 days of dosing. Maximal IOP reductions of 2.5±0.2 mmHg, 4.6±0.2 mmHg, 5.0±0.6 mmHg, and 8.1±0.7 mmHg were observed at 0.005%, 0.01%, 0.02% and 0.04%, respectively. In a 10-day rabbit study, IOP was measured following administration of AR-13324 to one eye at 0.02% (6 µg/eye) and 0.04% (12 µg/eye, clinical formulation). Maximum IOP reductions of 7.0 mmHg and 7.1 mmHg, respectively, were observed at 4 hours post dose on Day 3. In a 3-day study in Formosan Rock monkeys, IOP was measured following administration of AR-13324 to one eye at 0.01% (3 µg/eye), 0.02% (6 µg/eye) and 0.04% (12 µg/eye, clinical formulation). All three concentrations produced significant and dose-related reductions in IOP as compared to the contralateral control eye at all time points throughout the study. Maximal IOP reductions of 4.2±0.2 mmHg, 5.8±0.3 mmHg, and 7.5±1.1 mmHg were observed at 0.01%, 0.02% and 0.04%, respectively.

These studies indicated that netarsudil provided a durable, dose-responsive decrease in IOP when delivered once daily and that the IOP response at the end of dosing was typically greater than on the first day. Trace to mild hyperaemia (Draize score +0.5 to +1) was a typical ocular finding in most studies, which decreased over time with continued dosing. Hyperaemia is also reported as a common adverse reaction in clinical trials and is likely caused by smooth muscle cell relaxation causing local vasodilation.

Additional studies were performed to evaluate other components of the formulation. One 3-day study in rabbits examined the ocular hypotensive efficacy and tolerability of four formulations with varying pH and varying concentrations of BAK. There was no apparent pH-dependent effect on efficacy. The data suggest that increasing the BAK concentration from 0.0075% to 0.015% might yield a slight improvement in efficacy, without significantly reducing apparent tolerability.

Additional mechanism of action studies indicates that netarsudil may lower IOP through multiple mechanisms of action. A study in cynomolgus monkeys indicate that netarsudil lowers IOP by increasing aqueous humor outflow through the trabecular meshwork and decreasing the production of aqueous humor. The monkeys were treated for one day with two drops of 0.04% netarsudil (20µg/eye, clinical formulation) into one eye and mean IOP was reduced by ~25%, mean outflow facility was increased by ~53% and mean aqueous flow rate was reduced by ~20%, when compared to contralateral eye, or baseline. Further, a study in rabbits showed that netarsudil can reduce the episcleral venous pressure, an additional mechanism of action expected to contribute to the lowering of IOP. The rabbits were treated for three days with one drop of 0.04% netarsudil (12 µg/eye, clinical formulation) into one eye and mean IOP was reduced by ~39% and the episcleral venous pressure was decreased by ~35%, when compared to contralateral eye. These results are in agreement with findings in human eyes (see above).

Overall, the applicant proposes that netarsudil treatment lowers IOP by two main mechanisms; increasing aqueous humor outflow through the trabecular meshwork (outflow facility and lowering of episcleral venous pressure. Based on the available data, the proposed mechanisms seem plausible.

Secondary pharmacodynamics

Netarsudil was assessed for its off-target activity on 442 human protein kinases, including ROCK 1 and 2. At 500 nM (227 ng/mL), significant inhibition (<35% activity) was found on 24 human protein kinases in addition to ROCK 1 and 2. The active metabolite was not included in the off-target screen, but AR-13084, the metabolite of the racemate AR-13165 was examined. As AR-13084 is also a racemate composed of 50% of the active metabolite AR-13503, the testing strategy is considered acceptable. At 500 nM, AR-13084 showed significant inhibition on 17 human protein kinases in addition to ROCK 1 and 2. IC50 values were not further identified for any of the off-targets of netarsudil or AR-13084.

Furthermore, netarsudil and AR-13084 were assessed for its off-target activity on 39 G-protein coupled receptors (GPCRs), 4 nuclear hormone receptors, 15 ion channels/transporters and 7 targets of other classes. For netarsudil, an activity of >50% inhibition was found on 14 GPCRs, 7 ion channels/transporters, and 5 cytochrome P450s. One of the identified off-targets, the hERG potassium channel is further discussed below. Another target was the norepinephrine transporter (NET). In follow-up NET competitive binding assays, AR-13165 (racemate) was a competitive inhibitor of nisoxetine binding to NET with a Ki of 400 nM, whereas AR-13084 did not demonstrate inhibitory activity. Netarsudil was not tested in this assay. In a cell-based assay measuring uptake of fluorophore-labeled biogenic amine, none of the compounds (netarsudil, AR-13165 and AR-13084) showed significant inhibitory activity.

Based on the available data, it can be concluded that netarsudil and its metabolite are not selective inhibitors of Rho kinases. However, as the expression of the potential off-targets in ocular tissues is not known, it cannot be concluded if off-target interactions contribute to the observed local safety profile. Based on the off-target screen results, the selectivity of netarsudil and its metabolite is questioned.

Netarsudil, but not the active metabolite AR-13503, was shown to induce phospholipidosis in CHO-K1 cells with an EC50 of 1.1 µM (~500 ng/mL). Transmission electron microscopy revealed that netarsudil also induced the formation of lamellar bodies, confirming that the fluorescent phospholipid accumulation in netarsudil treated cells was due to phospholipidosis.

Safety pharmacology

Netarsudil was evaluated in dedicated CV safety pharmacology studies, and a functional observational battery to evaluate potential CNS effects was included in a 7-day rat iv study.

No CNS effects were observed after a single or 7 days repeated iv administration of netarsudil up to doses of 7.0 mg/kg/day. There were also no signs of CNS effects in repeat-dose studies with netarsudil following iv and topical ocular administration.

In the hERG potassium channel assay, netarsudil caused a dose-dependent inhibition with a measured IC50 of 0.4 µM (~181 ng/mL). The active metabolite was tested in the GLP hERG assay. However, AR-13084, the metabolite of the racemate AR-13165 (comprising of 50% AR-13503) was examined in the off-target screen of non-kinase proteins (including hERG), and showed no hERG inhibition at 10 µM.

In a dog safety pharmacology study (telemetry), QTc prolongation was not observed following single iv doses of AR-13324 up to 17.6 mg/kg (Cmax 872 ng/mL). Doses at or above 8.8 mg/kg produced decreased arterial pressure (by maximum 32%) and increased heart rate (by maximum 124%), with

clinical signs of vasodilation observed at 17.6 mg/kg. The NOEL for the effects on arterial pressure and heart rate was 0.7 mg/kg.

Cardiovascular parameters, including ECGs, were also evaluated in repeat-dose studies following iv administration in dogs. In a single dose iv dog study, marked decreases in arterial blood pressure were noted at 42 mg/kg. At this dose, the average maximal plasma levels of netarsudil were 3980 ng/mL for males and 3260 ng/ml for females. NOEL for the effects on arterial pressure and heart rate was 21 mg/kg corresponding to mean Cmax values of 2280 ng/ml in males and 1620 ng/ml in females. In a 28-day repeat-dose dog study, no cardiovascular effects were observed following iv administration of netarsudil at up to 0.53-0.67 mg/kg/day. At this dose, the Day 28 average Cmax of netarsudil was 63.3/51.51 ng/ml in males/females and the average Cmax of AR-13503 was 1.51/1.80 ng/ml in males/females.

Pharmacodynamic drug interactions

The potential for pharmacodynamic drug interaction between netarsudil and latanoprost was evaluated in normotensive Formosan Rock monkeys. A 3-day study was performed to evaluate the IOP-lowering efficacy of Netarsudil Ophthalmic Solution 0.02%, Xalatan® Ophthalmic Solution 0.005%, and a combination of netarsudil and latanoprost (PG324 Ophthalmic Solution) administered QD to one eye. All three formulations produced statistically significant reductions in IOP at all post-dose time points. No other drug interaction study was conducted. Based on negligible plasma concentrations of netarsudil and its metabolite (AR-13503) detected following topical ocular administration in humans, systemic pharmacodynamics drug interactions are considered unlikely. No drug interactions were reported in any of the clinical studies with netarsudil ophthalmic solution.

2.3.3. Pharmacokinetics

Methods of analysis

Netarsudil (AR-13324), its metabolite (AR 13503), the R-enantiomer of netarsudil mesylate (AR-13323) and the R-enantiomer of the metabolite of netarsudil mesylate (AR-13534) were quantified by liquid chromatography tandem mass spectrometry (LC-MS/MS) in plasma samples of rat, rabbit, dog and monkey.

Absorption

No dedicated PK studies were performed, but systemic absorption of netarsudil following intravenous (iv) and topical ocular administration was evaluated in toxicokinetics studies performed as part of the toxicology studies conducted in rats (iv), dogs (iv), rabbits (ocular) and monkeys (ocular).

After iv administration in rats and dogs, plasma concentrations of netarsudil declined in a monophasic manner. Plasma exposure (Cmax and AUC) was dose-dependent and approximately dose proportional to slightly greater than dose-proportional for netarsudil relative to administered netarsudil mesylate. As was the case for topical ocular administration in rabbits and monkeys, there were no gender differences relating to the exposure or elimination of netarsudil in rats or dogs.

In rabbits and monkeys, BID topical ocular administration of Netarsudil Ophthalmic Solutions up to 0.04% in the 6-month rabbit and 9-month monkey studies resulted in no clear evidence of plasma exposure to the parent compound (netarsudil), its metabolite (AR-13503), the enantiomeric impurity of netarsudil (AR-13323) or its metabolite (AR 13534) at 3 months or at the end of dosing.

In both rabbits and monkeys, plasma levels of netarsudil, AR-13323 and their respective metabolites were almost entirely below the quantitation limit at BID doses of up to 0.06% Netarsudil Ophthalmic

Solution in the 28 day/1-month repeated dose ocular studies. In shorter term studies (7 days), in which more concentrated Netarsudil Ophthalmic Solutions were administered up to 4 times daily, systemic concentrations of netarsudil and its active metabolite were sometimes observed.

Plasma concentrations of netarsudil were higher in rabbits per dose than in primates.

Distribution

The in vitro distribution studies indicate that netarsudil is highly protein bound in plasma (rat, dog and human) across a range of plasma concentrations and that it also binds to melanin. Protein binding in rabbit and monkey plasma was not investigated. The netarsudil metabolite AR-13503 binds less extensively to plasma proteins. AR-13503 binds melanin with similar affinity as netarsudil.

The systemic tissue distribution study in pigmented rats demonstrated that the tissues with the highest percent recovery of administered radioactivity were liver (~30% at 0.5 hours and ~14% at 4 hours) and skin (~8% at 0.5 hours, and ~6% at 4 hours). Elevated radioactivity concentrations were observed in melanin-containing tissues, such as the eye uvea, pigmented skin, and meninges. The concentration in these tissues did not decline over the study period, which suggested an association of 14C-netarsudil-derived radioactivity with melanin. This raises potential concerns for local phototoxicity, which are further discussed in the toxicology section.

The results of a tissue distribution study in rabbits following a single ocular dose of radioactively labelled netarsudil in both eyes revealed that the rank order of ocular tissue radioactivity concentrations was as follows: cornea>conjunctiva>>iris/ciliary body>> retina-choroid-plexus>aqueous humor>vitreous humor>lens. Elimination half-life (T1/2,e) values ranged from 12 to 27 hours for most ocular tissues, blood, plasma, liver, and kidney.

No placental transfer studies have been performed.

Metabolism

Netarsudil is cleaved by esterases in vitro and in vivo to form the active metabolite, AR 13503. No substantial metabolism of netarsudil was observed during in vitro exposure to cynomolgus monkey, human, rat or dog plasma. In contrast, netarsudil was rapidly metabolised when incubated with rabbit plasma. Metabolism was most rapid in dog corneas, followed by monkey corneas, rabbit corneas, pig corneas, and human corneas. When the metabolite AR-13503 was incubated directly with liver microsomes (rat, rabbit, dog, monkey and human), there was no evidence of further metabolism in any species tested. Thus, there do not appear to be multiple metabolites of netarsudil.

After topical doses of Netarsudil Ophthalmic Solution 0.02% for 1, 3 or 4 days in rabbits, it was shown that netarsudil was converted to AR-13503 such that the metabolite was present at higher levels in aqueous humor than the parent compound by 4 hours after instillation.

Overall, the metabolic pathway of netarsudil appears to be common to rats, rabbits, dogs, cynomolgus monkeys and humans.

Excretion

Excretion of netarsudil was studied in the systemic tissue distribution study in intact pigmented rats and in a topical ocular dosing study in Dutch Belted rabbits.

In the rat systemic distribution study, the primary route of elimination after iv administration was in the feces with 75.9% of the administered dose recovered in the feces and 14.4 % of the administered dose recovered in the urine. Excretion of radioactivity in feces was rapid; 72.9% of the administered dose was

eliminated in the initial 48 hours post-dose and only much lower amounts were detected after 72 hours post-dose.

Following a single ocular dose of 14C-netarsudil in both eyes of rabbits, approximately 80 ± 13.3% of the dosed radioactivity was recovered in the excreta by 48 hours post-dose. Percent recovery was ~3-fold greater from feces than from urine. Approximately 0.11% of radioactivity remained in the liver and kidneys and ~0.68% remained in the sum of the ocular tissues by 48 hours post-dose.

Thus, neither netarsudil nor its metabolite appears to be extensively retained in the body, and they are largely excreted in the feces.

Potential excretion in milk has not been evaluated.

Pharmacokinetic drug interactions

When tested at 10 µM in a secondary pharmacodynamics screen, netarsudil and AR-13165 (a racemic mixture of netarsudil and its enantiomer, AR-13323) showed significant inhibitory activity against five cytochrome P450s (1A2, 2C19, 2C6, 2D6 and 3A4). AR-13084, the metabolite of AR-13165, exhibited inhibitory activity against CYPs 2C19 and 2D6. The metabolite of netarsudil, AR-13503, was not tested in the assay but is considered covered by testing of AR-13084.

Based on the negligible plasma concentrations of netarsudil and its metabolite (AR-13503) detected following topical ocular administration, a risk for systemic DDIs is considered unlikely.

2.3.4. Toxicology

The toxicological profile of netarsudil has been evaluated both after ocular and systemic exposure. The pivotal studies for ocular administration were conducted in rabbits (6 months) and monkeys (9 months), and the systemic exposure in rats and dogs (28 days).

Single-dose toxicity

Single-dose toxicity studies of netarsudil administered i.v. have been performed in rats (1, 3, 45 mg/kg) and dogs (10, 30, 60 mg/kg). In rats the highest dose was associated with several clinical observations such as local irritation at the injection site, reduced activity, hunched posture, and pink extremities which was thought to be a pharmacological effect. In the dog, 30 and 60 mg/kg caused effects such as reduced acitivity and eye squinting. The highest dose (60 mg/kg) showed a clinical pathology spectrum indicative of an acute anemia (reduced erythrocytes, hemoglobin and hematocrit).

Repeat-dose toxicity

Ocular administration of netarsudil in different concentrations (0.01, 0.02, 0.04, 0.06 and-0.08%) and frequencies (1, 2 and 4 times daily) was investigated in rabbits (7 days, 28 days, 3 months and 6 months) and monkeys (7 days, 35 days and 9 months). The posology in the pivotal repeat-dose toxicity study was one drop in each eye, 0/0.01/0.02/0.04 % twice daily.

The systemic exposure after topical administration in the eye was very low in both rabbit and monkeys. After one drop in each eye of 0.04% netarsudil twice daily it was not possible (with the exception of one rabbit at one time point) to detect AR-13324 in the plasma in rabbits treated for 6 months or in monkeys treated for 9 months.

In order to evaluate the effects of netarsudil systemically several studies in rats and dogs were conducted where netarsudil was administered intravenously. Pivotal studies consisted of 28 days treatment with 14 days recovery period with the intended daily doses 0, 0.1, 0.3 and 1 mg/kg/day in rats and dogs.

Mortality / Morbidity

Male dogs were euthanized for humane reasons after 3 days of administration with iv netarsudil at 12.5 mg/kg (2/3 animals) and 25 mg/kg (3/3 animals). At day 3 of dosing the animals were observed with e.g. elevated body temperature, labored breathing, and decreased to no activity. The clinical pathology examination of these animals revealed decreased number of erythrocytes, hemoglobin, hematocrit and lymphocytes. The histopathological evaluation revealed granulocytic infiltrations in multiple organs. The plasma exposure expressed as AUC0-24h in these animals were at Day 1 3004 and 7021 ng*h/mL (12.5 and 25 mg/kg). No other mortalities or morbidities were observed in the investigated species (rat, rabbit, dog, and monkey).

Eyes

Ocular irritation

In all studies in rabbit and monkey with ocular administration of netarsudil the signs of irritation such as redness of the conjunctiva and/or sclera, chemosis, and discharge were observed. The overall incidence and severity appeared to be dose related and transient and decreased during the dosing phase and resolved after the recovery phase. In the pivotal 9 months repeat-dose toxicity study in monkeys, hyperaemia, chemosis and/or discharge were observed during the first week of dosing. There were no signs of ocular irritation after 8 weeks of treatment. Red eyes/sclera was also noted in dogs administered netarsudil intravenously, indicating not only irritation but also a pharmacologically induced hyperaemia in the eyes.

Cornea

In the rabbit degeneration/erosion of the cornea was observed with netarsudil concentrations of 0.04% and above. In two of the ocular toxicity studies in monkeys observations of hypertrophy/hyperplasia of the corneal epithelium were made. After 7 days treatment of 0.02%, 0.04, 0.06 and 0.08% netarsudil once or twice daily, subtle hypertrophy/hyperplasia was observed at all dose levels. After 35 days treatment, hypertrophy/hyperplasia was only observed in animals exposed to 0.06% twice daily.

Corneal haze described as diffuse and superficial and with the appearance of multiple, very fine, particulate depositions. Corneal haze was observed in monkeys in both the short (7 days) and long term studies (9 months). With higher doses, the haze appeared to develop earlier and was more pronounced. In the 9-months repeat-dose toxicity study in monkey, the incidence of haze increased with higher dose, but not the severity. The haze observed in the 7 day repeat-dose study with a high dose of netarsudil (0.12% QID) did not resolve after a period of 7 days without administration of netarsudil. In the longer studies where corneal haze was observed after 0.04% netarsudil, the haze had resolved after 2-4 treatment free weeks.

Retina

Electroretinography was conducted in the studies in monkeys and no treatment related changes were observed.

In one of the non-pivotal studies in monkeys where netarsudil was administered 4 times daily, vitreus haze, optic disc hyperaemia with indistinct optic disc margins, and retinal edema were observed in 2 and 3 animals in the 0.04% and 0.12% groups respectively. The histopathological examination showed no inflammation or anatomical alterations.

Intra ocular pressure

Rhokiinsa is indicated for the reduction of elevated intra ocular pressure (IOP). In the repeat-dose toxicity studies IOP was measured and dose-dependent reduction consistent with the intended pharmacology was indeed measured.

Ocular adnexa

There were several finding in the ocular adnexa (conjunctivae, nictitating membrane, Harderian gland, lacrimal gland) after ocular administration of netarsudil in both rabbit and monkey. The primarily microscopic finding included cellular infiltrates consistent with and/or related to an inflammatory response. Other findings were presence of lymphoid follicles in the palpebral conjunctivae (rabbit) hypertrophy and hyperplasia of the conjunctival epithelium (monkey). Lesions in the conjunctiva observed after 35 days of treatment in male monkeys did not resolve during 2 weeks recovery period.

Administration of netarsudil 0.06% BID in female rabbits for 28 days was associated with dark appearance of the lacrimal glands. No microscopic correlation was found in this study. However, in studies in monkey, microscopic findings such as lymphocytic infiltration, interstitial lymphoid aggregates and/or follicles in the lacrimal glands were observed. It is likely that these observations correspond to the inflammation seen in the eyelids and nasolacrimal ducts.

Injection site

Intravenous administration of netarsudil caused abnormal appearance and swelling of the injection site in rat, rabbit, and dog. In the pivotal study in dog, the severity and incidence was proportional to the dose and the reactions recovered during the 2 weeks of non-treatment. To ensure daily administrations in the embryofetal development studies in rats and rabbits, animals with indwelling catheters and vascular

access ports were used. The cause of these reactions is not fully understood but considered acceptable since the route of administration is not used in humans.

Other organ systems

Findings in rats and dogs toxicity studies regarding the haematological system were indications of anemia but are not considered relevant at the exposures observed after ocular administration.

From the systemic toxicity studies several sporadic non consistent findings were observed in the liver, kidney, pancreas, testes, and epididymides. Since the incidences were low and also included control animals, and/or only at clinically non-relevant exposures these findings are of no concern.

Toxicokinetics and interspecies comparison

It has not been possible to detect any systemic exposure in the human patients after the intended clinical dose. Thus, it was not possible to calculate an animal:human exposure multiple based on AUC. The lower limit of quantification (LLOQ) in the bioanalysis for human samples was 0.1 ng/ml. This value was used to compare with C_{max} values in animals and to calculate exposure multiples. In the pivotal repeat dose toxicity studies in rats and dogs an exposure multiple of approximately 600-fold was estimated in both species. In the pivotal embryofetal development studies, comparison with C_{max} and LLOQ rendered an exposure margin to NOAEL of 40 in rats and 200 in rabbits.

Another way to estimate the margin for the systemic toxicity is to convert the NOAEL for systemic toxicity after systemic administration to the amount of netarsudil mesilate required to achieve the human equivalent dose (HED). Accordingly, the NOAEL dose 1 mg/kg/day established in rat and dogs was converted to the HED. The HED per day for a 60 kg person is 9.6 mg and 32 mg based on the rat and dog data respectively. When netarsudil is administered in both eyes, the daily dose is 0.016 mg. Thus, the HED converted from the rat NOAEL was 600-fold, and from the dog 2000-fold the actual human dose.

To compare the topical doses, the doses were normalized to the amount of drug applied in the eyes per day. In humans the total dose per day is 16 µg if both eyes are treated. In the pivotal studies in rabbits and monkeys the dose ranged from 16 to 64 µg, maximum 4 times the clinical dose calculated on daily basis.

Genotoxicity

A complete package of genotoxicity studies in agreement with the ICH S2(R1) guideline, including tests for gene mutations in bacteria and mouse lymphoma cells, and micronuclei *in vivo*, has been performed with netarsudil. All tests were negative. Based on the results of the conducted genotoxicity studies, the overall conclusion is that netarsudil does not have any genotoxic potential.

Carcinogenicity studies

There was no carcinogenicity studies presented. The lack of carcinogenicity studies is acceptable considering the low plasma exposure to netarsudil, its enantiomer, and their metabolites in humans at the anticipated clinical dose.

Reproductive and developmental toxicity

Fertility and early embryonic development

No studies evaluating the effects on fertility and early embryonic development studies were performed.

Embryo-foetal development

Seven embryo-fœtal development studies (EFD studies) were conducted. Five were dose-range finding studies, two were in non-gravid animals (one rat and one rabbit) and three in gravid animals (one rat and two rabbit). Two pivotal GLP studies in each of the species rat and rabbit were conducted. None of the

studies were performed in pigmented animals although it has been shown that netarsudil binds to melanin. This is considered acceptable.

The observed injection site irritation observed in the dose range finding studies led to the decision to use animals with implanted vascular access ports in the pivotal study to ensure reliable administration in the animals. The information on how the catheters were implanted and if there was any concomitant medication (pain relief and antibiotics) is very limited.

Rats were administered 0, 0.03, 0.1, 0.3 and 3 mg/kg/day. Rabbits were administered 0, 0.5, 3 and 5 mg/kg.

In both studies a dose dependent increase in the % post implantation loss (from 8.6 to 100% in rats and from 1.2% to 12.7% in rabbits. There were no AR-13324 related fetal external, soft tissue, or skeletal fetal malformations or variations at any dose.

Prenatal and postnatal development, including maternal function

No studies were performed. The lack of pre- and postnatal studies is acceptable considering the low plasma exposure to netarsudil, its enantiomer, and their metabolites in humans at the anticipated clinical dose.

Juvenile animals

No studies were performed. The lack of studies in juvenile animals is acceptable considering the product-specific waiver for all subsets of paediatric population on the grounds that the specific medicinal product does not represent a significant therapeutic benefit over existing treatments for paediatric patients.

Metabolites

The ophthalmic formulations in the pivotal ocular studies were intentionally spiked with the ~~active~~ metabolite AR-13503.

Impurities

The *R*-enantiomer of netarsudil AR-13323 has been intentionally spiked in the solutions administered both intravenously and topical in the eyes. In the safety pharmacology studies the concentration of the *R*-enantiomer was approximately 11%, in the pivotal toxicity studies the formulations contained 5 % *R*-enantiomer. In the final formulation the level of the R-enantiomer in the product specification is set to 3.5%. The R-enantiomer is considered sufficiently qualified in the non-clinical toxicity studies.

The impurities 2,4-dimethyl benzoic acid, DBMPP acid, and the starting material 6-AIQ were added to a level of 0.5 % in the ophthalmic formulations used in the pivotal ocular toxicity studies. These impurities can be considered qualified at the proposed levels in the final product (0.25 %).

Phototoxicity

Netarsudil absorbs light in the lower range of the UV visible spectrum (<330 nm). At the absorbance maxima at 288 nm the molar extinction coefficient (MEC) of netarsudil (10914 Lmol-1/cm) was greater than the threshold (1000 Lmol-1/cm). To further investigate the phototoxic potential of netarsudil a 3T3 NRU-PT study was conducted which showed that netarsudil was not phototoxic at the UV spectra investigated (UVA, 320-400 nm).

Other studies

No specific studies on local tolerance, antigenicity, immunotoxicity, or dependence have been performed, which is considered acceptable.

2.3.5. Ecotoxicity / environmental risk assessment

The ERA is based on netarsudil which has a molecular weight of 454 g/mol (free base) and is freely soluble in water. The log Kow was reported to be 4.44, and the log D7.4 was reported to be 3.57. However, no sufficient references or reports have been provided and the details for the determination of log KOW and logD7.4 are therefore unknown. The applicant was in the first round asked to provide sufficient and assessable information regarding the determination. The requested report was provided but the determinations were however not performed with the methods that are clearly recommended by the EMA (see the ERA guideline). Since the presented LogKOW (4.44) was close to the value for when a screen for persistence, bioaccumulation and toxicity should be done (LogKOW >4.5), this is not acceptable and the applicant is requested to provide a study where determinations of LogKOW and LogD with EMA recommended methods. The applicant has stated that the requested study is ongoing and that the results will be submitted by the Day 180 responses or post approval. (Unresolved issue)

The PECSURFACE WATER for netarsudil is less than the action limit 0.01 µg/L. No further analysis is therefore required.

2.3.6. Discussion on non-clinical aspects

Pharmacology

Netarsudil (AR-13324) is a potent inhibitor of human ROCK 1 and 2 and its metabolite is about 5-fold more potent at these targets. However, the selectivity of netarsudil and its metabolite are questioned. Both the primary and secondary pharmacodynamics in vitro screens reveal that netarsudil and its metabolite have the potential to inhibit numerous human protein kinases and other non-kinase targets. As the systemic exposure is low/negligible in the clinical situation, the main concern is potential local off-target effects. Therefore, a discussion of the potential biological consequences of inhibiting these additional targets, locally in the eye, was requested. The applicant has not found any relevant literature information to predict whether inhibition of any of the off-targets would have the potential to cause local ocular toxicity. No data on expression of these targets in ocular tissues has been provided. In study AR-13324-IPH01, netarsudil and its metabolite (AR-13503) were tested at concentrations between 0.01 nM to 100 µM. Both netarsudil and its metabolite show potent inhibition on protein kinase N2, protein kinase A and protein kinase MRCK alpha with Kis in the same range as ROCK1 and 2. Thus, inhibition of these targets is very likely if they are expressed in ocular tissues. In study AR 13324 IPH02, netarsudil and AR-13084 (racemate of the metabolites of netarsudil and AR-13323) at 0.5 µM showed significant inhibition of 24 and 17, respectively, additional protein kinases, but IC50 values were not further determined. In the human non-kinase screen (AR 13324 IPH03), netarsudil at 10 µM showed significant inhibition of more than 20 non-kinase proteins. It is agreed that the test concentration was rather high, but as IC50 values were not further determined, it is not possible to reason on the likelihood for interaction with these targets in the clinical situation. Based on the available data, it can be concluded that netarsudil and its metabolite are not selective inhibitors of ROCK 1 and 2. However, as the expression of the potential off-targets in ocular tissues is not known, it is unclear if off-target interactions contribute to the observed ocular safety profile.

Overall, the applicant proposes that netarsudil treatment lowers IOP by three mechanisms; increasing aqueous humor outflow through the trabecular meshwork (outflow facility), decreasing the production of aqueous humor, and lowering of episcleral venous pressure. Based on the available data, the proposed mechanisms seem plausible.

The IOP-lowering effect of netarsudil was studied in normotensive rabbits and monkeys. It was noted that the ocular hypotensive effect did not increase proportionally to the increasing concentration of AR-13324. In rabbits (study AR-13324-APH04), the concentration of AR-13324 solution increased twice; from 0.02% to 0.04% but maximal IOP reductions were 7.0 mmHg and 7.1 mmHg at 4 hours after dosing, respectively and 1.3 mmHg and 1.5 mmHg at 24 hours after dosing, respectively. As all studies were performed in normotensive animals, this may explain a weak response on antihypertensive activity of AR-13324. The applicant was asked to elaborate on why no any animal model with elevated IOP or with glaucoma was chosen and to further discuss the correlation between results obtained in normotensive animals and results of studies performed in glaucoma patients. According to the applicant, the main reason for choosing normotensive animals was that the majority of models with elevated IOP have a damaged or altered function of the trabecular meshwork (TM) or the TM outflow pathway. As TM is the target tissue for netarsudil's IOP lowering effect the potential damage of this tissue could limit the ability to measure netarsudil's activity. Moreover, the correlation between the results of studies performed on normotensive animals (monkey) and patients with glaucoma (AR-13324-APH06) was discussed. In monkeys, once-daily AM dosing of netarsudil 0.02% for 3 days produced a maximum IOP reduction of 5.8 and trough IOP reduction of 4.9 mmHg 24 hours after dosing. In the AR-13324-CS201 clinical study, once-daily AM dosing of netarsudil 0.02% for 7 days produced a maximum IOP reduction of 6.9 mmHg and trough IOP reduction of 5.3 mmHg 24 hours after dosing. In addition, the applicant ensures that IOP reduction achieved by netarsudil in normotensive animals is larger than has been reported for other drug classes, and this is believed to be related to the ability of netarsudil to lower episcleral venous pressure, which limits IOP lowering due to the resistance to outflow contributed by episcleral venous pressure. However, even with this activity, the use of normotensive animals may limit the ability to measure the full dose response of netarsudil.

The effect of netarsudil on episcleral venous pressure was studied in Dutch Belted rabbits. Taking into account that prolonged continuous recordings of episcleral venous pressure are difficult due to technical problems and severe conjunctival oedema, which tended to develop 1-2 hours into the experiments - the applicant was asked to justify the choice of species for this experiment and to further discuss the reliability of the results. The applicant argues that Dutch-belted rabbits are relevant due to their pigmented ocular tissues as netarsudil bind to melanin. This is agreed. The applicant has further clarified that the decrease in episcleral venous pressure is indeed caused by netarsudil. Vehicle control animals demonstrated that procedure-related effects such as oedema do not produce a reduction in EVP but appear to cause an increase in episcleral venous pressure.

One of the identified off-targets was the norepinephrine transporter (NET). The applicant speculates that NET inhibition may contribute to the IOP lowering activity of netarsudil. However, this hypothesis has not been confirmed by solid experimental data. However, as no claims are made on this hypothesis, no further action is warranted.

A deficiency in the documentation is the lack of data on activity of netarsudil on ROCK 1 and 2 in the animal species used for safety evaluation. The applicant has provided a reference to the HomoloGene database showing a conserved amino acid homology of ROCK 1 across a diverse array of animal species. The database reports a homology of 99.6%, 97.6%, 94.8% and 96.6% in monkey, dog, rat and mouse, respectively, to the human ROCK 1 sequence. In published literature, the pharmacology of netarsudil and its metabolite (AR-13503), on ROCK1/2 has been shown in biochemical and cell-based assays, and in mouse, rabbit, pig, dog and monkey in vivo. Additionally, netarsudil causes reductions in IOP in rabbits and monkeys, and signs (trace to mild hyperaemia) likely to be related to the primary pharmacodynamics (i.e. vasodilation) were observed in pharmacology and toxicology studies in rats, dogs, rabbits and monkeys. Taken together, it is agreed that all species tested within the non-clinical program (rat, rabbit, dog and monkey) are likely relevant species and that safety aspects related to the primary pharmacodynamics have been adequately evaluated.

Hyperaemia is also reported as a common adverse reaction in clinical trials (SmPC section 4.8) and is likely caused by smooth muscle cell relaxation causing local vasodilation.

Netarsudil, but not its metabolite, was shown to induce phospholipidosis in CHO-K1 cells with an EC50 of 1.1 µM (~500 ng/mL). As observed in tissue distribution studies, once netarsudil is absorbed into the eye, it is rapidly converted to the active metabolite. Thus, intraocular concentrations of netarsudil are likely to be much lower than the micromolar concentrations required for phospholipidosis, while phospholipidosis might be seen within the cornea. Thus, it seems plausible that phospholipidosis may cause the corneal haze observed in monkey studies (see toxicology section), and the findings of "corneal deposits" and "corneal verticillata" observed in Phase 3 clinical studies. Corneal verticillata is a pattern of whorl-shaped opacities within the basal corneal epithelium and has been observed as a side effect of drugs across many pharmacologic classes causing intracellular phospholipid accumulation.

Both netarsudil and its metabolite are considered adequately evaluated with regards to safety pharmacology. No CNS effects were observed in any of the studies performed.

Netarsudil inhibits hERG with an IC50 of 0.4 µM (~181 ng/ml). The IC50 is about 1800-fold a maximal systemic netarsudil Cmax, bound (LLOQ 0.1 ng/ml) in the clinical situation. Taking into account the high plasma protein binding (99.8% at 100 µM), the free plasma concentrations in humans are considered negligible. The active metabolite was not tested in the GLP hERG assay. However, AR-13084, the metabolite of the racemate AR-13165 (comprising of 50% AR-13503) was examined in the off-target screen of non-kinase proteins (including hERG) and showed no hERG inhibition at 10 µM.

In the single iv dose dog telemetry study, no QTc prolongation was observed up to mean Cmax values of 872 ng/ml. At Cmax exposures of ~400 ng/ml and above, decreased arterial pressure and increased heart rate were observed. The NOEL for the effects on arterial pressure and heart rate was 0.7 mg/kg. At this dose, average plasma level of netarsudil was 26.6 ng/ml while the level of metabolite AR-13503 was below LLOQ (1.0 ng/ml). These effects are likely pharmacodynamics effects of netarsudil. Rho kinase inhibitors reduce blood pressure by decreasing vascular smooth muscle contractility and thereby reducing vascular tone causing vasodilation. The increased heart rate is likely a secondary effect. No cardiovascular effects were observed in the 28-day repeat-dose iv dog study up to average netarsudil Cmax values of 63.3/51.51 ng/ml in males/females and average AR-13503 Cmax values of 1.51/1.80 ng/ml in males/females.

Based on the available data, no CNS or CV effects are expected following ocular topical administration of netarsudil in man.

Pharmacokinetics

All bioanalytical method validation reports have been submitted. None of the method validations applied in pivotal toxicology studies were formally performed under GLP. The applicant has provided information on the aspects of the bioanalytic method validations that were not according to GLP and discussed the impact on the analysis of the samples collected in the pivotal toxicology GLP studies.

The Contract Laboratory, Tandem Labs, operates its laboratory in accordance with principles of GLP. Tandem Labs SOPs, analytical procedures, and methods were followed during the conduct of the method validations. Qualified analysts, using calibrated equipment with appropriate documentation, performed assays. The validations were conducted in accordance with Tandem Labs standard operating procedures, and methods, and followed pre-established standard procedures with pre-established acceptance criteria. The deviations from GLP include no formal designation of a Study Director (instead a responsible Principal Investigator), no formal study protocol (instead a Validation Analytical Plan) and some limitations in QAU

inspections. However, QAU reviewed all validation data and audited validation reports in agreement with specifications in the Validation Analytical Plan. Taken together, the deviations from GLP are not considered to have impact on the results in the pivotal GLP toxicity studies.

In vitro and in vivo studies show that netarsudil and its metabolite bind melanin, thus raising a potential concern for phototoxicity (see toxicology section).

Based on the proposed MoA, the assumed target tissues for ROCK 1/2 inhibition are the trabecular meshwork, the ciliary epithelium, and the episcleral veins. Based on the available data from topical ocular administration of netarsudil in rabbits, the applicant has provided estimation on target tissue exposure in the clinical situation. The applicant estimates that the concentration of AR-13503 in the target tissues in healthy rabbits could range from approximately 67 ng/g to 229 ng/g tissue (data from retina-choroid-plexus in study PG324-APK01). Using these data and the estimated molecular weight of AR-13503 (~306 g/mol), the estimated concentrations could range from 0.22 to 0.75 µM. As reported in the literature, ocular pharmacokinetics parameters of some glaucoma drugs (e.g. brimonidine and dexamethasone) are lower in the disease model compared to in normal animals, suggesting that ocular concentrations in glaucoma patients may be lower than that estimated from healthy rabbits.

Overall, the metabolic pathway of netarsudil appears to be common to rats, rabbits, dogs, cynomolgus monkeys and humans. Thus, the selected species are considered relevant from a metabolism perspective.

In a secondary pharmacology screen at 10 µM, netarsudil and AR-13165 (a racemic mixture of netarsudil and its enantiomer, AR-13323) showed significant inhibitory activity against five cytochrome P450s (1A2, 2C19, 2C6, 2D6 and 3A4). AR-13084, the metabolite of AR-13165, exhibited inhibitory activity against CYPs 2C19 and 2D6. The metabolite of netarsudil, AR-13503, was not tested in the assay but is considered covered by testing of AR-13084. Based on the low/negligible plasma concentrations of netarsudil and its metabolite (AR-13503) detected following topical ocular administration, a risk for systemic DDIs is considered minute. However, as all targeted CYPs with exception of CYP1A2, are reported to be expressed in human cornea, the applicant was asked to further discuss the potential for pharmacokinetic interactions of other topical ocular medicinal products likely to be used concomitantly in the intended patient population. As outlined by the applicant, various classes of topical ophthalmic medications could also be concomitantly used with Rhokiinsa. However, the clinical significance of potential DDIs, specifically within the cornea, is not well-characterised. There has been a lack of DDI-type events in large-scale human clinical studies conducted to date, and pharmacovigilance data since the launch of netarsudil ophthalmic solution 0.02% in the US. Taken together, the lack of reported DDI-type events in the clinical situation indicates that this may be a concern of low or no significance.

Toxicology

The repeat-dose toxicity studies of Rhokiinsa were conducted in rat, rabbit, dog and monkey. It is not clear why these species were chosen and why none of the species were evaluated for both ocular and systemic route of administration toxicity. The applicant was asked to further elaborate on the selection of species. Different aspects including pharmacokinetics and route of administration were taken into consideration during selection of species. No species-specific or gender differences have been observed regarding pharmacology or toxicity which supports the relevance of the selected species.

The systemic exposure after topical administration in the eye was very low in both rabbit and monkeys. The systemic toxicity was investigated in two pivotal repeat dose toxicity studies in rats and dogs for 28 days. The maximum dose administered was 1 mg/kg in both species. Based on the earlier shorter non pivotal repeat-dose studies, a maximum dose higher than 1 mg/kg would have strengthened the study as well as enabling to establish a NOAEL. However, since the systemic exposure after ocular administration is negligible, iv administration of 1 mg/kg is considered to provide a sufficient margin.

The main finding after topical administration in the eye in all species was signs of irritation. Severity and incidence increased with dose but ocular irritation was also observed in vehicle treated animals. In most cases, the irritation declined with time during pursued treatment. These types of findings were very common in patients. Conjunctival hyperaemia was reported in 50% of the patients. It is recommended to administer Rhokiinsa in the evening which might help the patients to tolerate the transient period of irritation.

In the rabbit degeneration/erosion of the cornea was observed with netarsudil concentrations of 0.04% twice daily and above. The overall epithelial layer was thinner but had not progressed to areas denuded of corneal epithelium. Histopathological examination showed corneal lesions consisting of peripheral vascularization, mixed cell inflammation and attenuation of the overlying corneal epithelium. In the treated patients, a few cases suggestive of corneal erosion were noted. In the first round of the procedure, the applicant was asked to discuss the possible mechanism of action for the corneal degeneration/erosion effects and the clinical relevance, especially concerning the long term continuous use in glaucoma. The applicant referred to data on laboratory rabbits which shows a high incidence of spontaneous corneal lesions. Furthermore, the animals are exposed to multiple ophthalmic tests and repeated topical ocular dosing procedure. The procedures in them self or the consequences of, such as decreased blinking could also contribute. In the clinical setting, the applicant suggests that the higher incidence eye pruritis and irritation could produce more frequent eye rubbing which could explain the higher incidence of punctuate keratopathy. It is not possible to draw any conclusions based on non-clinical data regarding the safety in this aspect for a long-term continuous treatment of netarsudil.

Another clinically relevant observation was corneal haze. Corneal haze was described as diffuse and superficial with the appearance of multiple, very fine, particulate depositions. It seems plausible that the corneal haze is caused by phospholipidosis.

In one of the non-pivotal studies in monkeys where netarsudil was administered 4 times daily, vitreus haze, optic disc hyperaemia with indistinct optic disc margins, and retinal oedema were observed in 2 and 3 animals in the 0.04% and 0.12% groups respectively. The histopathological examination showed no inflammation or anatomical alterations. The applicant argues that these findings can be explained by the reduced IOP. It is however not fully understood why these findings were specifically attributed to the reduced IOP or if other possibilities were considered. In the first round of the procedure the applicant was requested to further discuss the findings and possible clinical implications. In the response, the applicant states that uveal effusion syndrome and hypotony maculopathy are well-characterized ophthalmic clinical conditions caused by low IOP. This is only partly agreed since uveal effusion syndrome is associated with normal or elevated IOP while the hypotony maculopathy is indeed caused by low IOP and could be triggered by exaggerated pharmacology when elevated IOP is treated. The issue is not further pursued.

The eye drops solution contains 0.015% benzalkonium chloride (BAK) as a microbial preservative. In the pharmacology section it is described that increasing the BAK concentration from 0.0075% to 0.015% might yield a slight improvement in efficacy, without significantly reducing apparent tolerability. In the section above, however, several findings have been described that are indicative of reduced tolerability. The applicant was requested to discuss the possible role of BAK in the corneal damage findings. In the response, the applicant has discussed the findings from the studies with vehicle (including BAK) alone. No discussion regarding the potential effect of BAK on the tolerability of netarsudil was provided. In the studies, no control group without BAK was included; it is thus not possible to draw any conclusion if the background corneal lesions or damage are attributable to the treatment or the multiple ophthalmic tests. However, the applicant has committed to reviewing the concentration of benzalkonium chloride (BAK) in the existing formulation to determine if a concentration of less than the current 0.015% level would still ensure a safe and efficacious formulation (see further discussion in section 2.6.1).

Exposure margins for systemic toxicity with the negligible systemic exposure in the patients can be considered sufficient. For the ocular route and ocular effects the margins are substantially lower. In the pivotal animal studies the clinical concentration (0.02%) was investigated together with a lower (0.01%) and higher (0.04%) concentration. The margin consisted mainly of the fact that the animals were dosed twice daily and humans are dosed once daily. Similar ocular adverse reactions were observed in both rabbits and monkeys as well as humans.

The genotoxicity study package of netarsudil was in agreement with the ICH S2(R1) guideline. In the in vivo micronucleus assay historical control data was included as positive control. The applicant has presented “Rat micronucleus test historical control data 2006-2010” and the study was conducted during 2011. It is not clear from the report from which strain of rats the historical data is collected from. Nor is the reliability to detect increases in micronuclei demonstrated. These deficiencies are however not considered to have an impact on the conclusion of the study since the number of micronucleated polychromatic erythrocytes is very low in all treatment groups. In the first round of the procedure, the Applicant was asked to assess the genotoxicity of netarsudil mesylate R-enantiomer as a potential chiral impurity. The product specification (shelf life) is set to 3.5%, which renders 0.6 µg/day, presuming a 40 µL drop into each eye once daily. This level is not of toxicological concern for genotoxicity in Rhokiinsa finished product in accordance with ICH M7 (R1) (<1.5 µg/day).

The lack of carcinogenicity, fertility, and pre- postnatal studies is acceptable considering the low plasma exposure to netarsudil, its enantiomer, and their metabolites in humans at the anticipated clinical dose.

The in vitro study to investigate the phototoxic potential of netarsudil was conducted with the standard light spectra UVA (filter 320-400 nm). In the case of netarsudil, induction of phototoxicity by UVB is however more relevant and the experiment should have been conducted with modified irradiation conditions. In the first round of the procedure, the applicant was asked to submit a 3T3 NRU-PT study with modified irradiation conditions to assess the phototoxicity of UVB or justify the absence of such a study. The applicant did not provide a solid justification on why the study was not performed with the adjusted wavelengths, which would have been the scientific rational considering the ultraviolet absorption spectrum of netarsudil. The residence time of netarsudil in the cornea is stated to have a tmax of 0.5 to 8 hours post dose, which gives both time and a location where potential reactions could occur. This resident time is likely based on tissue distribution data following single topical ocular administration in rabbits. At 24 hours following a single topical ocular administration, the corneal concentrations were approximately 30% of the maximal concentrations indicating a significant exposure during day-time. Based on the estimated corneal half-life (~13 hours), drug accumulation seems likely following repeated administration. With respect to the long term treatment of patients, further efforts to adequately assess whether netarsudil has a phototoxic potential or not should be made. The applicant submitted a 3T3 NRU-PT study with modified irradiation conditions to assess potential UVB induced phototoxicity as a response to a request in the second round of the procedure. The study was performed both on AR-13324 and its active metabolite AR-13503. It was concluded that AR-13324 has a probable phototoxic potential and AR-13503 has a phototoxic potential. It is stated in the ICH Guidance S10 on Photosafety Evaluation of Pharmaceuticals that a positive 3T3 NRU-PT should not be regarded as indicative of a likely clinical phototoxic risk, but rather a flag for follow-up assessment. There are, however, no established non-clinical in vitro or in vivo ocular models that can be used for follow-up assessment of ocular phototoxicity. Other measures have thus to be taken into consideration to determine if the finding is clinically relevant.

The potential phototoxicity of AR-13324 and AR-13503 is included in section 5.3, as follow: “Netarsudil and its active metabolite AR-13503 were found to have a possible phototoxic potential in a modified 3T3 NRU-PT in vitro assay, where the wavelength was extended to include UVB light.”

From a non-clinical perspective, it is not possible to elucidate this further and the concern needs to be further pursued with clinical data.

2.3.7. Conclusion on the non-clinical aspects

There are no major objections to an approval of Rhokiinsa from a non-clinical point of view.

2.4. Clinical aspects

2.4.1. Introduction

Several substances are mentioned within the clinical section. These include the active substance netarsudil mesylate (AR-13323), its active metabolite (AR 13503), the R-enantiomer of netarsudil mesylate (AR-13323) and the R-enantiomer of the metabolite of netarsudil mesylate (AR-13534).

GCP

The clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Table 1 - Characteristics of All Completed Clinical Studies Conducted as part of Netarsudil Ophthalmic Solution 0.02% Development (Phase 1, 2, and 3 (cont'd)

Study Identifier Phase	Number of Study Centers Study Location	Study Start[1] Study Status	Study Design Control Type	Study Objectives	Treatment Groups Dosage Regimen	Number of Subjects Planned / Completed[2]	Treatment Duration	Gender Mean Age (range)	Primary Diagnosis	Primary Safety Endpoint(s)
AR-13324-CS101 Phase 1	1 USA	Nov-2013 Completed	Prospective, open-label uncontrolled	Ocular and systemic safety; systemic absorption	Netarsudil 0.02% QD AM	16/18	8 days	4M, 14F 47.6 yrs (24-74)	Healthy subjects ≥ 18 years; IOP 14-20 mmHg	AEs; VA; IOP; biomicroscopy; ophthalmoscopy; comfort; VFs
AR-13324-CS102 Phase 1	1 USA	May-2015 Completed	Prospective, randomized, double-masked, paired-comparison vehicle controlled	Aqueous humor dynamics; ocular and systemic safety	Netarsudil 0.02% (1 eye) and Vehicle (fellow eye) QD AM	10/11	7 days	1M, 10F 38.6 yrs (21-56)	Healthy subjects ≥ 18 years; IOP 14-21 mmHg	AEs; VA; biomicroscopy
AR-13324-CS201 Phase 2a	12 USA	March-2012 Completed	Prospective, randomized, double-masked, dose-respo	Ocular hypotensive efficacy; ocular and systemic safety	Netarsudil 0.01%, 0.02%; 0.04%; Vehicle	80/85	7 days	34M, 51F 64.0 yrs (27-88)	≥ 18 years; OAG or OHT with IOP 21-36 mmHg	AEs; VA; biomicroscopy; ophthalmoscopy; comfort

			nse vehicle controlled		QD AM					
AR-13324-CS202 Phase 2b	23 USA	Nov-2012 Completed	Prospective, randomized, double-masked, dose-response, parallel-group active controlled	Ocular hypotensive efficacy; ocular and systemic safety	Netarsudil 0.01%, 0.02%; Latanoprost 0.005% QD PM	210/224	28 days	92M, 132F 65.1 yrs (19-90)	≥ 18 years; OAG or OHT with IOP 22-36 mmHg	AEs; VA; biomicroscopy; ophthalmoscopy; pachymetry; comfort
AR-13324-CS204 Phase 2b	1 USA	Sept-2016 Completed	Prospective, randomized, double-masked vehicle controlled	Ocular hypotensive efficacy; nocturnal and diurnal, Ocular and systemic safety	Netarsudil 0.02% Vehicle QD PM	12/12	7 days	6M, 6F 64.4 yrs (47-75)	≥ 18 years; OAG or OHT with IOP 17-30 mmHg	AEs; VA; ocular signs and symptoms; biomicroscopy; ophthalmoscopy
AR-13324-CS301 Phase 3	37 USA	June-2014 Completed	Prospective, randomized, double-masked, parallel study active controlled	Ocular hypotensive efficacy; ocular and systemic safety	Netarsudil 0.02%; QD PM Timolol 0.5% BID	400/411[3]	3 months	161M, 250F 65.0 yrs (20-96)	≥ 18 years ; OAG or OHT with IOP 18-26 mmHg; pediatric 0-2 years	AEs; VA; biomicroscopy; ophthalmoscopy; comfort; pupil diameter; VFs
AR-13324-CS302 Phase 3	62 USA	June-2014 Completed	Prospective, randomized, double-masked, parallel study active controlled	Ocular hypotensive efficacy; ocular and systemic safety	Netarsudil 0.02% QD PM; 0.02% BID; Timolol 0.5% BID	690/755[4, 5]	12 months	293M, 463F 64.1 yrs (11-92)	≥ 18 years ; OAG or OHT with IOP 18-26 mmHg; pediatric 0-2 years	AEs; VA; biomicroscopy; ophthalmoscopy; comfort; pupil diameter; VFs; ECD
AR-13324-CS303 Phase 3	25 Canada	Aug-2014 Completed	Prospective, randomized, double-masked, active-controlled, parallel study	Ocular and systemic safety	Netarsudil 0.02% QD PM Netarsudil 0.02% BID Timolol 0.5% BID	240/93[6]	12 months	49M, 44F 63.8 yrs (26-84)	≥ 19 years; OAG or OHT with IOP 20-27 mmHg	AEs; VA; biomicroscopy; ophthalmoscopy; comfort; pupil diameter; VFs;
AR-13324-CS304 Phase 3	63 USA	Aug-2015 Completed	Prospective, randomized, double-masked, active-controlled, parallel-stu	Ocular hypotensive efficacy, ocular and systemic safety	Netarsudil 0.02% QD PM Timolol 0.5% BID	700/708	6 months	263M 445F 65.5 yrs (18, 91 yrs)	≥ 18 years; OAG or OHT with IOP 20-30 mmHg	AEs; VA; biomicroscopy; ophthalmoscopy; comfort; pupil diameter;

			dy							VFs
AR-13324-OBS01	10 USA	Apr 2016 Completed	Prospective, targeted, non-interventional (observational)	Evaluation of visual function in subjects with corneal verticillata	Non-interventional observational study	22[7]/25 Netarsudil QD 20[7]/20 Netarsudil BID	No set duration – subjects continued until resolution/stabilization of corneal deposits	22M 23F 69.4 yrs (50, 83 yrs)	Subjects from AR-13324-CS301 and AR-13324-CS302 who developed corneal verticillata	VF & contrast sensitivity

1. First subject screened.
2. Number of subjects included in the safety analyses.
3. No pediatric subjects were enrolled.
4. Two pediatric subjects were enrolled, one age 11 and one age 14.
5. 756 subjects randomized but only 755 in safety analyses since 1 subject who randomized never dosed.
6. Study was discontinued after 93 subjects enrolled due to slow enrollment
7. Per Study protocol, 150 subjects were identified from AR-13324-CS301 and AR-13324-CS302 who may have qualified for study AR-13324-OBS01, but per the CSR, only a total of 47 subjects actually met the inclusion and exclusion criteria, of whom, two had a history of cornea epithelial haze so were not entered into the study. The numbers given in the Table reflect the number entered into each arm of the study.

Table 2 - Characteristics of All Ongoing Clinical Studies Conducted as part of Netarsudil Ophthalmic Solution 0.02% Development (Phase 1, 2 and 3)

Study Identifier Phase	Number of Planned Study Centers Study Location	Study Status	Study Design Control Type	Study Objectives	Treatment Groups Dosage Regimen	Number of Subjects Planned/ Completed[2]	Treatment Duration	Primary Diagnosis	Primary Safety Endpoint (s)
AR-13324-CS104[1] Phase 1	2 USA	Ongoing	Randomized, double-masked, placebo-controlled	Ocular and systemic safety	Netarsudil 0.02% or 0.04% or placebo, QD AM. Topical ocular	24/Ongoing	7 days	Healthy subjects Japanese ethnicity IOP: 12 to 20 mmHg	Ocular and systemic safety.
AR-13324-CS205 Phase 2b	35 USA	Ongoing	Prospective, randomized, double-masked, placebo controlled	IOP lowering efficacy, ocular safety relative to placebo, systemic safety in subjects of Japanese ethnicity.	Netarsudil 0.02% or 0.04%, or placebo QD PM Topical ocular	180/Ongoing	28 days	Japanese ethnicity; OAG or OHT; IOP ≥ 15 mmHg and < 35 mmHg at Qualification 1 and12 2.	Ocular and systemic safety.
AR-13324-CS206 Phase 2b	2 USA	Ongoing	Randomized, double-masked, placebo controlled	Evaluate the effect on trabecular outflow facility, IOP and EVP,	Netarsudil 0.02% or Placebo QD AM Topical ocular	20/Ongoing	7 days.	POAG or OHT; IOP >17 mmHg to <30 mmHg at Qualification	Ocular and systemic safety.

				ocular and systemic safety.					

1. The Clinical Study Report was not final at the time of data lock point for this submission.
2. Number of subjects included in the safety analyses.

Table 3 - Characteristics of Clinical Studies Conducted as part of PG324 Ophthalmic Solution Development

Study Identifier Phase	Number of Study Centers Study Location	Study Start[1] Study Status	Study Design Control Type	Study Objectives	Treatment Groups Dosage Regimen	Number of Subjects Planned/ Completed[2]	Treatment Duration	Gender Mean Age (range)	Primary Diagnosis	Primary Safety Endpoint(s)
PG324-CS 201[1] Phase 2b	24 USA	Jan-2014 Completed	Prospective, randomized, double-masked active controlled	Ocular hypotensive efficacy; ocular and systemic safety	PG324[c] 0.01%, 0.02% Netarsudil 0.02% Latanoprost 0.005% QD PM	280/292	28 days	123M, 175F 64.9 yrs (26-92)	≥ 18 years; OAG or OHT with IOP >21 and <36 mmHg	AEs; VA; biomicroscopy; ophthalmoscopy; pachymetry comfort
PG324-CS 301[1] Phase 3	58 USA	Aug-2015 Completed	Prospective, randomized, double masked active-controlled,	Ocular hypotensive efficacy; ocular and systemic safety	PG324 0.02% QD PM Netarsudil 0.02% QD PM Latanoprost 0.005% QD PM	690/718 90 in the extension phase	12 months plus 2 months observation extension	312M 406F 64.8 yrs (18, 91 yrs)	≥ 18 years; OAG or OHT with IOP >17 to<36 mmHg	AEs; VA; biomicroscopy; ophthalmoscopy; pachymetry; comfort; pupil diameter; VFs
PG324-CS 302[1] Phase 3	60 USA and Canada	Feb-2016 Completed	Prospective, randomized, double masked active-controlled,	Ocular hypotensive efficacy; ocular and systemic safety	PG324 0.02% QD PM Netarsudil 0.02% QD PM Latanoprost 0.005% QD PM	690/750	3 months	301M 449F 64.3 yrs (24, 99 yrs)	≥ 18 or 19 years; OAG or OHT with IOP >17 to<36 mmHg	AEs; VA; biomicroscopy; ophthalmoscopy; pachymetry; comfort; pupil diameter; VFs

1. PG324 is a fixed combination of netarsudil/latanoprost containing netarsudil (0.01% or 0.02%) and latanoprost 0.005%.
2. Number of subjects included in the safety analyses.

2.4.2. Pharmacokinetics

Introduction

To support this application, one clinical pharmacokinetic (PK) study (AR-13324-CS101) in healthy volunteers was conducted to assess the systemic absorption of AR-13324, and its active metabolite AR-13503, following once daily topical ocular dosing of netarsudil ophthalmic solution 0.02%.

Analytical methods

Plasma concentrations of AR-13324 and its active metabolite AR-13503 were determined using a high performance liquid chromatography-tandem mass spectrometry method validated with respect to accuracy, precision, linearity, sensitivity, and specificity. The LLOQ for AR-13324 and AR-13503 was 0.100 ng/ml.

Absorption

Bioavailability

Study AR-13324-CS101, a Phase 1, open-label, non-comparative, single-arm, single-center study of AR-13324 ophthalmic solution 0.02% in 18 healthy volunteers, evaluated the systemic exposure of AR-13324 and its active metabolite AR-13503. Subjects received AR-13324 ophthalmic solution 0.02%, one drop in each eye in the morning, for 8 days.

On Days 1 and 8, a member of the Investigator's staff instilled the study medication. On Days 2 to 7, subjects self-administered their investigational medication at home. No formal measure was used to guarantee treatment adherence on Days 2 to 7. However, subjects recorded administration times in a diary, and the administration times of doses for each subject on all days were provided in the Appendices. Inspection of these administration times showed that all subjects administered all doses of the study medication at the appropriate time on all days, except for one dose in one patient. Further, the subject's eye drop instillation performance was evaluated at qualification visit, to assure that the subject could correctly instil 1 drop (and 1 drop only) of an artificial tear into each eye.

Blood samples were obtained for bioanalytical assessment of AR-13324 and its metabolite AR-13503 at the following times post dose on Day 1: 15 min, 30 min, 1, 2, 4, and 8 hours, and at the following times on Day 8: predose (-30 min), 15 min, 30 min, 1, 2, 4, 8, and 23.5 hours post dose.

All available data from all 18 subjects were included in the PK population. There were no observed plasma AR-13334 concentrations above the LLOQ (0.100 ng/ml) at any time point in any subject. Only 1 plasma concentration above the LLOQ for AR-13503 (metabolite) was observed in 1 subject on Day 8 at 8 hours post dose (0.11 ng/ml, LLOQ of 0.100 ng/ml). The maximum molar concentration of netarsudil (MW 453.21) in plasma was therefore <0.2 nM, which is more than 1000 times below the IC50 for netarsudil effects on actomyosin dynamics in human cells (219 nM; AR-13324-IPH04). For AR-13503 (MW 321.37), the maximum plasma concentration was 0.3 nM or lower, which is more than 200 times below its cell-based IC50 for effects on actomyosin dynamics (64 nM; AR-13324-IPH04).

Distribution

In vitro, AR-13324 showed high protein binding in human plasma (97-100% bound). Less protein binding in human plasma was observed with active metabolite AR-13503 (60-70% bound) (Study AR-13324-IPK01).

Elimination

- Metabolism

Preliminary studies investigating the *in vitro* metabolism of AR-13324 were performed using corneal tissue from humans. Based on these studies (AR-13324-IPK03), after topical ocular dosing, AR-13324 is metabolised by esterases in corneal tissues to ~~an active~~ metabolite AR-13503. There is no subsequent metabolism of metabolite AR-13503.

Dose proportionality and time dependency

In Study AR-13324-CS101, only one concentration of netarsudil ophthalmic solution was evaluated, 0.02%. Thus, no pharmacokinetic evaluation of dose proportionality was conducted. There was no evidence of accumulation of AR-13324 or metabolite AR-13503 with repeated once daily topical dosing.

Intra- and inter-individual variability

Blood levels of netarsudil and its principle metabolite, AR-13503, were insufficient to evaluate pharmacokinetic variability.

Pharmacokinetics in target population

No clinical PK or metabolism studies were conducted in patients with glaucoma or ocular hypertension. The PK of netarsudil in healthy volunteers determined in the phase 1 PK study were considered to be predictive of the PK in the target patient population.

Special populations

- Impaired renal or hepatic function

No studies were conducted in patients with renal impairment or hepatic impairment. Given the relatively low ocular dose (16 µg for bilateral, once-daily dosing of 40 µL of netarsudil ophthalmic solution 0.02%), it is unlikely that renal impairment or hepatic impairment would influence the pharmacokinetics of ocularly-instilled netarsudil 0.02%.

- Elderly

No dosage adjustment for elderly patients is specified in the proposed SmPC. Study AR-13324-CS101 included 18 healthy adult subjects of ages 24-74 years (mean 47.6 years). In all subjects at all time points, plasma concentrations of AR-13324 or its active metabolite AR-13503 were negligible. Therefore, the PK of AR-13324 or AR-13503 in older people are unlikely to be altered and a dosage adjustment in elderly patients is not necessary.

Table 4 - Number and percentage of subjects for Netarsudil 0.02% by Age group (all AR-13324 studies*) - Safety population, all subjects

	Age 65-74 (Older subjects number /total number)	Age 75-84 (Older subjects number /total number)	Age 85+ (Older subjects number /total number)
Controlled Trials	355 /971	171 /971	17 /971
Non Controlled[1] trials	4 /18	NA	NA

Source: AR-13324 Table 14.3.3.3.3.6.99
* Data from Studies
AR-13324-CS101, -CS102, -CS201, -CS202, -CS204, -CS206, -CS301, -CS302, -CS303 and -CS304
1. Only Study AR-13324-CS101 was not controlled
The Applicant notes that in response to Day 120 LoQ Q109, no data from uncontrolled studies was included in Table 11. This was an error (with all subjects counted as part of the controlled trials group). In fact Study AR-13324-CS101 was an uncontrolled study in healthy volunteers who received netarsudil in both eyes for 1 week. The error is corrected in this Table.

- Children

No studies were conducted in paediatric patients, which is acceptable since AR-13324 ophthalmic solution is only indicated for adult patients.

Interactions

In vitro (AR-13324-IPH03), when screened at 10 µM, netarsudil and AR-13165 (a racemic mixture of netarsudil and its enantiomer, AR-13323) showed significant inhibitory activity against five cytochrome P450s (1A2, 2C19, 2C6, 2D6 and 3A4). AR-13084, the metabolite of AR-13165, exhibited inhibitory activity against CYPs 2C19 and 2D6. The metabolite of netarsudil, AR-13503, was not tested in the assay but is considered covered by testing of AR-13165.

As all targeted CYPs except CYP1A2 are reported to be expressed in human cornea, the applicant was asked to further discuss the potential for local drug-drug interactions (DDIs) with other topical ocular medicinal products. As outlined by the applicant, various classes of topical ophthalmic medications may be used concomitantly with netarsudil ophthalmic solution. However, the clinical significance of potential DDIs, specifically within the cornea, is not well-characterized. There has been a lack of DDI-type events in large-scale human clinical studies conducted with netarsudil to date, and pharmacovigilance data since the launch of netarsudil ophthalmic solution 0.02% in the US. Therefore, the potential for topical DDIs in the clinical situation is considered to be a concern of low or no significance.

No *in vivo* drug-drug interaction studies were conducted. This is acceptable given the negligible exposure to AR-13324, or the active metabolite AR-13503, following topical ocular dosing once daily with netarsudil ophthalmic solution 0.02%. The potential for systemic drug-drug interactions is therefore minimal in the intended patient population.

Conclusion

The systemic exposure to AR-13324 and the metabolite AR-13503 was shown to be negligible following repeat topical ocular once daily administration of 0.02% AR-13324 Ophthalmic Solution in 18 healthy subjects. Given these low plasma concentrations, and the fact that AR-13324 and, to a lesser extent active metabolite AR-13503, are highly protein-bound in plasma (nonclinical study AR-13324-IPK01), it is unlikely that netarsudil would have any systemic pharmacological effects after topical ocular dosing in humans, nor the potential for systemic drug-drug interactions.

2.4.3. Pharmacodynamics

Introduction

To support this application, one clinical study (AR-13324-CS102) in healthy volunteers was conducted to study aqueous humor dynamics in the eye following once daily topical ocular dosing of netarsudil ophthalmic solution 0.02%.

Mechanism of action

Netarsudil is a potent Rho kinase inhibitor and a norepinephrine transporter inhibitor. Both of these biochemical activities likely contribute to the multiple mechanisms by which topical netarsudil influences aqueous humor dynamics and lowers IOP. In human and animal studies, netarsudil was shown to reduce IOP by multiple mechanisms of action including increasing trabecular outflow facility, decreasing the production of aqueous humor, and reducing episcleral venous pressure.

Primary pharmacology

Study AR-13324-CS102, a double-masked, randomised, single-centre, placebo-controlled, contralateral eye comparison study, evaluated the effect of AR-13324 Ophthalmic Solution, 0.02% on aqueous humor dynamics in healthy volunteers. Subjects were randomized to receive investigational product, AR-13324 Ophthalmic Solution 0.02%, one drop, once daily in one eye, and AR-13324 Ophthalmic Solution Placebo once daily in the fellow eye, for 7 days. 11 subjects were randomised and treated, and 10 subjects whom completed the study.

No formal measure was used to guarantee treatment adherence when subjects self-administered the eye drops at home. However, Listing 16.2.5.3 indicates that all subjects used the eye drops for 7 days. In addition, the subject's eye drop instillation performance was evaluated at screening, to assure that the subject could correctly instil 1 drop (and 1 drop only) of an artificial tear into each eye.

In study subjects, once daily topical ocular dosing of AR-13324 ophthalmic solution 0.02% lowered IOP (mean change from baseline -4.6 mmHg, ~27%) through multiple mechanisms of action including increasing outflow facility, decreasing episcleral venous pressure, and reducing aqueous humor production (Table 4), which is consistent with nonclinical studies.

The dominant effect produced by AR-13324 is an increase in trabecular outflow facility; accounting for about half of the measured decrease in IOP. This is consistent with the ability of AR-13503, the active metabolite of AR-13324 and the predominant form of the drug in aqueous humor, to increase trabecular outflow facility in perfused enucleated human eyes (Study AR-13324-IPH05), and the ability of AR-13324 to increase outflow facility in non-human primates (Wang 2015).

Secondary pharmacology

No secondary clinical pharmacology studies were conducted. In an in vitro study (AR-13324-IS03), the IC50 for the inhibitory effect of netarsudil on hERG potassium current was 0.4 µM (i.e. 181 ng/ml), which is well above the plasma concentrations detected in the clinical PK study (AR-13324-CS101). Therefore, with topical ocular dosing, the potential for QT prolongation is considered minimal.

Pharmacodynamic interactions with other medicinal products or substances

No studies of pharmacodynamic drug interactions were performed, other than as described in two nonclinical studies, where netarsudil and latanoprost were administered in combination in rabbits and monkeys to study tolerability and hypotensive efficacy.

Conclusion

Netarsudil mesylate (AR-13324) is a potent inhibitor of Rho kinase that also has inhibitory activity against norepinephrine transporter. AR-13324 appears to lower IOP through multiple mechanisms of action: increasing trabecular outflow facility (the dominant effect), decreasing the production of aqueous humor, and reducing episcleral venous pressure.

2.4.4. Discussion on clinical pharmacology

Pharmacokinetics

In the clinical pharmacokinetic study AR-13324-CS101, there were no observed plasma netarsudil concentrations above the lower limit of quantitation (LLOQ = 0.100 ng/ml) at any time point in any

subject, except for 1 plasma sample from one subject being very close to the LLOQ (i.e., 0.11 ng/ml) for the metabolite AR-13503. The maximum molar concentration of netarsudil (MW 453.21) in plasma was therefore <0.2 nM, which is more than 1000 times below the IC50 for netarsudil effects on actomyosin dynamics in human cells (219 nM; AR-13324-IPH04). For AR-13503 (MW 321.37), the maximum plasma concentration was 0.3 nM or lower, which is more than 200 times below its cell-based IC50 for effects on actomyosin dynamics (64 nM; AR-13324-IPH04). Given these low plasma concentrations, and the fact that netarsudil and, to a lesser extent, AR-13503 are highly protein-bound in plasma (AR-13324-IPK01), it is unlikely that netarsudil would have any systemic pharmacological effects after topical ocular dosing in humans, nor the potential for systemic drug-drug interactions.

Pharmacodynamics

Netarsudil is a potent Rho kinase inhibitor and a norepinephrine transporter inhibitor. In a clinical study of aqueous humor dynamics (AR-13324-CS102), AR-13324 was shown to reduce IOP by multiple mechanisms of action including increasing trabecular outflow facility (the dominant effect), decreasing the production of aqueous humor, and reducing episcleral venous pressure, which is consistent with nonclinical studies.

Netarsudil mode of action is different to that of the already approved authorised topical anti-glaucoma products. It is therefore proposed to restrict initiation of the treatment to ophthalmologists or healthcare professionals qualified in ophthalmology.

2.4.5. Conclusions on clinical pharmacology

The applicant's conclusions for the pharmacokinetic and pharmacodynamic assessments are supported.

2.5. Clinical efficacy

The applicant is seeking an authorisation for netarsudil (Rhokiinsa) in the following indication: for the reduction of elevated intraocular pressure (IOP) in adult patients with open-angle glaucoma or ocular hypertension.

The applicant has submitted five efficacy studies: 2 phase II and 3 phase III studies. All of the phase III studies and one phase II study were non-inferiority active controlled randomised trials.

The populations included in the phase 3 trials are broadly similar; all use Timolol maleate ophthalmic solution 0.05% as the control. On the other hand, the population included in the phase 2 RCTs had higher maximum baseline levels of intraocular pressure than those in the phase 3 studies. In addition, the control in the active controlled phase 2 study was latanaprost 0.002% rather than timolol 0.05%. The main features of the studies are shown in the following table.

Table 5 - Summary of efficacy studies

Study ID and dates	No. of study centres / locations	Design	Study Posology	Study Objective	Subjs by arm entered / compl.	Duration	Gender M/F Median Age	Diagnosis Incl. criteria	Primary endpoint
CS201 19.03.2012 to 13.07.2012	11	Randomised placebo controlled trial	Netarsudil 0.04% od Netarsudil 0.02% od Netarsudil 0.01% od	To evaluate the ocular hypotensive efficacy of 3 dose strengths of Netarsudil compared to placebo	Netarsudil 0.04% 19/18 Netarsudil 0.02% od 21/21 Netarsudil 0.01% od 22/22 Placebo 23/22	7 days	Males 47.4% Med age 69 Males 33.3% Med age 69 Males 36.4% Med age 62.5% Males 43.5% Med age 62	Raised intraocular pressure or open angle glaucoma Unmedicated (post-washout, p.r.n.) IOP ≥24 mmHg in one or both eyes at 08:00 hours, ≥ 21 mmHg at 10:00, 12:00 and 16:00 hours on post-washout measurement (Visit 1).	Mean IOP across subjects within treatment group on Day 8 at each post-treatment time point (08:00, 10:00, 12:00, and 16:00 hours
CS202 14.11.2012 to 14.03.2013	18	Randomised active controlled trial (phase 2)	Netarsudil 0.02% od Netarsudil 0.01% od Latanoprost ophthalmic soln 0.005% od	To evaluate the ocular hypotensive efficacy of Netarsudil 0.02% and netarsudil 0.01% compared to latanoprost	Netarsudil 0.02% 72/68 Netarsudil 0.01% 75/71 Latanoprost 77/74	28 days	Netarsudil 0.02% Males 37.5% Med age 68 Netarsudil 0.01% Males44 % Med age 65 Latanopr	Raised intraocular pressure or open angle glaucoma Unmedicated IOP ≥24mmHg at 2 visits (08:00hrs), 2-7 days apart, and ≥22mmHg at 10:00 and 16:00hrs	Mean diurnal OP across subjects within treatment group at D 28

							ost Males 41.6% Med age 66	at 2nd visiit IOP > 36mmHg exclusion criterion	
CS301 11.06.2014 to 04.03.2015	35	Randomised controlled trial	Netarsudil 0.02% od Timolol maleate 0.5% bd	To evaluate the ocular hypotensive efficacy of Netarsudil 0.02% od compared to timolol maleate 0.5% bd in both eyes	Netarsudil 0.02 202/171 Timolol maleate 209/196	3 months	Netarsudil Male 43.6% Med age 67 Timolol Males 34.9% Med age 65	Raised intraocular pressure or open angle glaucoma Unmedicated IOP > 20mmHg & < 27mmHg in the study eye on 2 occasions (08:00 hrs) 2-7 days apart. IOP > 17mmHg & < 27mmHg at 10:00 and16:00 hrs in same eye at 2nd qualification visit	Mean !OP at 8:00, 10:00, 16:00 at Wk 2, Wk 6 and Month 3 visit
CS302 16.06.2014 to 17.03.2016	61	Randomised controlled trial	Netarsudil 0.02% od Netarsudil 0.02% bd Timolol maleate 0.5% bd	To evaluate the ocular hypotensive efficacy of Netarsudil 0.02% od and Netarsudil 0.02% bd compared to timolol maleate 0.5% bd over a 3 month period	Netarsudil od 251/146 Netarsudil bd 254/86 Timolol maleate 251/204	12 months	Netarsudil od Male 38.7% Med age 68 Netarsudil bd Male 30.8% Med age 65 Timolol 40.5% Med age 64	Raised intraocular pressure or open angle glaucoma Unmedicated IOP > 20mmHg & < 27mmHg in the study eye on 2 occasions (08:00 hrs) 2-7 days apart. IOP > 17mmHg & < 27mmHg at 10:00 and 16:00 hrs	Mean IOP for subjects with baseline IOP (08:00) > 20mmg Hg and < 25mmHg (08:00, 10:00, 16:00) at week 2, 6 and month 3 visits

CS304 28.08.2015 to 16.12.2016	52	Randomised controlled trial	Netarsudil 0.02% od Timolol maleate 0.5% bd	To evaluate the ocular hypotensive efficacy of Netarsudil 0.02% od compared to timolol maleate 0.5% bd over a 3 month period	Netarsudil 351/243 Timolol maleate 357/314	6 months	Netarsudil Male 39.3% Timolol Males 32.5% Median age 66 both groups	Raised intraocular pressure or open angle glaucoma Unmedicated IOP > 20mmHg & < 30 mmHg in 1 or both eyes on 2 occasions (08:00 hrs) 2-7 days apart. IOP > 17mmHg & < 30 mmHg at 10:00 and 16:00 hrs at the 2nd qualification visit	Mean IOP for subjects with baseline IOP < 25mmHg in the study eye at the following time points: 08:00, 10:00, and 16:00 at Week 2, 6 and Month 3 visits

2.5.1. Dose response study(ies)

The dose chosen for the pivotal study was Netarsudil 0.02% daily.

The applicant conducted three studies that could broadly be considered as dose finding studies. The first a 7-day phase IIa study (Study AR-13324-CS201) compared 3 dose strengths of netarsudil (0.04%, 0.02% and 0.01%) with placebo. A subsequent 28 day phase IIb non-inferiority study (Study AR-13324-CS202) compared Netarsudil 0.02%, and Netarsudil 0.01% with latanoprost 0.002%. Inclusion and exclusion criteria were broadly similar in the two phase II studies and encompassed higher baseline IOPs than subsequent trials.

A phase III non-inferiority study (Study AR-13324-CS302) compared Netarsudil 0.02% OD and netarsudil 0.02% BID with Timolol maleate ophthalmic solution 0.5% BID.

Study AR-13324-CS201 had a primary efficacy endpoint of mean IOP across subjects within treatment groups in Day at each post-treatment time point (08:00, 10:00, 12:00, and 16:00 hours). mean change from baseline at day 8 was greater for Netardusil 0.02% and 0.04% than Netardusil 0.01% at most time points and marginally greater for Netarsudil 0.02% compared to 0.04%. It can be concluded that the top of the dose response curve was reached with a dose of Netarsudil 0.02% OD.

Study AR-13324-CS202 compared Netarsudil 0.02%, and Netarsudil 0.01% with latanoprost 0.002% in a non-inferiority study. The primary endpoint was the mean diurnal IOP across subjects within treatment groups at Day 28 in the modified intent to treat population (all randomised subjects who received at least one dose of study medication and had all 3 baseline measurements along with at least one post-treatment time specific measurement).

Latanoprost showed greater efficacy in reducing mean diurnal IOP from baseline at D28 and reduction of mean IOP from baseline at D 28 at all-time points than either netarsudil dose strength. Of the two netarsudil products netarsudil 0.02% showed marginally greater reduction in mean diurnal IOP at D28 and marginally greater reduction in mean IOP at 2 of 3 time points on D28 compared to netarsudil 0.01%. Neither netarsudil product demonstrated non-inferiority to latanoprost.

Study AR-13324-CS302 had markedly different inclusion/exclusion criteria for baseline IOP compared to the two phase II studies. All participants were required to have a baseline IOP < 27mmHg compared to 36mmHg in the phase II studies. In this study BID and OD doses of netarsudil 0.02% were compared with Timolol 0.5%.

The primary efficacy endpoint was changed during the course of the study and the ultimate primary endpoint was mean IOP for patients with baseline IOP > 20mmHg (0:800 hrs) and < 25mmHg at (08:00, 10:00 and 16:00 hrs) in the study eye at the following timepoints: 08:00, 10:00 and 16:00 hours at Weeks 2 and 6, and Month 3 as opposed to a similar endpoint in those with a maximum baseline IOP of < 27 mmHg.

All treatment groups showed a reduction in IOP by D15 which was sustained to 3 months (Table 13). At most time points Netarsudil 0.02% bid showed greater efficacy numerically than Timolol in the per protocol population with IOP < 25mmHg. This was not the case for the QD dose. However, both doses were non-inferior to Timolol (Table 14). The upper 95% confidence limit for the differences in mean IOP between netarsudil QD and timolol was within 1.5mmHg at all time points and within 1.00mmHg at 6 of 9 time points. Discontinuation rates were considerably higher for Netarsudil 0.02% BD (39.8%), than Netarsudil 0.02% OD (18.3%) and Timolol (5.6%) at 3 months in the randomised population. This is the likely reason why the Netarsudil 0.02% was chosen for further evaluation even though there was an indication of greater efficacy with a BID dose.

2.5.2. Main study

AR-13324-CS304

A double-masked, randomized, multi-center, active-controlled, parallel group, 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. RhoKinase elevated Intraocular Pressure Treatment Trial (ROCKET 4)

Methods

Study Participants

This non-inferiority study was conducted in adults with a diagnosis of open angle glaucoma or ocular hypertension in both eyes (subjects could have had OAG in one eye and OHT in the other).

Subjects had to meet the following IOP thresholds for inclusion: Un-medicated (post-washout) IOP > 20mmHg and < 30mmHg in one or both eyes at 2 qualification visits at 08:00 hrs, 2-7 days apart and IOP>17mmHg and <30mmHg in one or both eyes at 10:00 and 16:00 hours on the second qualification visit. For inclusion the same eye must qualify at all qualification visits. Best corrected visual acuity in each eye had to be +1.0 logMAR or better by ETDRS chart or its equivalent in each eye.

There were a number of exclusion criteria including: previous glaucoma surgery; pseudoexfoliation or pigment dispersion component glaucoma; history of closed angle glaucoma; use of more than 2 ocular hypotensive agents within 30 days of screening; refractive surgery; ocular trauma within 6 months prior to screening; ocular surgery within 3 months prior to screening; mean central corneal thickness > 620µm in either eye at screening; any abnormality preventing reliable applanation tonometry; and known hypersensitivity to any of the components in the formulations to be used in the trial. There were also a number of appropriate systemic exclusions.

The study was conducted at 52 clinical sites in the US.

Treatments

The applicant has stated that the dose chosen for this study was based on the results of the dose finding study AR-13324-CS202 (note in that study the comparator was latanoprost rather than timolol).

The treatments administered in this study were Netarsudil 0.02% QD and the active comparator Timolol maleate ophthalmic solution 0.5% administered BID.

As the treatment was double masked subjects in the netarsudil group instilled one drop of netarsudil placebo in the morning (between 7:30 and 8:30am) and one drop of netarsudil in the evening (between 20:00 and 22:00 hours). Subjects assigned to the timolol arm instilled timolol maleate ophthalmic solution for morning and evening doses.

Netarsudil ophthalmic solution 0.02% used in this study is a sterile, isotonic, buffered aqueous solution containing netarsudil (0.02%), boric acid, mannitol, Water for Injection, and preserved with benzalkonium chloride (0.015%). The product formulation is adjusted to approximately pH 5. Lot Numbers 228501 and 242811 were used during the 6-month study.

Netarsudil placebo was an identical formulation, but lacking the active ingredient, netarsudil (Lot Number 230271).

Timolol maleate ophthalmic solution 0.5% was supplied as a commercially-available generic product, presented as a sterile, isotonic, buffered, aqueous solution. Each ml contains 5 mg of timolol (6.8 mg of timolol maleate). Inactive ingredients are monobasic and dibasic sodium phosphate, sodium hydroxide to adjust pH, and Water for Injection. Benzalkonium chloride 0.01% is included as a preservative. Timolol Lot Numbers 229526F, 233643F, 246026F and 261895F were used throughout the study.

Objectives

The overall objective was to evaluate the efficacy (primary endpoint at Month 3) and safety of netarsudil 0.02% dosed QD compared to timolol maleate ophthalmic solution dosed bid.

A 3-month interim analysis was conducted to evaluate the ocular hypotensive efficacy and safety of netarsudil 0.02% compared to timolol 0.5% over a 3 month period.

The primary null hypothesis for the study was as follows: The difference between study eyes treated with netarsudil 0.02% QD and study eyes treated with timolol 0.5% (netarsudil OD minus timolol BID) in subjects whose study eyes have maximum baseline IOP < 25 mmHg, in the mean IOP at the following time points: 08:00, 10:00, and 16:00 at the Week 2, Week 6, and Month 3 Visits, is > 1.5 mmHg for at least one time point over all visits or is > 1.0 mmHg for a majority of time points over all visits.

The study would be considered a success if the null hypothesis was rejected.

The applicant has not provided any justification for the non-inferiority margins used.

Outcomes/endpoints

The primary efficacy outcome was the mean IOP for subjects with baseline IOP < 25 mmHg in the study eye at the following time points: 08:00, 10:00, and 16:00 hours at the Week 2, Week 6, and Month 3 visits. An interim analysis of these efficacy endpoints was conducted when all subjects had completed 3 months of treatment or discontinued from the study.

Intraocular pressure was measured by qualified individuals using a calibrated Goldmann applanation tonometer. Local aneasthetic was applied to facilitate IOP measurements. Two consecutive IOP measurements of each eye were obtained. If the 2 measurements differed by more than 2 mmHg, a third measurement was taken. IOP was analysed as the mean of 2 measurements or as the median of 3 measurements. Each Goldmann tonometry value was read as an integer. When calculating the mean or

median, it was possible to have a fractional value; for purposes of qualification, the number was to be rounded up.

The unit of analysis for efficacy was the study eye. If the subject qualified in both eyes, the study eye was to be the eye with the higher IOP at 08:00 hours on Visit 3. If both eyes had the same IOP at 08:00 hours on Visit 3, the right eye was to be designated the study eye.The secondary endpoints were as follows:

Mean IOP at the following time points: 08:00, 10:00, and 16:00 hours at the Day 15 (Week 2), Day 43 (Week 6), and Day 90 (Month 3) Visits in subjects entering the trial with maximum baseline IOP < 26 mmHg and < 27 mmHg (08:00, 10:00, and 16:00 hours) in the study eye, and in all subjects regardless of study eye IOP.

Additionally, the following endpoints were summarized for both populations of subjects (i.e., including maximum baseline IOP < 25 mmHg and < 27 mmHg):

- Mean change from baseline IOP at each post-treatment time point
- Mean percent change from diurnally-adjusted baseline IOP at each time point
- Mean diurnal and change from baseline diurnal IOP at each post-treatment visit

Sample size

Assuming zero difference between netarsudil ophthalmic solution 0.02% QD and timolol maleate ophthalmic solution 0.5% BID, a 2-tailed alpha of 0.05 at each of 9 time points, a common SD of 2.75 mmHg, and a correlation between time points of 0.60 or less, 140 PP subjects per arm with baseline IOP < 25 mmHg were necessary to have 90% power to show clinical non-inferiority of netarsudil ophthalmic solution 0.02% QD to timolol maleate ophthalmic solution 0.5% BID in the mean IOP.

Clinical non-inferiority was concluded if the upper limit of the 95% CIs around the difference (netarsudil - timolol) was within 1.5 mmHg at all time points and was within 1.0 mmHg at a majority of the time points. Power increases as the correlation among time points increases. Assuming 80% of enrolled subjects completed through Month 3 (the primary efficacy time point) without a major protocol deviation, approximately 175 subjects per arm (350 subjects total) with maximum baseline IOP <25 mmHg were to be randomized. Additionally, assuming that approximately 50% of randomized subjects had baseline IOP <25 mmHg, an estimated 350 subjects were to be randomized per arm for a total of approximately 700 subjects randomized.

Randomisation and blinding (masking)

A randomization code for allocating the treatments was prepared by an independent biostatistician who was not involved in the day-to-day conduct of the study. Subjects were randomized in a 1:1 ratio to receive netarsudil 0.02% or timolol 0.5%, stratified by Investigative site and maximum baseline IOP < 25 mmHg and ≥ 25 mmHg.

The container-closure system used for netarsudil and placebo was chosen to be similar to the timolol commercial product presentation including the use of a yellow cap for netarsudil bottles to match the timolol cap colour. The labels from the commercial bottles of timolol were removed and the product bottles were labelled with investigational labels with the study salient information.

The product for each individual treatment assignment was packaged into identical subject kits and each subject kit contained 2 bottles selected from one of the following IPs:

- Netarsudil ophthalmic solution placebo (labeled “AM”) and netarsudil ophthalmic solution 0.02% (labeled “PM”)
- Timolol maleate ophthalmic solution 0.5% (labeled “AM”) and timolol maleate ophthalmic

solution 0.5% (labeled “PM”)

To assist the subject in selecting the correct bottle for AM and PM dosing, the bottle labels were colour-coded to suitably distinguish the bottles for AM and PM dosing and also included “AM” or “PM” in clearly legible font size.

Statistical methods

Analysis Populations

The primary subset of subjects to be analyzed was to include those subjects with maximum Day 1 IOP < 25 mmHg at all 3 time points. Secondary analysis will be completed on all subjects enrolled in the trial.

Randomized Population

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

Intent-to-Treat Population (ITT)

The ITT population was to include all randomized subjects who received at least one dose of study medication. This population was to be used to summarize a subset of efficacy variables and was to summarize subjects as randomized.

Per-protocol Population (PP)

The PP population is a subset of the ITT population, which was to include those subjects (and their visits) who do not have major protocol violations 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 was to be used to summarize all efficacy variables. If the PP and ITT populations were exactly the same, then additional efficacy analyses on the ITT population were not to be performed. The PP population was to summarize subjects as treated.

Safety Population

The safety population was to 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.

Separate analysis populations were to be defined for the 0-2 year old subjects and the 18 years and older subjects.

Assessment of Protocol Deviation

Protocol deviations were to be evaluated for all subjects in the safety population. Major protocol violations were to be judged by a masked evaluation and summarized in writing prior to the unmasking of the study treatment, for the purpose of selecting the PP population.

Handling of Dropouts or Missing Data

Any missing, unused, or spurious data were to be noted in the final statistical report. Randomization was to occur until approximately 350 total subjects with maximum baseline IOP < 25 mmHg have been randomized. Assuming that approximately 50% of randomized subjects will have baseline IOP < 25 mmHg, an estimated 350 subjects will be randomized per arm for a total of 700 subjects randomized.

Analyses were to be performed primarily on observed data only (without imputation) and secondarily using:

- last observation carried forward (LOCF) where LOCF will be performed using time-relevant measures (i.e. from the same time point of the most recent visit with a nonmissing value)
- baseline observation carried forward (BOCF) using time-relevant measures
- multiple imputation analyses under the missing at random (MAR) assumption.

Analysis Methods

All primary and secondary efficacy variables, along with the planned analysis methods for those variables, are given in the table below. These analyses were to be performed for the ITT and PP populations. The PP population was to be used for all efficacy subgroup analyses.

The primary analysis of the primary outcome was to be completed using a two-sample 95% t-distribution confidence interval for the comparison of AR-13324 QD to timolol at each time point (08:00, 10:00, and 16:00 hours at the Week 2, Week 6, and Month 3 Visits) using the per protocol population with maximum baseline IOP < 25 mmHg (08:00, 10:00, and 16:00 hours) in the study eye. The study was to be considered a success and clinical non-inferiority of AR-13324 QD concluded if the upper limit of the 95% CIs around the difference (AR-13324 QD – timolol) is below 1.5 mmHg at all time points through Month 3 and is below 1.0 mmHg at a majority of the time points (at least 5 of 9) through Month 3.

The secondary efficacy analyses were to include repeating the primary efficacy analysis on all subjects and additional analyses of the primary efficacy endpoint as well as other analyses of the secondary endpoints.

The primary efficacy analysis was to be repeated on the PP population using observed data for study eyes with maximum baseline IOP <25 mm Hg, < 22 mm Hg, < 24 mm Hg, <26 mm Hg, <27 mm Hg, and 28 mmHg.

Secondary analyses of the primary endpoint were to 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 per protocol population. Baseline IOP was defined as the last non-missing measure at the corresponding time point prior to treatment. The least squares mean differences between AR-13324 and timolol was to be presented as well as the 2-sided 95% confidence intervals and p-values.

Similar analyses were to be completed using the PP and ITT populations with observed data only on the secondary endpoints.

Additionally, for the individual IOP values at each time point and their changes from baseline values, mixed model repeated measures were to 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 was to be used to model the within subject, between visit and time point variances. This model was to be run including the Week 2, Week 6, and Month 3 visits on the PP and ITT populations with observed data only. Proc MIXED will be used in SAS and the outputs were to include the following: LS Mean (SE) for each treatment at each visit and time point, differences in LS Mean (SE) between the AR-13324 treatment group and the Timolol treatment group and 2-sided 95% confidence intervals and p-values for the differences.

Table 6 - Summary of efficacy variables and analysis methods

	Two Sample T-test[a]	One Sample T-test[b]	ANCOVA[c]	MMRM[d]
Primary Analysis				
Mean IOP at each time point at Week 2, Week 6, and Month 3	X		X	X
Secondary Analyses				
Mean change from diurnally adjusted baseline IOP at each post-treatment time point	X	X		
Mean diurnal IOP at Week 2, Week 6, and Month 3	X		X	
Mean change from baseline for mean diurnal IOP at Week 2, Week 6, and Month 3	X	X		
Mean percent change from diurnally adjusted baseline IOP at each post-treatment time point	X			

[a] Two Sample T-test comparing actual mean IOP value at each time point between Netarsudil and timolol.
[b] One Sample T-test comparing the mean change from baseline with the null hypothesized difference of zero within each treatment group.
[c] ANCOVA model including treatment as the main effect and baseline as the covariate.
[d] Mixed Model Repeated Measures analysis including treatment as the main effect, and baseline IOP, visit, time point, treatment*visit, treatment*time point, visit*time point, and treatment*visit*time point as model terms. Repeated measures will be used to account for the correlation among measures within a subject. The model will include all post-dose visits and time points.

Note: All analyses will be performed on both the ITT and PP populations.

Subgroup analyses

Sub-group analyses based upon pre-study characteristics such as unmedicated baseline IOP, iris colour, pre-study ocular hypotensive medications, age category (< 65 years versus ≥ 65 years), gender, and ethnicity category (caucasian versus all other) were to be completed for subjects with maximum baseline IOP <25 mmHg and for all subjects to further investigate the efficacy measures.

For all subgroups, except those defined by unmedicated baseline IOP, IOP was to be compared at each post-dose time point between treatment groups within subgroups using an ANCOVA model with treatment as the main effect, baseline IOP and subgroup as covariates, and the interaction of treatment and subgroup. T-tests from the model were to be performed to test for a difference in treatment group LS means between AR-13324 and timolol within each subgroup and post-dose time point.

Iris colour was to be analyzed categorically using the following grouping: Brown/Black, Hazel, Blue/Grey/Green, Other. Pre-study hypotensive medication categories included in the subgroup analysis were Combination Therapy, Prostaglandins (monotherapy), Other (monotherapy) (including: β-adrenoceptor antagonists, Adrenergic agonists, Muscarinic agonists or Carbonic anhydrase inhibitors), and No Prior Therapy. A separate subgroup analysis was to be completed on pre-study hypotensive medication categories: prior prostaglandin therapy and no prior prostaglandin therapy. Statistical inference was not made on any subgroups groups with fewer than six subjects.

Multicenter Studies

This study was anticipated to have approximately 40 different sites enrolling and treating subjects. The homogeneity of treatment effect across investigative sites was to be examined by a model containing the additional factors of investigative site and its interaction with treatment for the primary IOP efficacy endpoint. Sites with fewer than nine subjects were to be pooled together for the analysis.

Results

Study Participant flow is shown in Table 11 for all subjects and those with IOP < 25mmHg.

The applicant has not provided any information on the number of persons screened for the study. Completion rates were considerably higher in the Timolol arm (88% v 69.2%) all subjects and in the population with IOP < 25mmHg (90% v 74.8%)

Major protocol deviation rates were similar in both treatment arms in the overall population (13.1% and 12%) and those with IOP < 25mmHg (13.6% and 11%) for netarsudil and timolol respectively.

Table 7 - Subject disposition in All subjects and subjects with IOP < 25mmHg by treatment group

	Subject disposition by treatment group All (IOP < 30mmHg)		Subject disposition by treatment group IOP < 25mmHg	
	Netarsudil 0.02% QD	Timolol 0.5% BID	Netarsudil 0.02% QD	Timolol 0.5% BID
Number Randomised	351	357	214	209
Intent to treat (ITT)*	351	357	214	209
Per protocol	306 (87.2%)	316 (88.5%)	186 (86.9%)	186 (89%)
Completed	243 (69.2%)	314 (88%)	160 (74.8%)	188 (90%)
Major protocol deviation	46 (13.1%)	43 (12%)	29 (13.6%)	23 (11%)

*ITT all randomised patients who received at least 1 dose of study medication

Recruitment

The first subject was screened on 28 August 2015 and the last subject completed on 16 December 2016. The protocol was dated 15 July 2015.

Sixty-three clinical sites in the US had agreed to participate in the study of which 52 enrolled study participants.

Conduct of the study

The applicant has stated that there were no protocol amendments over the course of the study

Baseline data

Baseline data for the whole study population and those with IOP < 25mmHg are summarised in the Table 12.

Both treatment groups were broadly similar in the IOP < 25mmHg population. There was a slightly higher proportion of males in the netarsudil group compared to timolol and median time since diagnosis was also higher in the netarsudil group. A broadly similar picture was seen in the 'All' subjects population. The median age was similar across all treatment groups in both populations.

There were no differences by treatment group in either the 'All' or < 25mmHg populations in terms of prior ocular hypertension therapy. Roughly 37% had no prior treatment and approximately 47% had been treated with a prostaglandin monotherapy.

Overall approximately 75% of the Study population were White and about 22% Black or African American.

Completion rates were higher in those treated with Timolol in both the 'All' and IOP < 25mmHg groups.

Table 8 - Baseline data for the whole randomised population and IOP < 25mmHg

	All (IOP < 30mmHg)		IOP < 25mmHg	
	Netarsudil 0.02% QD N = 351	Timolol 0.5% BID N = 357	Netarsudil 0.02% QD N = 214	Timolol 0.5% BID N = 209
Study eye diagnosis				
Ocular hypertension	128 (36.5%)	113 (31.7%)	77 (36.1%)	71 (34%)
Open angle glaucoma	223 (63.5%)	244 (68.3%	137 (64%)	138 (66%)
Sex				
Male	143(40.7%)	120 (33.6)	84 (39.3%)	68 (32.5%)
Female	208 (59.3)	237 (66.4)	130 (60.7%)	141 (67.5%)
Age (years)				
Mean ± SD	64.1 ± 11.55	64.5 ± 10.97	63.8 ±12.74	64.1 ±11.02
Median (min, max)	65 (18, 89)	66 (29, 91)	66 (18, 89)	66 (29, 91)
Race				
White	259 (73.8%)	274 (76.8)	156 (72.9%)	161 (77%)
Black or African American	84 (23.9)	75 (21)	52 (24.3%)	42 (20.1%)
Other	8 (2.3%)	8 (2.3%)	6 (2.8%)	6 (2.9%)
Weeks since current diagnosis				
Mean ± SD	364.1±367.25	344.2± 341.06	360.6±370.4	330.5±339.71
Median (min, max)	265 (1, 2141)	231 (1, 1791)	262 (1, 2141)	233.5 (1, 1679)
Prior hypotensive therapy				
Combination therapy	24 (6.8%)	21 (5.9%)	12 (5.6%)	10 (4.8%)
Prostaglandin (monotherapy)	163 (46.4%)	167 (46.8)	101 (47.2%)	100 (47.8%)
Other (monotherapy)	334 (9.7%)	34 (9.5%)	18 (8.4%)	19 (9.1%)

No prior therapy	139 (37%)	135 (37.8%)	83 (38.8%)	80 (38.3%)

Numbers analysed

The primary analysis was conducted in the per protocol population with an IOP < 25mmHg (n = 186 in each treatment arm).

Analysis of the per protocol population for the primary efficacy endpoint in a non-inferiority study is acceptable.

Outcomes and estimation

Primary Efficacy Analysis (Month 3, PP Population with Maximum Baseline IOP < 25 mmHg).

Both treatment arms showed reduction in IOP at all-time points on day 15. These reductions were sustained to day 90 (See Table 13 and Figure 4). Differences from baseline ranged from 3.88 mmHg to 4.74 mmHg for Netarsudil and 3.77 to 5.17 mmHg for timolol.

Differences in actual reduction from baseline were somewhat greater for Timolol 0.5% bid at 5 time points, about the same for 2 time points and greater for Netarsudil 0.02% at 2 time points.

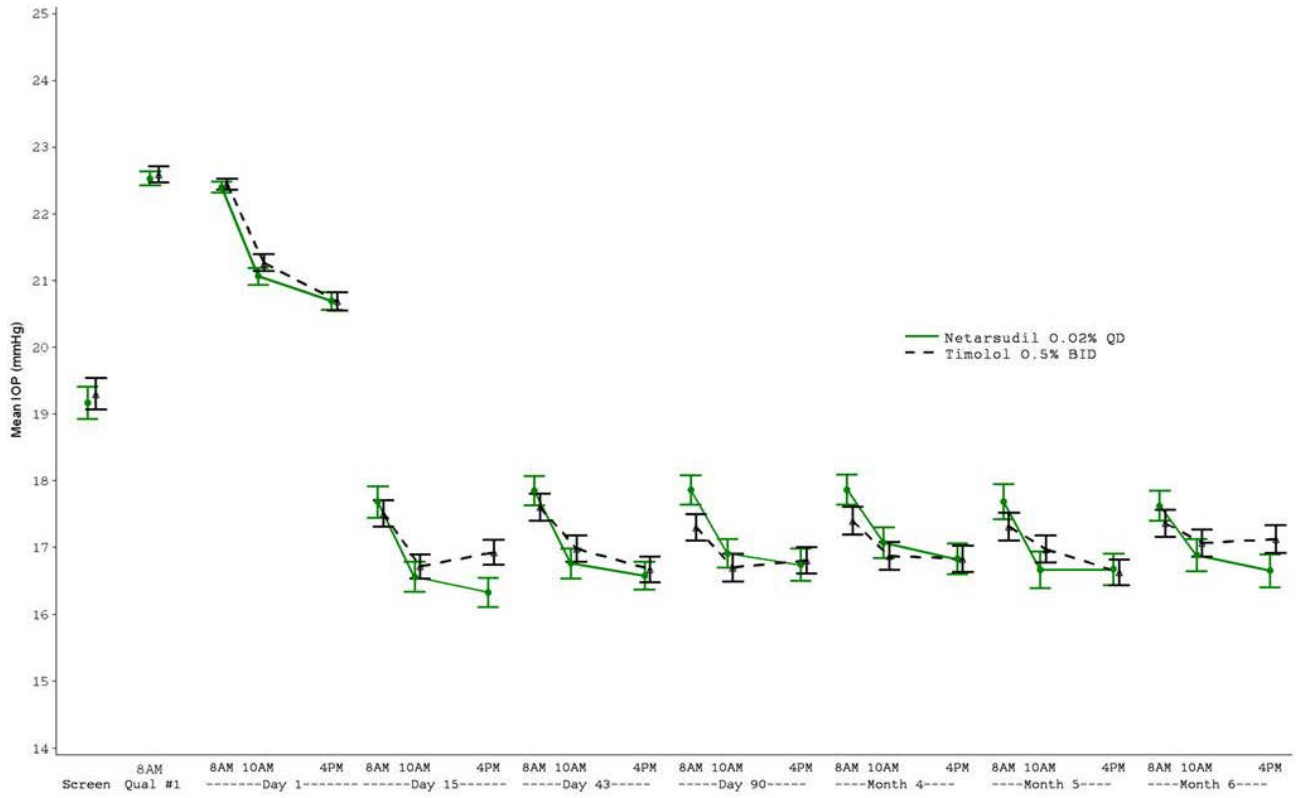
Table 9 - Mean IOP by visit and difference from baseline: PP Population with Baseline IOP <25mmHg

Study visit and time point		**Netarsudil 0.02% QD**			**Timolol 0.5% BID**		
		N	IOP	Actual difference from baseline	N	IOP	Actual difference from baseline
Baseline	08:00	186	22.4		186	22.44	
	10:00	186	21.06		186	21.27	
	16:00	186	20.69		186	20.69	
Day 15	08:00	184	17.68	-4.74	183	17.51	-4.94
	10:00	181	16.55	-4.51	183	16.71	-4.55
	16:00	181	16.32	-4.37	183	16.92	-3.77
Day 43	08:00	177	17.84	-4.55	183	17.6	-4.85
	10:00	177	16.75	-4.27	182	16.98	-4.29
	16:00	176	16.57	-4.09	182	16.67	-4.01
Day 90	08:00	167	17.86	-4.52	179	17.29	-5.17
	10:00	166	16.9	-4.1	179	16.69	-4.56
	16:00	165	16.73	-3.88	179	16.8	-4.54

Difference from baseline is Visit Value - Baseline Value and is tested against 0 within treatment with a 2-tailed 1-sample t-test.

Though no evaluation of efficacy beyond 3 months was undertaken, reduction is IOP were maintained up to 6 months in both treatment arms (Figure 4).

Figure 2 - Mean +/-1 SE Study Eye Intraocular Pressure (mmHg) by Day, Time point, and Treatment Group: Per-Protocol Population -- Subjects with Maximum Baseline IOP < 25 mmHg



Differences in reduction of IOP between treatment arms ranged from -0.6 mmHg to +0.56mmHg (See Table 14). The upper limit of the 95% confidence intervals for the difference in IOP reduction between Netarsudil 0.02% and Timolol 0.5% was < 1.5 mmHg at all time points and < 1 mmHg at 8 out of 9 timepoints thereby demonstrating non-inferiority of Netarsudil 0.02% QD to Timolol 0.5% BID.

Table 10 - Mean IOP difference of Netarsudil 0.02% from Timolol by visit: PP population baseline IOP < 25mmHg (95%CI)

Study visit and time point		Netarsudil 0.02% QD
Day 15	08:00	0.17 (-0.43, 0.77)
	10:00	-0.16 (-0.73, 0.41)
	16:00	-0.6 (-1.16, -0.04)
Day 43	08:00	0.25 (-0.34, 0.83)
	10:00	-0.22 (-0.82, 0.37)
	16:00	-0.1 (-0.66, 0.46)

Day 90	08:00	0.56 (-0.02, 1.15)
	10:00	0.21 (-0.37, 0.79)
	16:00	-0.07 (-0.68, 0.55)

Difference from Timolol 0.5% and two-sided CIs and p-values are based on 2-sample t-tests comparing Netarsudil 0.02% QD vs Timolol 0.5%.

A similar analysis was performed on the ITT population with a baseline IOP < 25mmHg where non-inferiority was also demonstrated when using observed data but not when using imputation methods (LOCF or MCMC).

Ancillary analyses

An analysis of the same endpoint as the primary endpoint in the PP population with baseline IOP <26mmgHg, with baseline IOP < 27mmHg, with baseline IOP < 28 mmHg and all subjects with baseline IOP < 30mmHg was conducted. The Mean IOP difference from Timolol is summarised in Table 15 for each of the different population groups. Results for 'All' subjects (maximum IOP < 30mHg will be presented in greater detail.

Table 11 - Mean IOP Difference from Timolol: PP Population with maximum Baseline IOP < 26 mmHg; < 27mmHg; and < 28 mmHg (95% CI)

Day	time	IOP < 26mmHg	IOP < 27mmHg	IOP < 28mm Hg
D 15	08:00	0.27 (-0.3, 0.84)	0.32 (-0.25, 0.89)	0.30 (-0.25, 0.86)
	10:00	-0.10 (-0.66, 0.45)	0 (-0.55, 0.56)	-0.11 (-0.64, 0.42)
	16:00	-0.45 (-0.99, 0.09)	-0.31 (-0.85, 0.23)	-0.41 (-0.93, 0.11)
D 43	08:00	0.3 (-0.24, 0.85)	0.4 (-0.14, 0.94)	0.37 (-0.16, 0.9)
	10:00	-0.19 (-0.76, 0.38)	-0.06 (-0.61, 0.49)	-0.16 (-0.69, 0.38)
	16:00	-0.03 (-0.57, 0.50)	-0.05 (-0.58, 0.49)	-0.31 (-0.85, 0.23)
D 90	08:00	0.67 (0.13, 1.22)	0.65 (0.11, 1.19)	0.57 (0.04, 1.10)
	10:00	0.37 (-0.18, 0.91)	0.55 (-0.01, 1.12)	0.46 (-0.1, 1.02)
	16:00	0.11 (-0.47, 0.68)	0.18 (-0.38, 0.75)	0 (-0.56, 0.55)

Difference from timolol 0.5% and two-sided CIs are based on 2 sample t-tests comparing netarsudil 0.02% vs timolol 0.5%.

All subjects (maximum IOP < 30mmHg)

As the applicant has sought a broad indication for raised intraocular pressure and open angle glaucoma without any limitation regarding maximum IOP the results in the whole per protocol population are presented here.

In the whole per protocol population (IOP < 30mmHg) as in the maximum IOP < 25mmHg population, mean IOP in both arms had decreased from baseline by D15 for all time points. This decrease was

maintained to D 90. Difference from baseline ranged from 3.95 to 4.74 for Netarsudil and 4.14 to 5.52 for Timolol 0.5%.

Table 12 - Mean IOP by visit and difference from baseline: PP Population all subjects maximum IOP < 30mmHg

Study visit and time point		Netarsudil 0.02% OD			Timolol 0.5% BID		
		N	IOP	Actual difference from baseline	N	IOP	Actual difference from baseline
Baseline	08:00	306	23.93		316	23.89	
	10:00	306	22.67		316	22.77	
	16:00	306	22.17		316	22.04	
Day 15	08:00	302	19.2	-4.74	312	18.6	-5.3
	10:00	297	17.93	-4.74	312	17.8	-4.97
	16:00	297	17.76	-4.39	312	17.85	-4.19
Day 43	08:00	289	19.45	-4.45	310	18.52	-5.37
	10:00	286	18.12	-4.47	309	17.89	-4.87
	16:00	285	17.89	-4.2	309	17.88	-4.14
Day 90	08:00	261	19.24	-4.52	300	18.35	-5.52
	10:00	259	18.3	-4.13	299	17.6	-5.11
	16:00	258	18.02	-3.95	299	17.66	-4.27

Difference from baseline is Visit Value - Baseline Value and is tested against 0 within treatment with a 2-tailed 1-sample t-test.

Decrease from baseline was numerically greater in the Timolol 0.5% arm at 7 out of 9 time points. At one time point the upper limit for the 95% confidence interval mean IOP difference between Netarsudil 0.02% and Timolol 0.5% at 1.52 (above 1.5), therefore non-inferiority to Timolol 0.5% cannot be concluded.

Table 13 - Mean IOP difference of Netarsudil 0.02% from Timolol by visit: PP population all subjects (95%CI)

Study visit and time point		Netarsudil 0.02% QD
Day 15	08:00	0.6 (0.02, 1.17)
	10:00	0.13 (-0.42, 0.691)
	16:00	-0.09 (-0.62, 0.44)
Day 43	08:00	0.93 (0.35, 1.52)
	10:00	0.23 (-0.31, 0.78)

	16:00	0.01 (-0.54, 0.56)
Day 90	08:00 10:00 16:00	0.89 (0.3, 1.49) 0.7 (0.13, 1.27) 0.36 (-0.2, 0.93)

Difference from Timolol 0.5% and two-sided CIs and p-values are based on 2-sample t-tests comparing Netarsudil 0.02% QD vs Timolol 0.5%.

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment.

Table 14 - Summary of efficacy for trial Study AR-13324-CS-304

Title: *A double-masked, randomized,multi-center, active-controlled, parallel group, 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. RhoKinase elevated Intraocular Pressure Treatment Trial (ROCKET 4)*			
Study identifier	**Study AR-13324-CS304 (phase 3)**		
Design	Randomized,multi-center, active-controlled, parallel group, 6-month study, with an efficacy analysis at 3 months.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		6 months not applicablenot applicable
Hypothesis	Non-inferiority		
Treatments groups	Netarsudil 0.02%		Netarsudil 0.02% OD Duration 6 months number randomized 351
	Timolol 0.5%		Timolol 0.5% BID. Duration 6 mpnths, number randomized 357
Endpoints and definitions	Primary endpoint	PE	The primary efficacy outcome was the mean IOP for subjects with baseline IOP < 25 mmHg in the study eye at the following time points: 08:00, 10:00, and 16:00 hours at the Week 2, Week 6, and Month 3 visits. An interim analysis of these efficacy endpoints was conducted when all subjects had completed 3 months of treatment or discontinued from the study.

	Secondary endpoint	SE1	Mean IOP at the following time points: 08:00, 10:00, and 16:00 hours at the Day 15 (Week 2), Day 43 (Week 6), and Day 90 (Month 3) Visits in subjects entering the trial with maximum baseline IOP < 30 mmHg
Database lock	Not provided		
Results and Analysis			

Table 15 - Primary Endpoint - Mean IOP by visit and difference from baseline: PP Population with Baseline IOP <25mmHg

Study visit and time point		Netarsudil 0.02% QD			Timolol 0.5% BID		
		N	IOP	Actual difference from baseline	N	IOP	Actual difference from baseline
Baseline	08:00	186	22.4		186	22.44	
	10:00	186	21.06		186	21.27	
	16:00	186	20.69		186	20.69	
Day 15	08:00	184	17.68	-4.74	183	17.51	-4.94
	10:00	181	16.55	-4.51	183	16.71	-4.55
	16:00	181	16.32	-4.37	183	16.92	-3.77
Day 43	08:00	177	17.84	-4.55	183	17.6	-4.85
	10:00	177	16.75	-4.27	182	16.98	-4.29
	16:00	176	16.57	-4.09	182	16.67	-4.01
Day 90	08:00	167	17.86	-4.52	179	17.29	-5.17
	10:00	166	16.9	-4.1	179	16.69	-4.56
	16:00	165	16.73	-3.88	179	16.8	-4.54

Difference from baseline is Visit Value - Baseline Value and is tested against 0 within treatment with a 2-tailed 1-sample t-test.

Table 16 - Mean IOP difference of Netarsudil 0.02% from Timolol by visit: PP population baseline IOP < 25mmHg (95%CI)

Study visit and time point		Netarsudil 0.02% QD
Day 15	08:00	0.17 (-0.43, 0.77)
	10:00	-0.16 (-0.73, 0.41)
	16:00	-0.6 (-1.16, -0.04)
Day 43	08:00	0.25 (-0.34, 0.83)
	10:00	-0.22 (-0.82, 0.37)
	16:00	-0.1 (-0.66, 0.46)
Day 90	08:00	0.56 (-0.02, 1.15)
	10:00	0.21 (-0.37, 0.79)
	16:00	-0.07 (-0.68, 0.55)

Table 17 - Mean IOP by visit and difference from baseline: PP Population all subjects maximum IOP < 30mmHg

Study visit and time point		Netarsudil 0.02% OD			Timolol 0.5% BID		
		N	IOP	Actual difference from baseline	N	IOP	Actual difference from baseline
Baseline	08:00	306	23.93		316	23.89	
	10:00	306	22.67		316	22.77	
	16:00	306	22.17		316	22.04	
Day 15	08:00	302	19.2	-4.74	312	18.6	-5.3
	10:00	297	17.93	-4.74	312	17.8	-4.97
	16:00	297	17.76	-4.39	312	17.85	-4.19
Day 43	08:00	289	19.45	-4.45	310	18.52	-5.37
	10:00	286	18.12	-4.47	309	17.89	-4.87
	16:00	285	17.89	-4.2	309	17.88	-4.14
Day 90	08:00	261	19.24	-4.52	300	18.35	-5.52
	10:00	259	18.3	-4.13	299	17.6	-5.11
	16:00	258	18.02	-3.95	299	17.66	-4.27

Difference from baseline is Visit Value - Baseline Value and is tested against 0 within treatment with a 2-tailed 1-sample t-test.

Decrease from baseline was numerically greater in the Timolol 0.5% arm at 7 out of 9 time points. At one time point the upper limit for the 95% confidence interval mean IOP difference between Netarsudil 0.02% and Timolol 0.5% at 1.52 (above 1.5), therefore non-inferiority to Timolol 0.5% cannot be concluded (see following Table).

Table 18 - Mean IOP difference of Netarsudil 0.02% from Timolol by visit: PP population all subjects (95%CI)

Day 15	08:00	0.6 (0.02, 1.17)
	10:00	0.13 (-0.42, 0.691)
	16:00	-0.09 (-0.62, 0.44)
Day 43	08:00	0.93 (0.35, 1.52)
	10:00	0.23 (-0.31, 0.78)
	16:00	0.01 (-0.54, 0.56)
Day 90	08:00	0.89 (0.3, 1.49)
	10:00	0.7 (0.13, 1.27)
	16:00	0.36 (-0.2, 0.93)

Difference from Timolol 0.5% and two-sided CIs and p-values are based on 2-sample t-tests comparing Netarsudil 0.02% QD vs Timolol 0.5%.

Analysis performed across trials (pooled analyses and meta-analysis)

Pooled data showing mean diurnal IOP reduction from baseline are presented for the netarsudil QD arm from Phase 3 efficacy studies conducted as part of the Rhokiinsa development program versus the active comparator timolol. Supportive pooled data are also presented for the netarsudil QD arm from the Phase 3 studies conducted as part of the fixed dose combination (PG324) development program versus the active comparator latanoprost (Table 7).

The pooled data from the AR-13324 studies show that the IOP-lowering effect of netarsudil ranged from -4.05 to -4.57 mmHg (per protocol group) in subjects with baseline pressures <25 mmHg and from -3.71 to -4.71 mmHg in subjects with baseline pressures ≥25 and <30 mmHg. Therefore, netarsudil was similarly effective at lowering IOP in subjects with higher baseline pressures compared to those with lower baseline pressures. In contrast, the IOP-lowering efficacy of timolol was more dependent upon baseline IOP, ranging from -4.31 to -4.36 mmHg (per protocol group) in subjects with baseline pressures <25 mmHg and from -5.24 to -5.36 mmHg in subjects with baseline pressures ≥25 and <30 mmHg.

Similar results were obtained in the supportive PG324 studies regarding the ability of netarsudil to produce similar IOP-lowering efficacy in subjects with higher baseline pressures as in subjects with lower baseline pressures. In the PG324 studies, the IOP-lowering effect of netarsudil ranged from -4.97 to -5.32 mmHg (PP group) in subjects with baseline pressures <25 mmHg and from -4.87 to -5.50 mmHg in subjects with baseline pressures ≥25 and <30 mmHg. In subjects with baseline pressures ≥30 to <36 mmHg, netarsudil produced somewhat larger IOP reductions, ranging from -5.74 to -6.35 mmHg. IOP reduction for latanoprost, like timolol, was more dependent upon baseline IOP, ranging from -5.24 to

-5.51 mmHg (PP group) in subjects with baseline pressures <25 mmHg, from -6.49 to -6.69 mmHg in subjects with baseline pressures ≥25 and <30 mmHg, and from -8.48 to -9.20 mmHg in subjects with baseline pressures ≥30 to <36 mmHg. Therefore, netarsudil's IOP-lowering effect was similar to that of latanoprost in subjects with baseline pressures < 25mm Hg but not those with higher pressures.

The relationship between baseline IOP and the IOP-lowering effect of timolol and latanoprost observed in the AR-13324 and PG324 studies, respectively, has been previously reported (e.g. Hedman 2000).

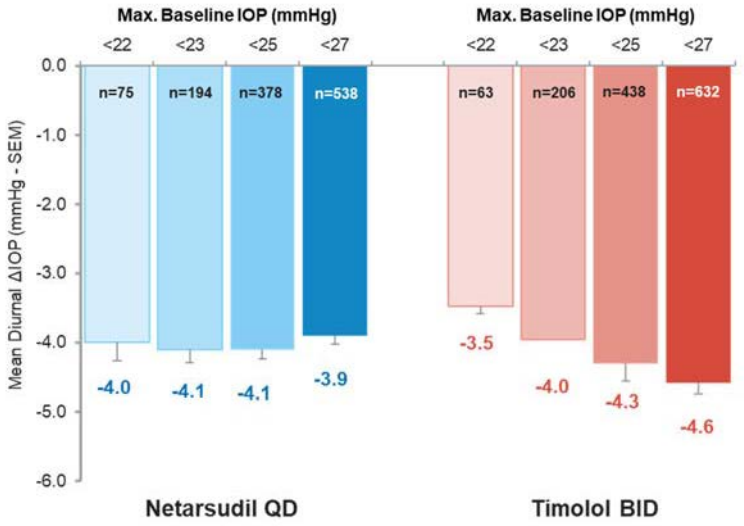
Table 19 - Mean Diurnal IOP of Netarsudil QD Relative to the Active Comparators, Timolol BID, and Latanoprost QD from Phase 3 Studies – Per Protocol and Intent-to-Treat Populations

Population	AR-13324 Phase 3 Studies		PG324 Phase 3 Studies	
Treatment Group	Netarsudil QD (N) Actual IOP / CFB	Timolol BID (N) Actual IOP / CFB	Netarsudil QD (N) Actual IOP / CFB	Latanoprost QD (N) Actual IOP / CFB
PP <25 mmHg at Baseline Day 15 4 3 9 0	(428) 16.86 / -4.57 17.13 / -4.28 17.33 / -4.05	453) 17.14 / -4.32 17.09 / -4.36 17.15 / -4.31	(231) 16.09 / -5.32 16.32 / -5.10 16.46 / -4.97	(225) 16.13 / -5.24 15.92 / -5.47 15.87 / -5.51
PP ≥25 mmHg & <30 mmHg at BL Day 15 4 3 9 0	(266) 19.99 / -4.71 20.59 / -4.11 20.92 / -3.71	(269) 19.24 / -5.24 19.13 / -5.36 19.15 / -5.30	(152) 19.41 / -5.50 19.99 / -4.91 20.05 / -4.87	(141) 18.39 / -6.49 18.37 / -6.51 18.19 / -6.69
PP ≥30 mmHg and <36 mmHg at BL Day 15 4 3 9 0	NA	NA	(49) 23.82 / -6.23 23.72 / -6.35 24.31 / -5.74	(55) 20.62 / -8.48 19.89 / -9.20 20.27 / -8.81
ITT <25 mmHg at Baseline Day 15 4 3 9 0	(494) 16.83 / -4.57 17.11 / -4.28 17.37 / -4.00	(510) 17.08 / -4.32 17.00 / -4.42 17.10 / -4.34	(269) 16.19 / -5.23 16.43 / -4.99 16.54 / -4.91	(262) 16.19 / -5.20 16.02 / -5.40 15.93 / -5.48

ITT ≥25 mmHg and <30 mmHg at BL Day 15 4 3 9 0	(310) 19.90 / -4.76 20.51 / -4.13 20.98 / -3.60	(307) 19.22 / -5.29 19.12 / -5.37 19.18 / -5.29	(176) 19.24 / -5.68 19.79 / -5.12 19.81 / -5.13	(165) 18.50 / -6.42 18.48 / -6.45 18.36 / -6.59
ITT ≥30 mmHg and <36 mmHg at BL Day 15 4 3 9 0	NA	NA	(56) 23.83 / -6.30 23.88 / -6.28 24.60 / -5.55	(59) 20.63 / -8.45 20.00 / -9.09 20.10 / -8.97

Another analysis from the AR-13324 Phase 3 efficacy studies of the IOP-lowering effect of netarsudil compared to timolol and its relationship to baseline IOP is presented in figure 5. The sub-populations presented differ by the upper limit of baseline IOP allowed in each population, ranging from <27 mmHg (the upper limit in the AR-13324-CS301 and -CS302 studies) to <22 mmHg. While the IOP-lowering effect of netarsudil was stable (approximately 4 mmHg) across the full range of baseline pressures, the efficacy observed with timolol was highest in the sub-population with the highest baseline pressures and it became progressively diminished at lower baseline pressures. As a result, netarsudil was slightly more effective than timolol in the lowest baseline group and slightly less effective than timolol in the highest baseline group.

Figure 3 - Intraocular Pressure-Lowering Efficacy Across a Range of Baseline Pressures - Pooled AR-13324 Data; Change from Baseline at Day 90 in Mean Diurnal IOP



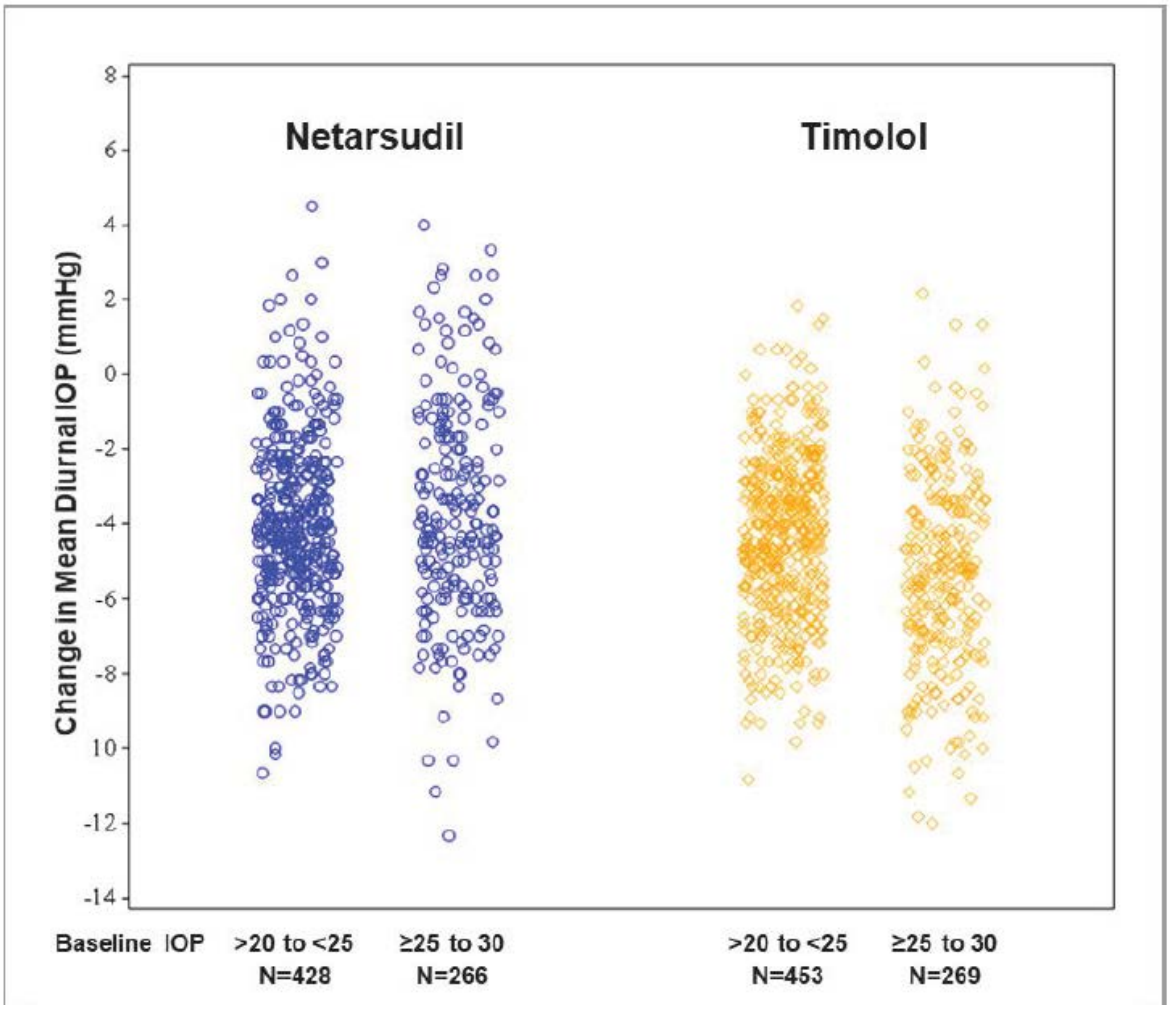
The data from the AR-13324 Phase 3 studies and the supporting PG324 studies demonstrate that netarsudil effectively lowers mean diurnal IOP by approximately 4 to 6 mmHg in subjects with baseline pressures ≥25 to <36 mmHg. While the magnitude of the IOP-lowering effect of netarsudil was not as great as that observed with timolol or latanoprost treatment in subjects with baseline IOPs ≥25 mmHg, it

was nevertheless still effective at reducing elevated IOP by a clinically-significant amount.

Even though the mean reduction in IOP between the netarsudil and timolol groups favours timolol at baseline pressures >25 mmHg, the distribution of IOP reductions achieved by individual subjects is highly overlapping for the two treatments. Figure 5 presents a Scatter Plot of individual subject data across the pooled Phase 3 studies grouped by baseline IOP. It shows that a similar range of reductions in mean diurnal IOP for netarsudil and timolol for subjects with baseline pressures between 25 and 30 mmHg were observed. However, there are proportionally more non-responder subjects (defined as mean diurnal IOP reduction < 2 mmHg) in the netarsudil group relative to the timolol group in this higher-baseline population, which at the population level produces a smaller mean IOP reduction for netarsudil compared to timolol. This does not negate the fact a large proportion of subjects achieved clinically-significant reductions in IOP with netarsudil as well as with timolol.

The scatter plot of individual responses in subjects with baseline pressures between 25 and 30 mmHg is relevant to the practice of medicine. At these high baseline IOPs, subjects are likely to require IOP reductions of 7 to 10 mmHg to reach target pressure based upon recommendations in the European Glaucoma Society Guidelines 4th Edition (EGS 2014). The scatter plot suggests that both netarsudil and timolol have the potential to achieve this level of IOP reduction as monotherapy, but only for a minority of subjects. In practice, these high baseline patients are most likely to start on a prostaglandin medication as first line therapy, and timolol or netarsudil would be added as an adjunctive medication if monotherapy proved insufficient to reach the patient's target pressure (as expected for at least half of these high-baseline subjects, Schmier 2014). In other words, netarsudil is most likely to be used as an adjunctive medication in patients with high baseline IOPs.

Figure 4 - Individual IOP Reductions Achieved by Subjects with Baseline IOPs <25 mmHg and >/=25 mmHg - Pooled Data from Phase 3 Netarsudil (AR-13324) studies; Change from Baseline on Day 90.



Clinical studies in special populations

No studies were conducted in special populations. This is acceptable.

	Age 65-74 (Older subjects number /total number)	Age 75-84 (Older subjects number /total number)	Age 85+ (Older subjects number /total number)
Controlled Trials	355 /971	171 /971	17 /971
Non Controlled[1] trials	4 /18	NA	NA

Source: AR-13324 Table 14.3.3.3.3.6.99
* Data from Studies
AR-13324-CS101, -CS102, -CS201, -CS202, -CS204, -CS206, -CS301, -CS302, -CS303 and -CS304
1. Only Study AR-13324-CS101 was not controlled
The Applicant notes that in response to Day 120 LoQ Q109, no data from uncontrolled studies was included in Table 11. This was an error (with all subjects counted as part of the controlled trials group). In fact Study AR-13324-CS101 was an uncontrolled study in healthy volunteers who received netarsudil in both eyes for 1 week. The error is corrected in this Table.

Supportive study

AR-13324-CS301. 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.

The study was conducted at 35 sites in the US and was run in parallel with AR-13324-CS302. The study was initiated on 11 June 2014 and completed on 4 March 2015.

The inclusion criteria were the same as those for Study CS-302. Adults aged 18 or over and children age 0 to 2 years were eligible for recruitment. To be eligible subjects had to have a diagnosis of open angle glaucoma or ocular hypertension in both eyes. It was acceptable to have OHT in one eye and OAG in the other. For adults the un-medicated IOP should be > 20mmHg and < 27mmHg in the study eye at 2 qualification visits (08:00hrs), 2-7 days apart and > 17mmHg and < 27mmHg at the second qualification visit at 10:00 and 16:00 hrs (in the same eye).

The efficacy objective of the study was to evaluate the ocular hypotensive efficacy of Netarsudil 0.02% ophthalmic solution QD, in both eyes, compared to timolol maleate 0.5% ophthalmic solution BID.

The primary efficacy outcome was to be the mean IOP at 08:00, 10:00, and 16:00 hours at Days 15, 43 and 90.

Clinical non-inferiority was to be concluded if the upper limit of the 95% confidence intervals around the difference (Netarsudil 0.02% - timolol) was within 1.5mmHg at all time points and was within 1.0 mmHg at, at least 5 of 9 time points.

The unit of analysis for efficacy was the study eye. If a subject qualified in both eyes the study eye was the eye with the higher IOP at 08:00 hours at Visit 3. If both eyes had the same IOP on that date the right eye was designated the study eye.

Intraocular pressure was to be measured by qualified personnel using a calibrated Golmann applanation tonometer after application of local anaesthetic. Two consecutive measures were to be taken. If they differed by more than 2 mmHg, a third measurement was to be obtained. IOP was to be analysed as the mean of 2 measurements or the median of 3.

The per protocol population was the primary population for efficacy analysis.

550 subjects were screened and 411 were randomized and treated

Table 20 - Summary of subject disposition (randomized population)

	Netarsudil	Timolol
No. randomised	202	209
Completed	171 (84.7%)	196 (93.8%)
Intent to treat	202	209
Per Protocol	182	188

No paediatric patients were enrolled.

Like the other netarsudil studies where timolol was the active comparator discontinuation rates were higher in the netarsudil arm.

Demographic and other baseline characteristics were similar across the groups.

Efficacy results

At D15 at all time points both treatment groups showed reductions from baseline in mean IOP which were maintained to D90. These reductions were all statistically significant (See Table 25).

The upper 95% confidence limit for the difference in mean IOP in the per protocol study population (maximum baseline IOP < 27mmHg) was greater than 1.5mmHg for 3 of time points and greater than 1mmHg for 5 of 9 time points, therefore Netarsudil 0.02% did not meet the criteria for non-inferiority to Timolol 0.5%.

The applicant conducted a pre-specified analysis in the PP population with IOP < 23mHg which did demonstrate non-inferiority to timolol. A further post hoc analysis in in the PP population with baseline IOP < 25mmHg did demonstrate non-inferiority to timolol.

Table 21 - Study eye Intraocular Pressure (mmHg) by visit per protocol population

Day and Time	Mean IOP		AR-13324 – Timolol (95% CI)	
	AR-13324 (N = 182)	Timolol (N = 188)	Mean Difference[1]	95% CI
Baseline (Visit 3)				
08:00 hours	23.42 (N = 182)	23.37 (N = 188)	0.06	(-0.29, 0.41)
10:00 hours	22.28 (N = 182)	21.92 (N = 188)	0.36	(-0.07, 0.79)
16:00 hours	21.78 (N = 182)	21.45 (N = 188)	0.33	(-0.15, 0.82)
Day 15				
08:00 hours	18.68 (N = 177)	18.33 (N = 187)	0.35	(-0.27, 0.96)
10:00 hours	17.29 (N = 176)	17.55 (N = 186)	-0.26	(-0.87, 0.36)
16:00 hours	17.24 (N = 176)	17.70 (N = 186)	-0.45	(-1.08, 0.17)
Day 43				
08:00 hours	19.35 (N = 170)	18.24 (N = 184)	1.11	(0.42, 1.80)
10:00 hours	18.14 (N = 170)	17.44 (N = 184)	0.70	(0.04, 1.36)
16:00 hours	17.86 (N = 170)	17.71 (N = 183)	0.15	(-0.52, 0.83)
Day 90				
08:00 hours	19.81 (N = 157)	18.47 (N = 181)	1.33	(0.64, 2.03)
10:00 hours	18.92 (N = 158)	17.96 (N = 181)	0.96	(0.26, 1.66)
16:00 hours	18.48 (N = 158)	17.74 (N = 181)	0.74	(0.07, 1.42)

Source: Table 14.2.1.1

CI = confidence interval

Note: All subjects had baseline IOP ≤ 27 mmHg.

[1] Difference from timolol 0.5% and two-sided CIs and p-values are based on 2-sample t-tests comparing AR-13324 0.02% vs timolol 0.5%.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The applicant has sought a broad indication for Rhokiinsa (netarsudil 0.02%) in the treatment of ocular hypertension and open angle glaucoma. In support of the indication the applicant submitted five studies. All studies were randomised and, apart from one phase II study, had an active control arm. All of the active controlled studies were non-inferiority studies.

To participate in the studies all subjects had to have a diagnosis of ocular hypertension or open angle glaucoma.

Of the five studies three were open to adults only. CS301 and CS302 were open to children under two years of age as well as adults. No children were recruited to CS301 and two children to CS302.

All studies excluded patients with glaucoma with pseudo-exfoliation or pigment dispersion component, and a history of acute angle closure or narrow angle.

Inclusion criteria with regard to IOP were different across studies, with the most marked difference between the two earliest studies (CS201 and CS202) and the later three studies. The first two studies had an upper limit for post-washout IOP of < 36mmHg, whereas later studies had an upper limit of < 27mmHg (CS 301, CS302) and 30mmHg (CS304). In addition, the lower limit of IOP was lower in the CS 301, 302 and 304 compared to CS201 and 202. In other words, the later studies recruited a population with less severe ocular hypertension. This change would appear to have been driven by the results of earlier studies. It must be noted that the population included in the three later studies does not reflect the total population for which the indication is sought.

The active comparator was latanoprost in the earliest comparator study (CS202). This was appropriate given that prostaglandins are the most widely used therapy for open angle glaucoma and raised intraocular pressure and in the pivotal study approximately 47% of participants had received prior monotherapy with prosataglandins. It should be noted that neither Netarsudil 0.01% nor Netarsudil 0.02% demonstrated non-inferiority to Latanoprost.

The use of timolol as comparator in the phase III non-inferiority studies and in particular the pivotal study (CS304) is questioned given that prostaglandins are the first line topical IOP lowering therapy and there is some evidence that timolol may have less efficacy than latanoprost (Li T et al. Ophthalmology 2016; British Journal of Ophthalmology 2017[)].

The primary endpoint in the pivotal study (CS304) was non-inferiority of netarsudil 0.02% QD to timolol 0.5% BID for subjects entering the study with maximum baseline IOP <25 mmHg (08:00, 10:00, and 16:00 hrs) in the study eye, with a non-inferiority limit of 1.5 mmHg at all-time points from Day 15 to Day 90 at the following time points: 08:00, 10:00, and 16:00 hrs at the Week 2, Week 6, and Month 3 visits. Non-inferiority of netarsudil to timolol was to be demonstrated if the upper 95% confidence limit for the differences in mean IOP (*reduction from baseline*) between netarsudil and timolol was within 1.5mmHg at all 9 time points and within 1.0 mmHg at the majority of time points (5/9).

The same endpoint in the total per protocol population (maximum baseline IOP < 30 mmHg) was a secondary endpoint.

The primary endpoint was evaluated in the per protocol population with a maximum baseline IOP of < 25 mmHg. The end point of reduction in IOP is acceptable given that the aim of treatment with anti-glaucoma medication is reduction in IOP and there is evidence that reduction of IOP delays progression of glaucoma. [4]

The non-inferiority design of the comparative studies was appropriate. In all of the studies the non-inferiority margin was 1.5mmHg. The applicant's clinical justification of the non-inferiority margin is based on an appeal to published literature and CHMP Scientific Advice and can be accepted.

Efficacy data and additional analyses

Three studies were performed that could be considered to be dose finding studies. A comparison of three dose strength (0.01%, 0.02% and 0.04% QD) with study duration of eight days showed that netarsudil 0.02% and 0.04% showed similar reductions in IOP three time points on D8 with the data suggesting that the top of the dose response curve was reached at 0.02% dosed once a day. A further study comparing

a QD and BID dose of netarsudil 0.02% demonstrated greater efficacy for the BID dose but at the expense of a higher rate of adverse events and lower completion rates. Thus the choice of dose for the pivotal study has been informed by a trade-off between efficacy and adverse events that could interfere with patient's concordance with therapy.

In the pivotal study both timolol and netarsudil reduced baseline IOP at all time points in both PP and ITT populations with maximum IOP < 25mmHg and the total PP and ITT populations with IOP < 30mmHg. In the ITT population with maximum IOP < 25mmHg reductions in baseline IOP at across the 9 time points for netarsudil ranged from -3.71 to -4.87mmHg and from -3.81 to -5.18 mmHg for timolol. In the all subjects (maximum IOP < 30mmHg) ITT population reductions in IOP from baseline at the 9 time points ranged from -3.78 to – 4.83 mmHg for netarsudil and from -4.25 to -5.57mmH for timolol.

A beneficial effect was demonstrated only in a limited, milder population in the pivotal study (CS304), i.e. the primary open angle glaucoma and ocular hypertension population with a baseline IOP > 17mmHg and < 25mmHg. Non-inferiority compared to timolol was not demonstrated in the overall study population (baseline IOP < 30mmHg). This reflects the findings of earlier studies where the efficacy of netarsudil appeared to be poorer in those with higher IOP compared to timolol. Those with an IOP ≥ 30mmHg were not reflected in any of the Phase 3 studies submitted to support the application. Therefore, the study population was not considered to be reflective of the overall population for which the claimed indication was sought. In addition, almost 40% of participants in both the < 25 mmHg and < 30mmHg populations had not been on any prior glaucoma therapy A potential extrapolation outside the study population was requested as well as well as summarised data comparing IOP reduction by netarsudil and comparators (ie. timolol and latanoprost) in those patients with a baseline IOP < 25mmHg, those with an IOP ≥25mmHg and < 30mmHg and those with an IOP ≥30mmHg and < 36mmHg were also requested.

To answer these concerns, the applicant stated that the range of baseline IOPs treated in CS-304 reflects the real world population of POAG and has supported this with data from the Baltimore Eye Survey (1991) which demonstrated that approximately 78% of those diagnosed in the study with POAG had a baseline IOP < 25mmHg (Sommer A et al 1991). This study was conducted in the US and the underlying demography of the study population was dissimilar to an average European population. Further data was provided from the Early Manifest Glaucoma Trial (conducted in Sweden), however the data provided by the applicant refers to the distribution of IOPs at screening only in those randomised to the subsequent trial rather than the range and distribution of IOPs in the complete screening population (Leske 1999). The fact that for other anti-glaucoma medication approved in the EU the study populations for registration studies reflected patients with higher baseline IOPs therefore necessitating an extrapolation of benefit to the patient group with lower IOPs who were not included in the studies is acknowledged.

With regard to the population with an IOP > 30mmHg which were not included in any of the phase 3 trials the applicant claims that data from the Phase 2 studies and phase 3 studies with a fixed combination of netarsudil and latanoprost which compared the FDC to the individual components showed that netarsudil produced a clinically-meaningful and statistically significant reduction in mean IOP from baseline in the full OAG/OHT study population in the phase 2 studies, with similar results seen in the phase 3 FDC studies.

The pooled data from the AR-13324 studies show that netarsudil was similarly effective at lowering IOP in subjects with higher baseline pressures compared to those with lower baseline pressures. In contrast, the IOP-lowering efficacy of timolol was more dependent upon baseline IOP. Similar results were obtained in the supportive PG324 studies.

The applicant has presented a scatter plot with pooled data from phase 3 netarsudil studies versus timolol showing change in IOP from baseline to D90 in the population with baseline IOP < 25mmHg and the

population with IOP ≥25 mmHg and < 30 mmHg. There were higher non response rates (< 2mmHg reduction in IOP from baseline) in those treated with netarsudil in the higher baseline IOP group than in those treated with timolol. This would also appear to be the case for the < 25mmHg netarsudil population. The applicant asserts that this may be the reason why non-inferiority was not shown versus timolol in the ≥25 mmHg and < 30 mmHg population. From the scatter plot it can be seen that some patients in the netarsudil group achieved quite large reductions in baseline IOP (-7 mm Hg or more) though not as many as those treated with timolol. Nevertheless, there is evidence of large reductions in baseline IOP in some patients treated with netarsudil with higher baseline IOPs.

The applicant states that patients with baseline IOP ⩾25mmHg are more likely to require more than 1 therapy to achieve target reductions in IOP and that given the evidence from the fixed dose combination studies of netarsudil with latanoprost, netarsudil has demonstrated its efficacy in the adjunctive setting.

In order to demonstrate non-inferiority, the upper bound of the 95% CI for the primary analysis using the two-sample t-test needed to be within 1.5mmHg at all 9 time points and within 1mmHg for 5 out of 9 time points. For one of the nine time points the upper 95% CI was 1.52 which is just outside the NI margin of 1.5. Whilst this from a strictly statistical point of view makes netarsudil not non-inferior to timolol in the per-protocol population with an IOP < 30mmHg, it is of lesser importance from a clinical point of view. It is also acknowledged that non-inferiority was demonstrated in the Per-Protocol population when using an ANCOVA model using treatment as a factor and baseline as a covariate.

Overall it is acknowledged that netarsudil has demonstrated a similar degree of absolute IOP lowering in the population with IOP < 25mmHg, those with an IOP ≥25 and < 30 mmHg and those with an IOP ≥ 30 and < 36 mmHg. However, comparators such as timolol and latanoprost tend to have a greater absolute effect at higher IOPs than at baseline IOPs < 25mmHg, hence the difficulty with demonstrating non-inferiority in the total population. The applicant has also postulated that an additional reason for not demonstrating non-inferiority may be due to a higher rate of non-responders in the netarsudil arm of the ≥25 and < 30 mmHg population. In spite of not demonstrating non-inferiority in the total population in the pivotal study, pooled data from the phase 3 studies has demonstrated that some patients treated with netarsudil with baseline IOPs ≥25 and < 30 mmHg demonstrated quite large reductions in IOP (-7mmHg or more).

In addition, the applicant has also agreed to include a table in section 5.1 of the SmPC showing change in IOP by treatment visit compared to timolol. This will allow prescribers to make a more informed decision with regard to use of netarsudil in this population and is endorsed.

In contrast to several other approved glaucoma/OHT agents, patients with secondary OAG (e.g. pseudoexfoliation or pigment dispersion syndrome) were excluded from the pivotal studies. Considering (i) the proposed indication for use in patients with open angle glaucoma or ocular hypertension; (ii) the mechanism of action of netarsudil as an enhancer of trabecular outflow facility; and (iii) the pathophysiology of elevated IOP in pseudoexfolation syndrome and pigment dispersion syndrome, inclusion of patients with secondary OAG was questioned.

The applicant acknowledges that patients with secondary glaucoma were excluded from their registration studies. A number of registration studies for other anti-glaucoma products are cited in which the proportion of secondary glaucoma patients (pseudo-exfoliative or pigmentary glaucoma) included were too small to draw any conclusion regarding efficacy in this population. The applicant also provides some data on the use of netarsudil in 5 patients with secondary glaucoma (3 with pseudo-exfoliative glaucoma, one with pigmentary glaucoma and one with open angle glaucoma, who should not have been included as it appears she did not have a secondary glaucoma); only in this latter case was netarsudil used as a monotherapy.

The applicant also refers to data on other Rhokinase inhibitors (AR-12286) and ripasudil that have been shown to lower IOP in patients with secondary(pseudo-exfoliative) glaucoma as well as providing anecdotal reports from the USA in which physicians have prescribed netarsudil to their secondary glaucoma patients on (maximum- tolerated) therapy and have seen an additional IOP-lowering effect of adding netarsudil.

The applicant states that there is pre-clinical evidence that netarsudil could be of benefit in secondary glaucoma (e.g. in vitro studies with netarsudil have demonstrated that it blocks the profibrotic effects of the cytokine, transforming growth factor-beta (TGF-β), on human trabecular meshwork cells) as well as the clinical evidence regarding the mode of action of netarsudil (relaxes the tissues in the TM outflow pathway, including the episcleral veins, and thereby lowers IOP by reducing the resistance to aqueous outflow). Whilst this is accepted it is unclear to what extent netarsudil is likely to demonstrate an effect on the TM outflow tract which is in the case of pseudo-exfoliative or pigmentary secondary glaucoma could to be scarred as a consequence of secondary glaucoma and thus less capable of relaxing in response to netarsudil.

The lack of data available is reflected in section 5.1.

Even though it is acknowledged that patients with pseudo-exfoliative and pigmentary glaucoma frequently present late and have a rapid rate of progression and poorer prognosis, at the present time the evidence submitted by the applicant in support of the broader inclusion is very limited and is insufficient to support the inclusion of secondary glaucoma in the indication.

Therefore, the final indication is: *Rhokiinsa is indicated for the reduction of elevated intraocular pressure (IOP) in adult patients with **primary** open-angle glaucoma or ocular hypertension.*

2.5.4. Conclusions on the clinical efficacy

Efficacy of Rhokiinsa (netarsudil) 0.02% QD (as in non-inferiority to timolol maleate ophthalmic solution 0.5%) has been demonstrated in the pivotal study (CS304) population with a maximum baseline IOP < 25mmHg. Non-inferiority was not demonstrated in the total study population with maximum baseline IOP < 30 mmHg. However, in spite of not demonstrating non-inferiority in the total population in the pivotal study, pooled data from the phase 3 studies has demonstrated that some patients treated with netarsudil with baseline IOPs ≥25 and < 30 mmHg demonstrated quite large reductions in IOP (-7mmHg or more).

There is insufficient efficacy data to substantiate the inclusion of the secondary glaucoma such as pseudo-exfoliative and pigmentary glaucoma within the broad indication of open angle glaucoma and ocular hypertension. Therefore Rhokiinsa is indicated for the reduction of elevated intraocular pressure (IOP) in adult patients with primary open-angle glaucoma or ocular hypertension.

2.6. Clinical safety

The development program conducted in support of netarsudil ophthalmic solution 0.02% comprises 10 completed clinical studies (Phases 1 to 3). Characteristics of all the completed clinical studies are provided in Table 1. Three studies were ongoing at the data lock point for this application and the applicant provided an update on these studies in the responses to the day 120 LoQ. No new safety concerns arise from these studies.

Overall, the safety analysis of Netarsadil ophthalmic solution 0.02% is based on the results obtained from the following data sources:

- 7 prospective, randomized, double-masked, multi-centre, active or vehicle-controlled, parallel group

studies in subjects with OAG or OHT:

i. Two Phase 2 studies (AR-13324-CS201 and AR-13324-CS202) were conducted to evaluate the dose-response and dosing regimen of netarsudil prior to initiation of the Phase 3 studies

ii. A third Phase 2 study (AR-13324-CS204) was conducted to evaluate the efficacy of netarsudil during nocturnal and diurnal periods.

iii. Four Phase 3 multi-centre, active-controlled studies (AR-13324-CS301, AR-13324-CS302, AR-13324-CS303, and AR-13324-CS304), of 3, 6 or 12 months duration, were conducted to evaluate the long-term safety and ocular hypotensive efficacy of netarsudil.

iv. In addition, two Phase 1 studies were completed in healthy subjects: a pharmacokinetics study to evaluate systemic plasma concentrations of netarsudil following ocular administration (AR-13324-CS101), and a mechanism of action study to evaluate the effect of netarsudil on aqueous humor dynamics (AR-13324-CS102).

- A non-interventional Corneal Deposit Observational Study (AR-13324-OBS01) was completed in which visual function (e.g., visual acuity, contrast sensitivity, VF-14 Questionnaire) and corneal deposit resolution was evaluated in subjects who developed corneal deposits (cornea verticillata) or corneal opacity while participating in the Phase 3 studies AR-13324-CS301 or AR-13324-CS302.
- A follow-up Phase 2 mechanism of action study (AR-13324-CS206) has been initiated in subjects with OAG or OHT, and in support of product development in Japan, a Phase 1 study (AR-13324-CS104) and a Phase 2 study (AR-13324-CS205) have also been initiated.
- An overview of supportive safety data from studies conducted as part of the parallel clinical development programme for PG324 Ophthalmic Solution, a fixed-dose combination of netarsudil 0.02% and latanoprost 0.005% has also been provided.

The most relevant safety information was obtained in the Phase 2 and 3 studies since these studies were randomized, double-masked, and active or vehicle-controlled and conducted in the patient population (OAG and OHT) for which the product is intended, whereas the Phase 1 studies were conducted in healthy subjects.

The description of safety will thus focus primarily on the Phase 2 and Phase 3 studies.

Patient exposure

In the netarsudil 0.02% development program a total of 1,258 subjects were treated with netarsudil 0.02% (once daily or QD: 969 subjects; twice daily or BID: 289 subjects), the concentration for which this application seeks approval.

Number of subjects exposed to netarsudil ophthalmic solution are presented across both Netarsudil and PG324 (FDC with 0.005% lantanoprost) development programs below.

When combined with the PG324 development program a total of 3,454 subjects were randomized to therapy across all treatment groups (netarsudil and comparators) in completed trials, which included 501 subjects in the Phase 1 and Phase 2 studies and 2,953 subjects in the Phase 3 studies.

This included a total of 1,950 subjects across all concentrations (0.01%, 0.02%, and 0.04%) of netarsudil with greater numbers in the Phase 3 studies (1,626 subjects) compared to the Phase 1 and 2 studies (324 subjects).

Within the netarsudil 0.02% treatment group, 1,834 subjects were treated (QD: 1,545; or BID: 289). The active comparators in these studies included latanoprost 0.005% (638 subjects) and timolol 0.5% (Phase 3 only, 839 subjects). With the exception of a single study (AR-13324-CS202), latanoprost was used as a comparator only in the supportive PG324 studies. An overview of subject exposure by study and treatment group is provided in Table below.

Table 22 - Overview of Subject Exposure to Study Drug by Study and Treatment Group (All Completed Studies)

Protocol Number	Safety N	Netarsudil				Timolol	Latanoprost	Vehicle
		0.01% QD[1] (N=97)	0.02% QD[2] (N=1,545)	0.02% BID (N=289)	0.04% QD (N=19)	0.5% BID (N=839)	0.005% QD (N=638)	QD (N=38)
Netarsudil Phase 1 and 2 Studies								
AR-13324-CS101	18		18					
AR-13324-CS102	11[3]		11					11[3]
AR-13324-CS201	85	22	21		19			23
AR-13324-CS202	224	75	72				77	
AR-13324-CS204	12		8					4
Subtotal	**350**	**97**	**130**		**19**		**77**	**38**
Netarsudil Phase 3 Studies								
AR-13324-CS301	411		203			208		
AR-13324-CS302	755		251	253		251		
AR-13324-CS303	93		34	36		23		
AR-13324-CS304	708		351			357		
Subtotal	**1, 967**		**839**	**289**		**839**		
Supportive PG324 Studies								
PG324-CS201	151[4]		78				73	
PG324-CS301	480[4]		243				237	
PG324-CS302	506[4]		255				251	
Subtotal	**1, 137**		**576**				**561**	
Total	**3,454**	**97**	**1,545**	**289**	**19**	**839**	**638**	**38**

1. 0.01% QD includes AM and PM dosing groups.
2. 0.02% QD includes AM and PM dosing groups.
3. Vehicle dosed in the fellow eye. The safety N reflects only 11 subjects since both eyes were dosed concurrently.
4. Safety N only includes the netarsudil and latanoprost monotherapy treatment groups.

The duration of exposure to study drug by treatment group combined over all the netarsudil studies is provided in Table 7. Within the netarsudil treatment group, 395 subjects were exposed to netarsudil 0.02% (QD: 361 subjects; BID: 34 subjects) for a duration of 6 months to 12 months.

In addition, a total of 339 subjects completed over 12 months of therapy with netarsudil 0.02%. (QD: 252 subjects; BID: 87 subjects). Approval is being sought for once daily dosing of netarsudil ophthalmic solution.

Table 23 - Duration of Exposure to Study Drug by Treatment Group (All Completed Studies)

Treatment	Total	< 3 months	3 to < 6 months	6 months to <1 year	≥ 1 year
	N	N (%)	N (%)	N (%)	N (%)
Netarsudil 0.01% QD[1]	97	97 (100)	0	0	0
Netarsudil 0.02% QD[2]	1545	457 (29.6)	475 (30.7)	361 (23.4)	252 (16.3)
Netarsudil 0.02% BID	289	111 (38.4)	57 (19.7)	34 (11.8)	87 (30.1)
Netarsudil 0.04% QD	19	19 (100)	0	0	0
Timolol 0.5% BID	839	48 (5.7)	237 (28.2)	335 (39.9)	219 (26.1)
Latanoprost 0.005% QD	638	201 (31.5)	218 (34.2)	69 (10.8)	150 (23.5)
PG324 QD	555	157 (28.3)	221 (39.8)	66 (11.9)	111 (20.0)
Vehicle[3]	38	38 (100)	0	0	0

1. 0.01% QD includes AM and PM dosing groups.
2. 0.02% QD includes AM and PM dosing groups
3. Vehicle dosed in the fellow eye in study AR-13324 CS102

Note: Table includes the following studies: AR-13324-CS101, AR-13324-CS102, AR-13324-CS201, AR-13324-CS202, AR-13324-CS204, AR-13324-CS301, AR-13324-CS302, AR-13324-CS303, AR-13324-CS304, PG324-CS201, PG324-CS301 and PG324-CS302.

In several of the clinical studies, the dosage of netarsudil 0.02% ophthalmic solution was administered topically as either a once daily or twice daily administration. There was an increased frequency of AEs with Netarsudil 0.02% when administered twice daily versus once daily. However, it is important to note that the currently proposed posology is Netarsudil 0.02% administered on a once daily dosing schedule and the twice daily posology is not being pursued.

In this context, 969 patients were exposed to once daily dosing with Netarsudil 0.02% solution in the clinical development for the mono constituent product.

Demographic and Other Characteristics of Study Population

The demography of the overall study population is representative of those who would receive the product once marketed in Europe and is similar to that reported in clinical studies evaluating comparable products (Garway-Heath 2017, Goldberg 2014).

The Phase 2 studies (other than AR-13324-CS204) included 309 randomized subjects ranging in age from 19 to 90 years with a mean age across all studies ranging from 57.8 to 69.1 years.

Demographic characteristics for Phase 3 are presented for the pooled safety population. The pooled safety population from the 4 AR-13324 Phase 3 studies included 1967 randomized subjects ranging in age from 11 to 96 years, with a mean age of 64.3 years. The proposed indication is for use in adult patients only.

In patients treated with netarsudil 0.02% once daily, 55.8% of patients were ≥65 years, reflective of the target population. Paediatric patients under 18 years were not specifically studied.

Most subjects were white (73.6%) and had brown/black irises (62.9%).

The pooled population included a higher percentage of females (61.1%) compared to males (38.9%).

A higher percentage of subjects had a study eye diagnosis of OAG (64.3 %) compared to OHT (35.7%). Overall, no clinically relevant differences were observed among the treatment groups across all studies in the assessment of demographic characteristics. The demographic profile of the pooled safety population from the AR-13324 Phase 3 studies is presented by study and treatment group in Table below.

In addition to the populations already studied, clinical studies are currently ongoing in patients of Japanese ethnic origin.

Table 24 - Demographics of Subjects in Netarsudil Phase 3 Clinical Studies (Safety Population)

Demographic Characteristic		Pooled Phase 3 Studies			
		Netarsudil 0.02% QD	Netarsudil 0.02% BID	Timolol 0.05% BID	All Subjects
		N=839	N=289	N=839	N=1967
Study Eye Diagnosis n (%)	Ocular Hypertension	299 (35.6)	120 (41.5)	283 (33.7)	702 (35.7)
	Open Angle Glaucoma	540 (64.4)	169 (58.5)	556 (66.3)	1265 (64.3)
Race n (%)	Native Hawaiian or other Pacific Islander	0	0	1 (0.1)	1 (0.1)
	Asian	11 (1.3)	7 (2.4)	19 (2.3)	37 (1.9)
	Black or African American	199 (23.7)	70 (24.2)	203 (24.2)	472 (24.0)
	Native American	2 (0.2)	0	0	2 (0.1)
	White	625 (74.5)	211 (73.0)	611 (72.8)	1447 (73.6)
	Multiple	0	0	3 (0.4)	3 (0.2)
	Other	2 (0.2)	1 (0.3)	2 (0.2)	5 (0.3)
Ethnicity n (%)	Hispanic or Latino	158 (18.6)	44 (15.2)	157 (18.7)	359 (18.3)
	Not Hispanic or Latino	681 (81.2)	245 (84.8)	682 (81.3)	1608 (81.7)
Age (years) n (%)	< 65 years	371 (44.2)	139 (48.1)	407 (48.5)	917 (46.6)
	≥ 65 years	468 (55.8)	150 (51.9)	432 (51.5)	1050 (53.4)
Age (years)	Mean (SD)	64.9 (11.42)	64.2 (12.02)	63.9 (11.36)	64.3 (11.49)
	Range (Min, Max)	14, 96	18, 92	11, 91	11. 96
Sex n (%)	Male	349 (41.6)	107 (37.0)	309 (36.8)	765 (38.9)
	Female	490 (58.4)	182 (63.0)	530 (63.2)	1202 (61.1)
Iris Color n (%)	Blue/Grey/Green	214 (25.5)	76 (26.3)	225 (26.8)	515 (26.2)
	Brown/Black	521 (62.1)	178 (61.6)	538 (64.1)	1237 (62.9)
	Hazel	103 (12.3)	35 (12.1)	76 (9.1)	214 (10.9)
	Other	1 (0.1)	0	0	1 (0.1)

Note: The pooled population includes subjects from the AR-13324-CS301, AR-13324-CS302, AR-13324-CS303 and AR-13324-CS304 clinical studies.

Adverse events

In the Phase 3 studies, the proportion of subjects treated with netarsudil experiencing an AE was higher than in the Phase 2 trials, reflective of the longer duration of treatment in these studies.

The incidence of AEs in subjects receiving netarsudil 0.02% QD was generally consistent across the four Phase 3 studies, (with the exception of AR-13324-CS303 having a higher incidence), AR-13324-CS301, AR-13324-CS302, AR-13324-CS303, and AR-13324-CS304: 81.2% (165/203), 87.6% (220/251), 97.1% (33/34), 80.1% (281/351), respectively.

As noted in the Phase 2 studies, the large majority of the netarsudil QD AEs were ocular in nature, most were judged as treatment-related and most were of mild severity.

In the 12-month AR-13324-CS302 and AR-13324-CS303 studies, a similar incidence of AEs was recorded for subjects receiving netarsudil BID, 88.9% (225/253) and 100% (36/36); however, the overall duration of dosing for netarsudil BID was shorter than for netarsudil QD due to its higher discontinuation rate due to AEs [BID: 53.8% (136/253) and 86.1% (31/36) vs. QD: 30.3% (76/251) and 47.1% (16/34), respectively].

In addition, there was a higher incidence of subjects with AEs scored as moderate or severe in the netarsudil BID group compared to the netarsudil QD group.

In the Phase 3 studies, the incidence of AEs in subjects treated with netarsudil was higher than for those treated with timolol: 53.8% (112/208), 63.3% (159/251), 87.0% (20/23), and 60.2% (215/357) for timolol, respectively.

With regard to the pooled Phase 3 population, of those subjects who experienced a TEAE, the majority in the netarsudil QD (58.5%; 409/699) and timolol (73.3%; 371/506) groups experienced TEAEs that were mild in intensity.

A higher incidence of netarsudil BID subjects (46.4%; 121/261) experienced TEAEs of moderate intensity compared to netarsudil QD (35.2%; 246/699) and timolol (21.9%; 111/506) subjects.

A higher proportion of subjects in the netarsudil groups (QD: 73.1%; BID: 84.1%) compared to those in the timolol group (42.3%) experienced AEs that were considered treatment related events.

With respect to the subgroup analyses in the pooled Phase 3 population, whites had a higher incidence of both overall adverse events and ocular adverse events when compared to subjects of other ethnicities. The comparative incidences (white vs. other ethnicities) of ocular events were as follows: netarsudil QD (89.0 vs. 66.8%); netarsudil BID (93.8 vs. 80.8%); timolol (64.2 vs. 50.0%). An analysis of adverse event severity indicated that in the netarsudil treatment groups, white subjects had greater incidences of moderate and severe adverse events compared to subjects of other ethnicities.

Table 25 - Overall Summary of Adverse Events by Phase 2* Clinical Study and Treatment Group (Safety Population)

	AR-13324-CS201				AR-13324-CS202		
	Netarsudil 0.01% QD AM (N=22) n (%)	Netarsudil 0.02% QD AM (N=21) n (%)	Netarsudil 0.04% QD AM (N=19) n (%)	Vehicle QD AM (N=23) n (%)	Netarsudil 0.01% QD PM (N=75) n (%)	Netarsudil 0.02% QD PM (N=72) n (%)	Latanoprost 0.005% QD PM (N=77) n (%)
Number of AEs	17	29	27	3	82	97	47
Number of subjects with at least one AE	13 (59.1)	16 (76.2)	17 (89.5)	3 (13.0)	50 (66.7)	50 (69.4)	28 (36.4)
Number of ocular AEs	16	27	25	3	76	90	33
Number of subjects with at least one ocular AE	13 (59.1)	16 (76.2)	17 (89.5)	3 (13.0)	47 (62.7)	48 (66.7)	23 (29.9)
Number of serious AEs	0	0	0	0	1	0	2
Number of subjects with at least one serious AE	0	0	0	0	1 (1.3)	0	2 (2.6)
Number of treatment-related AEs	15	19	25	2	66	80	29
Number of subjects with at least one treatment-related AE	12 (54.5)	14 (66.7)	17 (89.5)	2 (8.7)	46 (61.3)	45 (62.5)	19 (24.7)
Number of treatment-related	0	0	0	0	0	0	0

serious AEs							
Number of subjects with at least one treatment-related serious AE	0	0	0	0	0	0	0
Number of subjects with AEs by maximum severity	13 (59.1)	16 (76.2)	17 (89.5)	3 (13.0)	45 (60.0)	41 (56.9)	23 (29.9)
Moderate	0	0	0	0	4 (5.3)	7 (9.7)	3 (3.9)
Severe	0	0	0	0	1 (1.3)	2 (2.8)	2 (2.6)
Number of subjects with AEs resulting in test article discontinuation	0	0	0	0	3 (4.0)	2 (2.8)	1 (1.3)

Note: Table only includes the netarsudil and latanoprost monotherapy treatment groups.
* No AEs were reported in study AR-13324-CS204.

Table 26 - Overall Summary of Adverse Events by Netarsudil Phase 3 Clinical Study and Treatment Group (Safety Population)

	AR-13324-CS301		AR-13324-CS302			AR-13324-CS303			AR-13324-CS304	
	Netarsudil 0.02% QD PM (N=203) n (%)	Timolol 0.5% BID (N=208) n (%)	Netarsudil 0.02% QD PM (N=251) n (%)	Netarsudil 0.02% BID (N=253) n (%)	Timolol 0.5% BID (N=251) n (%)	Netarsudil 0.02 % QD PM (N=34) n (%)	Netarsudil 0.02% BID (N=36) n (%)	Timolol 0.5% BID (N=23) n (%)	Netarsudil 0.02% QD PM (N=351) n (%)	Timolol 0.5% BID (N=357) n (%)
Number of AEs	473	193	930	1086	430	232	238	57	1061	462
Number of subjects with at least one AE	165 (81.3)	112 (53.8)	220 (87.6)	225 (88.9)	159 (63.3)	33 (97.1)	36 (100.0)	20 (87.0)	281 (80.1)	215 (60.2)
Number of ocular AEs	413	141	762	962	248	201	218	41	938	322
Number of subjects with at least one ocular AE	156 (76.8)	92 (44.2)	209 (83.3)	222 (87.7)	124 (49.4)	33 (97.1)	36 (100.0)	18 (78.3)	267 (76.1)	180 (50.4)
Number of non-ocular AEs	60	52	168	124	182	31	20	16	123	140
Number of subjects with at least one non-ocular AE	41 (20.2)	40 (19.2)	81 (32.3)	68 (26.9)	82 (32.7)	17 (50.0)	9 (25.0)	10 (43.5)	82 (23.4)	91 (25.5)
Number of serious AEs	3	6	22	9	18	0	1	1	11	12
Number of subjects with at least one serious AE	3 (1.5)	4 (1.9)	17 (6.8)	7 (2.8)	12 (4.8)	0	1 (2.8)	1 (4.3)	8 (2.3)	10 (2.8)
Number of treatment-related AEs	367	121	630	803	167	176	193	25	793	247
Number of subjects with at least one treatment-related AE	148 (72.9)	89 (42.8)	192 (76.5)	207 (81.8)	98 (39.0)	32 (94.1)	36 (100.0)	16 (69.6)	241 (68.7)	152 (42.6)
Number of treatment-related serious AEs	1	0	0	0	0	0	1	0	0	0
Number of subjects with at least one treatment-related serious AE	1 (0.5)	0	0	0	0	0	1 (2.8)	0	0	0
Number of subjects with AEs by maximum severity										
Mild	120 (59.1)	91 (43.8)	115 (45.8)	100 (39.5)	111 (44.2)	10 (29.4)	4 (11.1)	12 (52.5)	164 (46.7)	157 (44.)
Moderate	39 (19.2)	16 (7.7)	87(34.7)	102 (40.3)	37 (14.7)	17 (50.0)	19 (52.8)	7 (30.4)	103 (29.3)	51 (14.3)

	AR-13324-CS301		AR-13324-CS302			AR-13324-CS303			AR-13324-CS304	
	Netarsudil 0.02% QD PM (N=203) n (%)	Timolol 0.5% BID (N=208) n (%)	Netarsudil 0.02% QD PM (N=251) n (%)	Netarsudil 0.02% BID (N=253) n (%)	Timolol 0.5% BID (N=251) n (%)	Netarsudil 0.02 % QD PM (N=34) n (%)	Netarsudil 0.02% BID (N=36) n (%)	Timolol 0.5% BID (N=23) n (%)	Netarsudil 0.02% QD PM (N=351) n (%)	Timolol 0.5% BID (N=357) n (%)
Severe	6 (3.0)	5 (2.4)	18 (7.2)	23 (9.1)	11 (4.4)	6 (17.6)	13 (36.1)	1 (4.3)	14 (4.0)	7 (2.0)

Phase 3 Studies

AEs reported in at least 2% of the pooled Phase 3 study population are discussed, except in the case of treatment-related non-ocular AEs which are reported in at least 1% of the pooled population.

In the 4 Phase 3 studies, the most frequently reported ocular AEs in the netarsudil treatment groups were conjunctival hyperaemia, cornea verticillata and conjunctival haemorrhage (Table 31 and Table 32). The incidence of these AEs for netarsudil QD was lower in the shorter duration studies AR-13324-CS301 (53.2% (108/203), 5.9% (12/203), 15.8% (32/203)) and AR-13324-CS304 (47.9% (168/351), 24.5% (86/351), 16.0% (56/351)) than in the longer duration studies AR-13324-CS302 (60.6% (152/251), 25.5% (64/251), and 19.5% (49/251)), and AR-13324-CS303 (82.4% (28/34), 38.2% (13/34), 20.6% (7/34)), respectively. The incidence of these AEs was similar for netarsudil BID in studies AR-13324-CS302 and AR-13324-CS303.

For the large majority of netarsudil QD and BID subjects in studies AR-13324-CS302 and AR-13324-CS303 (both 12 months) who experienced conjunctival hyperaemia and completed the study, conjunctival hyperaemia was sporadic in nature (QD: 80.5% (66/82) and 78.6% (22/28) respectively; BID: 80.0% (44/55) and 82.4% (28/34)).

In addition, only 28.3% (43/152) of QD subjects and 25.0% (42/168) of BID subjects in the AR-13324-CS302 study and 53.6% (15/34) QD subjects and 79.4% (27/36) BID subjects) in the AR-13324-CS303 study had the event reported at >3 consecutive visits.

The incidence of conjunctival hemorrhage across the four Phase 3 studies was higher in the netarsudil groups (QD: 15.8 to 20.6%; BID: 16.7 to 19.4%) compared to timolol (0.8 to 3.1%). When present, conjunctival hemorrhage was typically reported as mild and was considered treatment-related.

Another frequently reported ocular AE (only reported in Phase 3 studies) was corneal deposits (cornea verticillata). The term “cornea verticillata” refers to a whorl-like pattern of deposits typically localized to the basal corneal epithelium (Mantyjarvi 1998; Hollander 2004). A variety of drugs that are both cationic and amphiphilic are known to induce cornea verticillata, which arise due to the lysosomal accumulation of phospholipids within corneal epithelial cells through a process called phospholipidosis. Netarsudil is a cationic amphiphilic drug and Aerie has shown that netarsudil can induce phospholipidosis in Chinese hamster ovary cells (AR-13324-IPH07), suggesting that the etiology of the netarsudil-induced corneal deposits is phospholipidosis. It is unusual for cornea verticillata to result in reduction of visual acuity or ocular symptoms and the deposits typically resolve with discontinuation of the drug (Mantyjarvi 1998).

Cornea verticillata occurred at a higher incidence in the longer 6- and 12-month studies (AR-13324-CS302: QD 25.5%, BID 25.3%; AR-13324-CS303: QD 38.2%, BID 38.9%; and AR-13324-CS304: QD 24.5%) compared to the 3-month study (AR-13324-CS301 QD 5.9%).

In the timolol group, this event was only reported in Study AR-13324-CS302 at an incidence of 0.8% (Table 25).

Aerie also conducted a Corneal Deposit Observation Study (AR-13324-OBS01) to further evaluate visual function in subjects who developed corneal deposits in the AR-13324-CS301 and -CS302 clinical studies. At the completion of the observational study, there was no clinically meaningful impact of cornea verticillata on visual function as measured by visual acuity, contrast sensitivity, and a visual function questionnaire. The AE resolved in all but 3 subjects (4 eyes); in these 3 subjects the corneal deposit grade had decreased and the event stabilized by the completion of the study (Section 2.3). After study completion, cornea verticillata resolved in 1 of these subjects and had improved in the other 2 subjects (3 out of 4 eyes).

Other ocular AEs recorded for netarsudil across the four Phase 3 studies included:

- Instillation site pain (QD: 14.8%, 17.9%, 26.5%, and 23.6%; BID: 17.8% and 22.2%),
- vision blurred (QD: 5.4%,10.8%, 5.9%, and 5.4%; BID: 17.4% and 13.9%)
- instillation site erythema (QD: 5.6%,11.8%, 5.9%, and 10.3%; BID: 12.6% and 5.6%).

With the exception of instillation site pain, these same events were reported at much lower incidences in the timolol group as presented in Table 31. An evaluation of ocular events that were considered treatment-related provided very similar results as presented in Table 32.

The most frequently reported (≥2%) ocular AEs in the pooled Phase 3 population is presented in Table 27.

The most common ocular events reported for netarsudil included conjunctival hyperaemia (QD: 54.4%; BID: 69.9%), cornea verticillata (QD: 20.9%; BID: 27.0%), conjunctival hemorrhage (QD: 17.2; BID: 19.0%), instillation site pain (QD: 19.9%; BID: 18.3%), vision blurred (QD: 7.4%; BID: 17.0%), and instillation site erythema (QD: 9.1%; BID: 11.8%).

Less common events included vital dye staining cornea present (QD: 9.4%; BID: 8.7%), lacrimation increased (QD: 7.2%; BID: 10.0%), erythema of eyelid (QD: 6.8%; BID: 7.6%), visual acuity reduced (QD: 5.2%; BID: 8.0%), eye pruritus (QD: 4.1%; BID: 8.0%), conjunctival edema (QD: 3.1%; BID: 7.6%), eye irritation (QD: 3.8%; BID: 5.5%), eyelid edema (QD:3.5%;BID: 6.6%), foreign body sensation in eyes (QD: 2.5%; BID: 6.2%), and corneal opacity (considered to be 'cornea verticillata') (QD: 1.3%; BID: 5.2%).

These same events were all reported at lower incidences in the timolol group with the exception of instillation site pain (21.6%).

The most frequently reported non-ocular AEs for netarsudil across the four Phase 3 studies, respectively, included headache (QD: 0%, 2.4%, 2.9% and 1.7%; BID: 4.0% and 8.3%) and upper respiratory tract infection (QD: 0%, 2.0%, 0% and 2.8%; BID: 3.6% and 0%), which were reported at similar incidences in the timolol groups (0.5 to 4.3%) (Table 34).

Reports of treatment-related non-ocular AEs were minimal (Table 35).

In the pooled safety analysis, the most frequently reported non-ocular AEs in the netarsudil treatment groups included upper respiratory infection (QD: 1.8%; BID: 3.1%), headache (QD: 1.5%; BID: 4.5%) and allergic dermatitis (QD: 0.5%; BID: 2.8%). Similarly, low incidences of these events were reported for the timolol group (Table 36).

Treatment-related non-ocular TEAEs were reported in single subjects within a treatment group with the exception of dermatitis allergic (netarsudil QD: 3 subjects, 0.4%; BID: 7 subjects, 2.4%), dermatitis contact (netarsudil QD: 5 subjects, 0.6%; BID: 3 subjects, 1.0%), headache (netarsudil QD: 6 subjects, 0.7%; BID: 4 subjects, 1.4%; timolol: 2 subjects, 0.2%), dizziness (netarsudil BID: 2 subjects, 0.7%),

dysgeusia (timolol: 3 subjects, 0.4%), bradycardia (timolol: 2 subjects, 0.2%), nausea (timolol: 2 subjects, 0.2%), hypersensitivity (netarsudil QD: 2 subjects, 0.2%) and dyspnea (timolol: 3 subjects, 0.4%).

Table 27 - Ocular Adverse Events Reported for ≥ 2% of Subjects by Netarsudil Phase 3 Clinical Study and Treatment Group (Safety Population)

SOC PT	AR-13324 CS301		AR-13324 CS302			AR-13324 CS303			AR-13324 CS304	
	Netarsudil 0.02% QD PM (N=203) n (%)	Timolol 0.5% BID (N=208) n (%)	Netarsudil 0.02% QD PM (N=251) n (%)	Netarsudil 0.02% BID (N=253) n (%)	Timolol 0.5% BID (N=251) n (%)	Netarsudil 0.02% QD (N =34) n (%)	Netarsudil 0.02% BID (N=36) n (%)	Timolol 0.5% BID (N=23) n (%)	Netarsudil 0.02 % QD (N = 351) n (%)	Timolol 0.5% BID (N=357) n (%)
Eye Disorders	136 (67.0)	34 (16.3)	198 (78.9)	215 (85.0)	86 (34.3)	33 (97.1)	34 (94.4)	11 (47.8)	242 (68.9)	94 (26.3)
Conjunctival hyperaemia	108 (53.2)	17 (8.2)	152 (60.6)	168 (66.4)	35 (13.9)	28 (82.4)	34 (94.4)	2 (8.7)	168 (47.9)	33 (9.2)
Cornea verticillata	12 (5.9)	0	64 (25.5)	64 (25.3)	2 (0.8)	13 (38.2)	14 (38.9)	0	86 (24.5)	0
Conjunctival hemorrhage	32 (15.8)	2 (1.0)	49 (19.5)	49 (19.4)	2 (0.8)	7 (20.6)	6 (16.7)	0	56 (16.0)	11 (3.1)
Erythema of eyelid	12 (5.9)	0	14 (5.6)	12 (4.7)	2 (0.8)	5 (14.7)	10 (27.8)	2 (8.7)	26 (7.4)	2 (0.6)
Vision blurred	11 (5.4)	1 (0.5)	27 (10.8)	44 (17.4)	7 (2.8)	2 (5.9)	5 (13.9)	0	22 (6.3)	4 (1.1)
Lacrimation increased	8 (3.9)	0	19 (7.6)	25 (9.9)	0	7 (20.6)	4 (11.1)	0	26 (7.3)	5 (1.4)
Visual acuity reduced	8 (3.9)	3 (1.4)	22 (8.8)	22 (8.7)	6 (2.4)	0	1 (2.8)	0	14 (4.0)	4 (1.1)
Eye pruritus	4 (2.0)	0	14 (5.6)	20 (7.9)	3 (1.2)	3 (8.8)	3 (8.3)	0	12 (3.4)	1 (0.3)
Conjunctival oedema	4 (2.0)	0	8 (3.2)	19 (7.5)	0	3 (8.8)	3 (8.3)	0	11 (3.1)	1 (0.3)
Eye irritation	8 (3.9)	1 (0.5)	11 (4.4)	13 (5.1)	8 (3.2)	1 (2.9)	3 (8.3)	0	12 (3.4)	3 (0.8)
Foreign body sensation in eyes	2 (1.0)	1 (0.5)	7 (2.8)	14 (5.5)	1 (0.4)	0	4 (11.1)	0	12 (3.4)	4 (1.1)
Punctate Keratitis	4 (2.0)	1 (0.5)	12 (4.8)	12 (4.7)	5 (2.0)	0	0	0	11 (3.1)	8 (2.2)
Eyelid oedema	4 (2.0)	2 (1.0)	11 (4.4)	12 (4.7)	3 (1.2)	4 (11.8)	7 (19.4)	0	10 (2.8)	1 (0.3)
Corneal opacity	0	0	1 (0.4)	11 (4.3)	0	5 (14.7)	4 (11.1)	0	5 (1.4)	1 (0.3)
Blepharitis	4 (2.0)	2 (1.0)	4 (1.6)	8 (3.2)	1 (0.4)	2 (5.9)	5 (13.9)	1 (4.3)	7 (2.0)	2 (0.6)
Eye pain	2 (1.0)	0	10 (4.0)	11 (4.3)	8 (3.2)	2 (5.9)	3 (8.3)	0	5 (1.4)	8 (2.2)
Eyelid pruritis	3 (1.5)	0	2 (0.8)	4 (1.6)	1 (0.4)	1 (2.9)	3 (8.3)	0	12 (3.4)	1 (0.3)
Lenticular opacities	0	1 (0.5)	0	0	0	3 (8.8)	1 (2.8)	0	0	1 (0.3)
Conjunctivochalasis	0	0	1 (0.4)	0	0	2 (5.9)	1 (2.8)	0	0	0
Eye discharge	0	1 (0.5)	0	0	0	2 (5.9)	1 (2.8)	0	8 (2.3)	2 (0.6)
Photophobia	4 (2.0)	0	5 (2.0)	8 (3.2)	1 (0.4)	2 (5.9)	1 (2.8)	0	2 (0.6)	1 (0.3)
Eyelid allergy	0	0	0	0	0	0	0	0	0	0
Eyelid pain	0	0	0	0	0	0	2 (5.6)	0	1 (0.3)	0
Optic disc hemorrhage	0	0	0	0	0	0	2 (5.6)	1 (4.8)	0	0
Dry eye	2 (1.0)	3 (1.4)	6 (2.4)	4 (1.6)	6 (2.4)	1 (2.9)	0	2 (8.7)	9	4
Conjunctivitis allergic	6 (3.0)	0	6 (2.4)	11 (4.3)	1 (0.4)	0	2 (5.6)	0		
Corneal disorder	1 (0.5)	0	1 (0.4)	3 (1.2)	0	1 (2.9)	1 (2.8)	0		
Abnormal sensation in eye	1 (0.5)	0	0	0		1 (2.9)	0	0		
Conjunctival follicles	0	0	1 (0.4)			1 (2.9)	0	0		
Corneal deposits	0	0	0			0	1 (2.8)	0		

SOC PT	AR-13324 CS301		AR-13324 CS302			AR-13324 CS303			AR-13324 CS304	
	Netarsudil 0.02% QD PM (N=203) n (%)	Timolol 0.5% BID (N=208) n (%)	Netarsudil 0.02% QD PM (N=251) n (%)	Netarsudil 0.02% BID (N=253) n (%)	Timolol 0.5% BID (N=251) n (%)	Netarsudil 0.02% QD (N=34) n (%)	Netarsudil 0.02% BID (N=36) n (%)	Timolol 0.5% BID (N=23) n (%)	Netarsudil 0.02% QD (N = 351) n (%)	Timolol 0.5% BID (N=357) n (%)
				3 (1.2)	0				(2.6)	(1.1)
				1 (0.4)	0				9 (2.6)	0
					0				2 (0.6)	0
									0	0
									2 (0.6)	0
									3 (0.9)	
Corneal infiltrates			0	0	0	0	1 (2.8)	0	0	0
Eczema eyelids			0	0	0	1 (2.9)	0	0	0	0
Eye disorder	0	0	0	0	0	0	1 (2.8)	0	0	1 (0.3)
Eye swelling	0	0	0	1 (0.4)	0	1 (2.9)	0	0	1 (0.3)	0
Eyelid disorder	0	0	0	1 (0.4)	0	0	1 (2.8)	0	1 (0.3)	0
Iridocyclitis	0	0	0	0	0	0	1 (2.8)	0	0	0
Non-infective conjunctivitis	1 (0.5)	0	1 (0.4)	1 (0.4)	0	1 (2.9)	0	1 (4.3)	0	0
Ocular discomfort	0	0	1 (0.4)	4 (1.6)	2 (0.8)	0	1 (2.8)	0	1 (0.3)	0
Ocular hypertension	1 (0.5)	0	0	0	0	1 (2.9)	0	0	0	0
Refraction disorder	0	0	0	1 (0.4)	0	0	1 (2.8)	0	1 (0.3)	0
Vitreous detachment	1 (0.5)	0	4 (1.6)	3 (1.2)	2 (0.8)	1 (2.9)	0	1 (4.3)	0	0
Vitreous floaters	2 (1.0)	1 (0.5)	1 (0.4)	1 (0.4)	2 (0.8)	0	1 (2.8)	0	0	0
Cataract	1 (0.5)	1 (0.5)	3 (1.2)	2 (0.6)	5 (2.0)	0	0	0	0	2 (0.6)
	0	0								0
General Disorders and Administration Site Conditions	59 (29.1)	57 (27.4)	68 (27.1)	78 (30.8)	53 (21.1)	16 (47.1)	13 (36.1)	7 (30.4)	104 (29.6)	110 (30.8)
Instillation site pain	30 (14.8)	42 (20.2)	45 (17.9)	45 (17.8)	41 (16.3)	9 (26.5)	8 (22.2)	6 (26.1)	83 (23.6)	92 (25.6)
Instillation site discomfort	10 (4.9)	9 (4.3)	9 (3.6)	7 (2.8)	5 (2.0)	6 (17.6)	2 (5.6)	1 (4.3)	4 (1.1)	7 (2.0)
Instillation site erythema	24 (11.8)	4 (1.9)	14 (5.6)	32 (12.6)	5 (2.0)	2 (5.9)	2 (5.6)	0	36 (10.3)	4 (1.1)
Instillation site pruritis	3 (1.5)	2 (1.0)	3 (1.2)	2 (0.8)	3 (1.2)	2 (5.9)	0	0	4 (1.1)	4 (1.1)
Investigations	22 (10.8)	24 (11.5)	36 (14.3)	28 (11.1)	24 (9.6)	17 (50.0)	9 (25.0)	7 (30.4)	43 (12.3)	31 (8.7)
Vital dye staining cornea present	17 (8.4)	19 (9.1)	14 (5.6)	17 (6.7)	14 (5.6)	14 (41.2)	8 (22.2)	7 (30.4)	34 (9.7)	24 (6.7)
Intraocular pressure increased	0	0	4 (1.6)	1 (0.4)	2 (0.8)	3 (8.8)	1 (2.8)	0	7 (2.0)	1 (0.3)

Note: Table includes all related and not-related AEs reported for ≥2% of subjects in any treatment group within a study. Events are presented by SOC and PT.

Table 28 - Treatment-Related Ocular Adverse Events Reported for ≥ 2% of Subjects by Netarsudil Phase 3 Clinical Study and Treatment Group (Safety Population)

SOC	AR-13324-CS301		AR-13324-CS302			AR-13324-CS303			AR-13324-CS304	
	Netarsudil 0.02% QD PM (N=203) n (%)	Timolol 0.5% BID (N=208) n (%)	Netarsudil 0.02% QD PM (N=251) n (%)	Netarsudil 0.02% BID (N=253) n (%)	Timolol 0.5% BID (N=251) n (%)	Netarsudil 0.02% QD PM (N=34) n (%)	Netarsudil 0.02% BID (N=36) n (%)	Timolol 0.5% BID (N=23) n (%)	Netarsudil 0.02% QD PM (N=351) n (%)	Timolol 0.5% BID (N=357) n (%)
Eye Disorders	127 (62.6)	25 (12.0)	178 (70.9)	199 (78.7)	47 (18.7)	31 (91.2)	34 (94.4)	6 (26.1)	211 (60.1)	62 (17.4)
Conjunctival hyperaemia	105 (51.7)	16 (7.7)	139 (55.4)	160 (63.2)	26 (10.4)	25 (73.5)	33 (91.7)	2 (8.7)	151 (43.0)	28 (7.8)
Conjunctival hemorrhage	19 (9.4)	1 (0.5)	24 (9.6)	21 (8.3)	0	5 (14.7)	3 (8.3)	0	30 (8.5)	6 (1.7)
Cornea verticillata	11 (5.4)	0	62 (24.7)	61 (24.1)	2 (0.8)	13 (38.2)	14 (38.9)	0	85 (24.2)	0
Vision blurred	9 (4.4)	0	20 (8.0)	36 (14.2)	4 (1.6)	1 (2.9)	4 (11.1)	0	19 (5.4)	3 (0.8)
Lacrimation increased	7 (3.4)	0	15 (6.0)	19 (7.5)	0	7 (20.6)	4 (11.1)	0	22 (6.3)	3 (0.8)
Eye pruritus	4 (2.0)	2 (1.0)	12 (4.8)	19 (7.5)	1 (0.4)	3 (8.8)	3 (8.3)	0	13 (3.7)	2 (0.6)
Visual acuity reduced	6 (3.0)	0	14 (5.6)	16 (6.3)	1 (0.4)	0	1 (2.8)	0	9 (2.6)	2 (0.6)
Erythema of eyelid	11 (5.4)	0	13 (5.2)	12 (4.7)	0	5 (14.7)	8 (22.2)	0	23 (6.6)	1 (0.3)
Conjunctival edema	3 (1.5)	0	7 (2.8)	14 (5.5)	0	3 (8.8)	2 (5.6)	0	9 (2.6)	0
Corneal opacity	0	1 (0.5)	1 (0.4)	10 (4.0)	0	5 (14.7)	4 (11.)	0	5 (1.4)	1 (0.3)
Eyelid edema	4 (2.0)	0	9 (3.6)	9 (3.6)	0	2 (5.9)	6 (16.7)	0	8 (2.3)	0
Eye pain	2 (1.0)	1 (0.5)	7 (2.8)	11 (4.3)	0	2 (5.9)	3 (8.3)	0	2 (0.6)	3 (0.8)
Foreign body sensation in eye	2 (1.0)	0	6 (2,4)	11 (4.3)	0	0	4 (11.1)	0	8 (2.3)	3 (0.8)
Blepharitis	1 (0.5)	1 (0.5)	3 (1.2)	4 (1.6)	0	1 (2.9)	3 (8.3)	0	2 (0.6)	0
Eye irritation	8 (3.9)	0	10 (4.0)	11 (4.3)	0	0	2 (5.6)	0	12 (3.4)	3 (0.8)
Eyelid pruritis	3 (1.5)	1 (0.5)	2 (0.8)	3 (1.2)	0	2 (5.9)	3 (8.3)	0	9 (2.6)	1 (0.3)
Photophobia	4 (2.0)	0	4 (1.6)	6 (2.4)	0	2 (5.9)	1 (2.8)	0	2 (0.6)	0
Eye allergy	0	0	0	0	0	2 (5.9)	0	0	3 (0.9)	0
Lenticular opacities	0	0	6 (2.4)	11 (4.3)	0	0	1 (2.8)	0	7 (2.0)	8 (2.2)
Conjunctivitis allergic	6 (3.0)	0	11 (4.4)	9 (3.6)	0	1 (2.9)	0	0	8 (2.3)	0
Punctate keratitis	4 (2.0)	0	1 (0.4)	0	0	0	1 (2.8)	0	2 (0.6)	0
Corneal disorder	1 (0.5)	0	0	3 (1.2)	0	0	1 (2.8)	0	0	0
Blepharitis allergic	0	0	1		0	0		0	0	0
Conjunctival follicles	0	0			0	0		0	0	0
Corneal deposits	0	0			0	0		0	0	0
Corneal infiltrates	0	0			0	0		0	0	0
Corneal striae	0	0			0	0		0	0	0

SOC	AR-13324-CS301		AR-13324-CS302			AR-13324-CS303			AR-13324-CS304	
	Netarsudil 0.02% QD PM (N=203) n (%)	Timolol 0.5% BID (N=208) n (%)	Netarsudil 0.02% QD PM (N=251) n (%)	Netarsudil 0.02% BID (N=253) n (%)	Timolol 0.5% BID (N=251) n (%)	Netarsudil 0.02% QD PM (N=34) n (%)	Netarsudil 0.02% BID (N=36) n (%)	Timolol 0.5% BID (N=23) n (%)	Netarsudil 0.02% QD PM (N=351) n (%)	Timolol 0.5% BID (N=357) n (%)
			(0.4) 0 0 0	1 (0.4) 0 0			(2.8) 1 (2.8) 1 (2.8)		2 (0.6) 2 (0.6) 0 0	

SOC	AR-13324-CS301		AR-13324-CS302			AR-13324-CS303			AR-13324-CS304	
	Netarsudil 0.02% QD PM (N=203) n (%)	Timolol 0.5% BID (N=208) n (%)	Netarsudil 0.02% QD PM (N=251) n (%)	Netarsudil 0.02% BID (N=253) n (%)	Timolol 0.5% BID (N=251) n (%)	Netarsudil 0.02% QD PM (N=34) n (%)	Netarsudil 0.02% BID (N=36) n (%)	Timolol 0.5% BID (N=23) n (%)	Netarsudil 0.02% QD PM (N=351) n (%)	Timolol 0.5% BID (N=357) n (%)
Dry eye Eczema eyelids Eye discharge Eye disorder Eye swelling Eyelid pain Iridocyclitis Non-infective conjunctivitis Ocular discomfort Ocular hypertension Optic disc hemorrhage Refraction disorder Vitreous floaters Age-related macular degeneration Asthenopia	1 (0.5) 0 0 1 (0.5) 0 0 0 0 1 (0.5) 0 0 0 0 0	2 (1.0) 0 1 (0.5) 0 0 0 0 0 0 0 0 0 0 0	4 (1.6) 0 3 (1.2) 0 0 0 0 1 (0.4) 1 (0.4) 0 0 0 0 1 (0.4)	3 (1.2) 0 6 (2.4) 0 0 0 0 3 (1.2) 0 0 0 0 1 (0.4)	1 (0.4) 0 3 (1.2) 0 1 (0.4) 0 0 0 0 0 0 0 0 0	1 (2.9) 1 (2.9) 1 (2.9) 0 1 (2.9) 0 0 1 (2.9) 0 1 (2.9) 0 0 0 0 0	0 0 0 1 (2.8) 0 1 (2.8) 1 (2.8) 0 1 (2.8) 0 1 (2.8) 1 (2.8) 1 (2.8) 0 0	2 (8.7) 0 0 0 0 0 0 0 0 0 0 0 1 (4.3) 1 (4.3)	3 (0.9) 0 0 0 1 (0.3) 0 0 0 1 (0.3) 0 0 1 (0.3) 0 0 0	4 (1.1) 0 0 1 (0.3) 0 0 0 0 0 0 0 0 0 0 1 (0.3)
General Disorders and Administration Site Conditions	58 (28.6)	56 (26.9)	63 (25.1)	76 (30.0)	51 (20.3)	15 (44.1)	11 (30.6)	7 (30.4)	103 (29.3)	108 (30.3)
Instillation site pain Instillation site	30 (14.8)	41 (19.7)	43 (17.1)	43 (17.0)	41 (16.3)	9 (26.5) 5 (14.7)	8 (22.2)	6 (26.	82 (23.4)	92 (25.8)

discomfort	10 (4.9)	9 (4.8)	9 (3.6)	7 (2.8)	5 (2.0)	2 (5.9)	2 (5.6)	1) 1 (4,3)	3 (0.9)	7 (2.0)
Instillation site erythema	24 (11.8)	4 (1.9)	14 (5.6)	32 (12.6)	4 (1.6)	2 (5.9)	2 (5.6)	0 0	36 (10.3)	4 (1.1)
Instillation site pruritis	3 (1.5)	2 (1.0)	3 (1.2)	2 (0.8)	3 (1.2)		0	0	4 (1.1)	4 (1.1)
Investigations	15 (7.4)	16 (7.7)	19 (7.6)	20 (7.9)	13 (5.2)	13 (38.2)	6 (16.7)	7 (30. 4)	32 (9.1)	18 (5.0)
Vital dye staining cornea present	14 (6.9)	15 (7.2)	12 (4.8	15 (5.9)	12 (4.8)	11 (32.4)	5 (13.9)	6 (26. 1)	26 (7.4)	16 (4.5)
Intraocular pressure increased	0	0	2 (0.8)	1 (0.4)	2 (0.8)	3 (8.8)	1 (2.8)	0	7 (2.0)	1 (0.3)

Note: Table includes all related AEs reported for ≥ 2% of subjects in any treatment group within a study. Events are presented by SOC and PT.

Table 29 - Ocular Adverse Events Reported in ≥ 2.0% of Subjects by Treatment Group in Netarsudil

SOC PT	Netarsudil 0.02% QD (N=839) n (%)	Netarsudil 0.02% BID (N=289) n (%)	Timolol 0.5% BID (N=839) n (%)
Eye Disorders	609 (72.6)	249 (86.2)	225 (26.8)
Conjunctival Hyperaemia	456 (54.4)	202 (69.9)	87 (10.4)
Cornea Verticillata	175 (20.9)	78 (27.0)	2 (0.2)
Conjunctival Hemorrhage	144 (17.2)	55 (19.0)	15 (1.8)
Vision Blurred	62 (7.4)	49 (17.0)	12 (1.4)
Lacrimation Increased	60 (7.2)	29 (10.0)	5 (0.6)
Erythema of Eyelid	57 (6.8)	22 (7.6)	6 (0.7)
Visual Acuity Reduced	44 (5.2)	23 (8.0)	13 (1.5)
Eye Pruritus	34 (4.1)	23 (8.0)	7 (0.8)
Conjunctival Edema	26 (3.1)	22 (7.6)	1 (0.1)
Eye Irritation	32 (3.8)	16 (5.5)	12 (1.4)
Eyelid Edema	29 (3.5)	19 (6.6)	6 (0.7)
Foreign Body Sensation in Eyes	21 (2.5)	18 (6.2)	6 (0.7)
Punctate Keratitis	27 (3.2)	12 (4.2)	15 (1.8)
Conjunctivitis Allergic	21 (2.5)	13 (4.5)	1 (0.1)
Eye Pain	19 (2.3)	14 (4.8)	17 (2.0)
Blepharitis	17 (2.0)	13 (4.5)	5 (0.6)
Corneal Opacity	11 (1.3)	15 (5.2)	1 (0.1)
Eyelids Pruritus	18 (2.1)	7 (2.4)	2 (0.2)
Eye Discharge	14 (1.7)	9 (3.1)	6 (0.7)
Dry Eye	18 (2.1)	4 (1.4)	15 (1.8)
Photophobia	13 (1.5)	9 (3.1)	2 (0.2)
General Disorders and Administration Site Conditions	247 (29.4)	91 (31.5)	227 (27.1)
Instillation Site Pain	167 (19.9)	53 (18.3)	181 (21.6)
Instillation Site Erythema	76 (9.1)	34 (11.8)	13 (1.5)
Instillation Site Discomfort	29 (3.5)	9 (3.1)	22 (2.6)
Investigations	118 (14.1)	37 (12.8)	86 (10.3)
Vital Dye Staining Cornea Present	79 (9.4)	25 (8.7)	64 (7.6)
Infections and Infestations	92 (11.0)	39 (13.5)	84 (10.0)
Conjunctivitis	14 (1.7)	8 (2.8)	4 (0.5)

Note: Table includes all related and not-related AEs reported for ≥ 2% of subjects in any treatment group within a study. Events are presented by SOC and PT.

Table 30 - Non-Ocular Adverse Events Reported for ≥ 2% of Subjects by Netarsudil Phase 3 Clinical Study and Treatment Group (Safety Population)

SOC T	AR-13324-CS301		AR-13324-CS302			AR_13324-CS303			AR-13324-CS304	
	Netarsudil 0.02% QD PM (N=203) n (%)	Timolol 0.5% BID (N=208) n (%)	Netarsudil 0.02% QD PM (N=251) n (%)	Netarsudil 0.02% BID (N=253) n (%)	Timolol 0.5% BID (N=251) n (%)	Netarsudil 0.02% QD PM (N=34) n (%)	Netarsudil 0.02% BID (N=36) n (%)	Timolol 0.5% BID (N=23) n (%)	Netarsudil 0.02% QD PM (N=351) n (%)	Timolol 0.5% BID (N=357) n (%)
Infections and Infestations	14 (6.9)	14 (6.7)	28 (11.2)	37 (14.6)	29 (11.6)	10 (29.4)	2 (5.6)	4 (17.4)	40 (11.4)	37 (10.4)
Upper respiratory tract infection Nasopharyngitis Hordeolum	0 3 (1.5) 0	2 (1.0) 2 (1.0) 1 (0.5)	5 (2.0) 5 (2.0) 1 (0.4)	9 (3.6) 2 (0.8) 0	7 (2.8) 3 (1.2) 2 (0.8)	0 2 (5.9) 0	0 1 (2.8) 0	0 0 2 (8.7)	10 (2.8) 4 (1.1) 1 (0.3)	14 (3.9) 4 (1.1) 2 (0.6)
Nervous System Disorders	4 (2.0)	8 (3.8)	16 (6.4)	18 (7.1)	17 (6.8)	3 (8.8)	4 (11.1)	2 (8.7)	11 (3.1)	16 (4.5)
Headache Dizziness	0 1 (0.5)	1 (0.5) 2 (1.0)	6 (2.4) 4 (1.6)	10 (4.0) 1 (0.4)	9 (3.6) 1 (0.4)	1 (2.9) 0	3 (8.3) 2 (5.6)	1 (4.3) 0	6 (1.7) 0	5 (1.4) 1 (0.3)
Skin and Subcutaneous Tissue Disorders	1 (0.5)	1 (0.5)	13 (5.2)	15 (5.9)	7 (2.8)	0	4 (11.1)	0	9 (2.6)	8 (2.2)
Dermatitis allergic	0	0	2 (0.8)	6 (2.4)	0	0	2 (5.6)	0	2 (0.6)	0
Gastrointestinal Disorders	7 (3.4)	4 (1.9)	2 (0.8)	10 (4.0)	9 (3.6)	3 (8.8)	2 (5.6)	0	7 (2.0)	11 (3.1)
Respiratory, Thoracic and Mediastinal Disorders	8 (3.9)	3 (1.4)	10 (4.0)	6 (2.4)	14 (5.6)	0	1 (2.8)	1 (4.3)	7 (2.0)	8 (2,2)
Injury, Poisoning and Procedural Complications	3 (1.5)	4 (1.9)	13 (5.2)	6 (2.4)	11 (4.4)	1 (2.9)	0	2 (8.7)	13 (3.7)	13 (3.6)
Vascular Disorders	2 (1.0)	2 (1.0)	2 (0.8)	6 (2.4)	9 (3.6)	1 (2.9)	1 (2.8)	1 (4.3)	2 (0.6)	6 (1.7)
Metabolism and Nutrition Disorders	2 (1.0)	0	7 (2.8)	9 (3.6)	11 (4.4)	1 (2.9)	0	1 (4.3)	3 (0.9)	2 (0.6)
Type 2 Diabetes Mellitus	0	0	2 (0.8)	3 (1.2)	2 (0.8)	1 (2.9)	0	1 (4.3)	0	0
Musculoskeletal and Connective Tissue Disorders	2 (1.0)	2 (1.0)	12 (4.8)	3 (1.2)	17 (6.8)	5 (14.7)	0	2 (8.7)	13 (3.7)	12 (3.4)
Arthralgia	0	0	0	0	5 (2.0)	3 (8.8)	0	1 (4.3)	2 (0.6)	1 (0.3)
Cardiac Disorders	1 (0.5)	1 (0.5)	9 (3.6)	2 (0.8)	7 (2.8)	0	1 (2.8)	0	5 (1.4)	5 (1.4)
Renal and Urinary Disorders	0	0	1 (0.4)	7 (2.8)	3 (1.2)	1 (2.9)	0	0	3 (0.9)	2 (0.6)
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)	1 (0.5)	1 (0.5)	6 (2.4)	1 (0.4)	6 (2.4)	0	0	1 (4.3)	6 (1.7)	3 (0.8)

Note: Table includes all related and not-related AEs reported for ≥ 2% of subjects in any treatment group within a study. Events are presented by SOC and PT.

Table 31 - Treatment-Related Non-Ocular Adverse Events Reported for ≥ 1% of Subjects by Netarsudil Phase 3 Clinical Study and Treatment

SOC	AR-13324-CS301		AR-13324-CS302			AR-13324-CS303			AR-13324-CS304	
	Netarsudil 0.02% QD PM (N=203) n (%)	Timolol 0.5% BID (N=208) n (%)	Netarsudil 0.02% QD PM (N=251) n (%)	Netarsudil 0.02% BID (N=253) n (%)	Timolol 0.5% BID (N=251) n (%)	Netarsudil 0.02% QD PM (N=34) n (%)	Netarsudil 0.02% BID (N=36) n (%)	Timolol 0.5% BID (N=23) n (%)	Netarsudil 0.02% QD PM (N=351) n (%)	Timolol 0.5% BID (N=357) n (%)
Nervous System Disorders	1 (0.5)	2 (1.0)	8 (3.2)	8 (3.2)	3 (1.2)	0	1 (2.8)	1 (4.3)	2 (0.6)	1 (0.3)
Headache	0	0	4 (1.6)	4 (1.6)	2 (0.8)	0	0	0	2 (0.6)	0
Dizziness	1 (0.5)	1 (0.5)	0	1 (0.4)	0	0	1 (2.8)	0	0	0
Disguesia	0	1 (05)	0	0	0	0	0	1 (4.3)	0	1 (0.3)
Skin and Subcutaneous Tissue Disorders	1 (0.5)	0	3 (1.2)	9 (3.6)	0	0	3 (8.3)	0	7 (2.0)	0
Dermatitis allergic	0	0	1 (0.4)	5 (2.0)	0	0	2 (5.6)	0	2 (0.6)	0
Dermatitis contact	1 (0.5)	0	1 (0.4)	3 (1.2)	0	0	1 (2.8)	0	3 (0.9)	0
Dermatitis atopic	0	0	0	0	0	0	1 (2.8)	0	0	0
Gastrointestinal Disorder	1 (0.5)	1 (0.5)	0	1 (0.4)	1 (0.4)	0	1 (2.8)	0	1 (0.3)	0
Nausea	0	1 (0.5)	0	0	1 (0.4)	0	1 (2.8)	0	0	0
Immune System Disorders	1 (0.5)	0	1 (0.4)	0	0	0	1 (2.8)	0	0	0
Drug hypersensitivity	1 (0.5)	0	1 (0.4)	0	0	0	1 (2.8)	0	0	0
Musculoskeletal and Connective Tissue Disorder	0	0-	0	0	1 (0.4)	1 (2.9)	0	0	0	0
Polychondritis	0	0	0	0	0	1 (2.9)	0	0	0	0
Respiratory, Thoracic and Mediastinal Disorder	0	1 (0.5)	1 (0.4)	0	2 (0.8)	0	1 (2.8)	0	0	2 (0.6)
Dyspnoea	0	1 (0.5)	0	0	1 (0.4)	0	1 (2.8)	0	0	1 (0.3)

Note: Table includes all related AEs reported for ≥ 1% of subjects in any treatment group within a study. Events are presented by SOC and PT.

Table 32 - Non-Ocular Adverse Events Reported in ≥ 2% of Subjects by Treatment Group in Netarsudil Phase 3 Studies (Pooled Safety Population)

SOC	Pooled Phase 3 Studies		
	Netarsudil 0.02% QD	Netarsudil 0.02% BID	Timolol 0.5% BID
	(N=839)	(N=289)	(N839)
PT	n (%)	n (%)	n (%)
Infections and Infestations	92 (11.0)	39 (13.5)	84 (10.0)
Upper respiratory tract infection	15 (1.8)	9 (3.1)	23 (2.7)
Nervous System Disorders	34 (4.1)	22 (7.6)	43 (5.1)
Headache	13 (1.5)	13 (4.5)	16 (1.9)
Skin and Subcutaneous Tissue Disorders	23 (2.7)	19 (6.6)	16 (1.9
Dermatitis Allergic	4 (0.5)	8 (2.8)	0

Events are presented by SOC and PT (MedDRA Version 19.0).

Serious adverse event/deaths/other significant events

Deaths

Four deaths were reported during the 10 completed clinical studies with netarsudil. These were not considered as related to the study treatment.

Table 33 - Deaths (All completed studies)

Subject	Study Number	Age (years)	Sex	Treatment Group	Adverse Event (PT)	Adverse Event Characteristics
123-019[1]	AR-13324-CS202	80	female	netarsudil 0.1% QD	acute leukemia	severe, not related
217-021	AR-13324-CS302	74	male	netarsudil 0.02% QD	myocardial infarction	severe, not related
258-002	AR-13324-CS302	82	male	netarsudil 0.02% QD	myocardial infarction	severe, not related
419-029	AR-13324-CS304	77	male	netarsudil 0.02% QD	cardiac arrest	severe, not related

1. Diagnosis of the AE that ultimately was the cause of death of the subject was made after she had completed the study.

Other Serious Adverse Events

Eighty-six (86) SAEs, which included 4 deaths, were reported during the 10 completed clinical studies with netarsudil. SAEs were reported by a total of 66 subjects with the greatest number of reports in the Cardiac Disorders SOC. The majority of SAEs were either moderate or severe in intensity. All SAEs were non-ocular with the exception of single ocular reports of ulcerative keratitis (severe, not-related), cataract (mild, not-related) and iridocyclitis (severe, possibly related).

Phase 3 Studies

Across the Phase 3 studies, a similar proportion of SAEs were reported in the netarsudil QD (1.5%, 3/203; 6.8%, 17/251; 0%; 2.3%, 8/351)) and timolol (1.9%, 4/208; 4.8%, 12/251; 4.3%, 1/23; 2.8%, 10/357) groups. A similar incidence of SAEs were reported for netarsudil BID (2.8%, 7/253 and 2.8% 1/36), which was tested in two Phase 3 studies (AR-13324-CS302 and AR-13324-CS303, respectively).

All SAEs were non-ocular with the exception of a single ocular report of cataract (mild, not related) for timolol and iridocyclitis (severe, possibly related) for netarsudil BID.

No SAEs occurred during the Phase 3 clinical trials which raise a concern regarding the safety of Netarsudil.

Two SAEs were considered by the Investigator to be related to study medication: exacerbation of coronary artery disease in a single subject in the netarsudil QD group and iridocyclitis in the netarsudil BID group.

As mentioned above only 1 other serious TEAE in the netarsudil QD group was ocular, namely, worsening cataract requiring surgical intervention. The event was considered not related to treatment.

All SAEs for the pooled safety population were almost all non-ocular and were reported in 3.3%, 2.8% and 3.2% of subjects in the netarsudil QD, BID and timolol groups, respectively.

Laboratory findings

Clinical Laboratory Evaluation

Laboratory parameters were assessed in the clinical development programme.

In general, there were no clinically significant changes in clinical chemistry or haematology in subjects exposed to netarsudil for up to 12 months. There were selected, sporadic, adverse events regarding abnormal values in selected categories. There was a single subject treated with netarsudil who was discontinued from the study due to an abnormal lab value (hypoglycemia). The relationship of that subject's discontinuation was judged as not related to study treatment. Thus, there was no evidence of clinical laboratory or haematology safety issues with netarsudil treatment.

Vital Signs, Physical findings and other observations related to safety.

Visual Acuity

Corrected distance visual acuity was assessed using an ETDRS or equivalent chart. Visual acuity testing preceded IOP measurement, the administration of topical anesthetic agents, or any examination requiring contact with the anterior segment. In order to standardize the assessment of visual acuity for a subject, all measurements were performed using the same lighting conditions and viewing distance. Visual acuity testing was performed in the Phase 1, 2 and 3 studies at the screening and/or qualifying, and post-randomization visits as outlined in Table 39 (Phase 1 and 2) and Table 40 (Phase 3).

The presentation of visual acuity results includes evaluations of mean changes from baseline and worst changes from baseline including a ≥3 line change. All visual acuity changes that were reported as AEs were identified in addition to any subjects that discontinued test article or study participation due to these events. Reductions in visual acuity were reported as AEs based on the judgement of the investigator.

Mean changes from baseline in visual acuity were small, similar among all treatment groups and not clinically relevant. An analysis of worst change from baseline in visual acuity demonstrated that the majority of subjects had less than a 1-line loss of vision. Higher incidences of subjects in the netarsudil groups (QD and BID) experienced a ≥3-line reduction in visual acuity compared to timolol. In addition,

higher incidences of AEs were reported for visual acuity reduced and more subjects discontinued test article or study participation with this event in the netarsudil groups compared to timolol.

Phase 1 and 2 Studies

In the Phase 1 studies, mean changes from baseline were small in the netarsudil groups ranging from 0.017 to 0.044 and a mean change of 0.02 (AR-13324 CS102). An analysis of worst change from baseline in visual acuity demonstrated that the majority of subjects had a worst change of less than a 1 line loss of vision in the netarsudil groups in Study AR-13324-CS101, (50.0%; 9/18 subjects) and Study AR-13324 CS102 (70.0%; 7/10 subjects). None of the subjects in either study experienced a ≥3-line loss of vision. No AEs were reported and no subjects discontinued test article or study participation due to a reduction in visual acuity.

In the Phase 2 studies, mean changes from baseline in the study eye visual acuity scores were small in the netarsudil QD groups across all studies: 0.01% (0.001 to 0.037); 0.02% (-0.019 to 0.021); 0.04% (-0.008 to 0.047). Similar results were obtained in the control groups in these same studies: vehicle (-0.032 to 0.026); latanoprost (-0.016 to 0.001). In the pilot study AR-13324-CS204, mean change from baseline in the study eye was comparable with the other Phase 2 studies (-0.003, netarsudil and no change in the vehicle group).

Similar results were obtained in the fellow eye.

An analysis of worst change from baseline in study eye visual acuity demonstrated that the majority of subjects in all of the Phase 2 studies had a worst change of less than a 1-line loss of vision. These results were similar across all netarsudil QD groups in these studies as follows: 0.01% (50.0 to 66.7%); 0.02% (66.6 to 85.7%); 0.04% (73.7%). Similar results were obtained in the control groups in these same studies as follows: vehicle: (60.9 to 100.0%); latanoprost (75.4%). Similar results were obtained in the fellow eye.

Six subjects in the netarsudil treatment groups (0.01%: 3; 0.02%: 2; 0.04%: 1) experienced a ≥3-line loss of vision as presented in Table 40. There was no evidence for a dose-response for this occurrence.

Two AEs were reported for visual acuity reduced (netarsudil 0.02% QD: 1; latanoprost: 1) and no subjects discontinued test article or study participation due to this AE as presented in Table 38. Similar results were obtained in the fellow eye.

Phase 3 Studies

In the Phase 3 studies, mean changes from baseline in the study eye visual acuity scores were small across the netarsudil QD (0.010 to 0.044); netarsudil BID (0.018 to 0.048), and timolol (-0.004 to 0.027) groups. Similar results were obtained in the fellow eye.

Within each treatment group, similar ranges were observed in the study eye for the following subgroups: age (<65 years vs ≥65 years), gender (females vs males), ethnicity (white vs other ethnicities) and iris color (blue/green/grey vs black/brown vs. hazel).

Within each treatment group, similar ranges were also observed in the fellow eye for the following subgroups: age (<65 years vs ≥65 years), gender (females vs males), ethnicitie (white vs other ethnicities) and iris color (blue/green/grey vs black/brown vs hazel).

Similar mean changes in visual acuity were also seen in the following subgroups; prior prostaglandin treatment, no prior prostaglandin treatment and no prior hypotensive therapy.

An analysis of worst change from baseline in study eye visual acuity demonstrated that the majority of subjects in the Phase 3 studies had less than a 1 line loss of vision. These results were similar across the

netarsudil QD (54.0%), netarsudil BID (51.9%), and timolol (66.7%) groups. Similar results were obtained in the fellow eye.

Sixty-eight subjects experienced a ≥3-line loss of vision across the Phase 3 studies in the netarsudil QD (3.8%), netarsudil BID (7.3%) and timolol (1.8%) groups. Similar results were obtained in the fellow eye.

Within each treatment group, similar non-clinically relevant differences were seen for the subgroups of age (< 65 years vs ≥65 years), gender (females vs males), ethnicity (white vs other races) and iris color (blue/green/grey vs black/brown vs hazel).

Eighty (80) AEs were reported for visual acuity reduced across the Phase 3 studies in the netarsudil QD (5.2 %), netarsudil BID (8.0%) and timolol (1.5 %) groups. More of these events were judged as related to test article in the netarsudil QD (65.9 %; 29 /44) and netarsudil BID (73.9 %; 17 /23) groups compared to timolol (38.5 %; 5 /13).

Eighteen (18) subjects discontinued test article due to the AE with visual acuity reduced as an AE at the exit visit across the Phase 3 studies. The incidence was higher with netarsudil QD (1.2 %, 10/839) and netarsudil BID (2.8%, 8 /289) compared to timolol 0%.

Table 34 - Incidence of Adverse Event and Subject Discontinuations for Visual Acuity Reduced in Netarsudil Phase 3 Studies (Pooled Safety Population)

	Pooled Phase 3 Population		
SOC	**Netarsudil 0.02% QD PM (N=839) n (%)**	**Netarsudil 0.02% BID (N=289) n (%)**	**Timolol 0.5% BID (N=839) n (%)**
Eye Disorders	609 (72.6)	249 (86.2)	225 (26.8)
Visual acuity reduced	44 (5.2)	23 (8.0)	13 (1.5)
Subject Discontinuations Associated with Visual Acuity Reduced	10 (1.2)	8 (2.8)	0

Table 35 - Worst Change in Visual Acuity Scores (logMAR) in the Study Eye at any Post-Treatment Visit in Phase 2 Studies* (Safety Population)

	AR-13324-CS201				AR-13324-CS202		
Change in Visual Acuity Scores (logMAR)	**Netarsudil 0.01% QD AM (N=22) n (%)**	**Netarsudil 0.02% QD AM (N=21) n (%)**	**Netarsudil 0.04% QD AM (N=19) n (%)**	**Vehicle QD AM (N=23) n (%)**	**Netarsudil 0.01% QD PM (N=75) n (%)**	**Netarsudil 0.02% QD PM (N=72) n (%)**	**Latanoprost 0.005% QD PM (N=77) n (%)**
0 or less	8 (36.4)	8 (38.1)	8 (42.1)	9 (39.1)	22 (29.3)	23 (31.9)	32 (41.6)
>0 to +0.09	3 (13.6)	10 (47.6)	6 (31.6)	5 (21.7)	28 (37.3)	25 (34.7)	26 (33.8)
+0.10 to +0.19	9 (40.9)	3 (14.3)	3 (15.8)	8 (34.8)	18 (24.0)	19 (26.4)	15 (19.5)
+0.20 to +0.29	0	0	1 (5.3)	1 (4.3)	5 (6.7)	4 (5.6)	4 (5.2)
+0.30 or more	2 (9.1)	0	1 (5.3)	0	2 (2.7)	1 (1.4)	0

Note: The worst change is defined as the largest positive change from baseline in the study eye across all post-treatment visits.
* Excluding AR-13324-CS204

Table 36 - Worst Change in Visual Acuity Scores (logMAR) in the Study Eye at any Post-Treatment Visit in Netarsudil Phase 3 Studies (Pooled Safety Population)

Change in Visual Acuity Scores (logMAR)	Pooled Phase 3 Population		
	Netarsudil 0.02% QD PM (N=839) n (%)	Netarsudil 0.02% BID (N=289) n (%)	Timolol 0.5%BID (N=839) n (%)
0 or less	187 (22.3)	57 (19.9)	247 (29.5)
>0 to +0.09	266 (31.8)	93 (32.5)	313 (37.4)
+0.10 to +0.19	275 (32.9)	80 (28.0)	223 (26.6)
+0.20 to +0.29	77 (9.2)	35 (12.2)	39 (4.7)
+0.30 or more	32 (3.8)	21 (7.3)	15 (1.8)

Note: The worst change is defined as the largest positive change from baseline in the study eye across all post-treatment visits.

Biomicroscopy

External examination of the eye and anterior segment were performed with slit lamp biomicroscopy using magnification consistent with clinical practice. The examination included an assessment of the eyelids, conjunctiva, cornea, anterior chamber, iris, pupil and lens. Biomicroscopy grading was done with the use of standardized scales provided in each of the study protocols. Biomicroscopy evaluations were performed in all Phase 1, 2 and 3 studies at the screening and/or qualifying, and post-randomization visits. Changes in biomicroscopy parameters were reported as AEs based on the judgment of the investigator. In addition, changes in biomicroscopy parameters were identified as clinically significant by the investigator.

In the Phase 2 studies, the major biomicroscopic finding observed with netarsudil treatment by the investigators was conjunctival hyperaemia. While this was in agreement with the AE reports of conjunctival hyperaemia (and related terms), the incidence of objective findings in biomicroscopy was less than with AEs. This difference was interpreted as the AEs including observations made by subjects at any time during the study versus observations made solely by the investigator during a biomicroscopic examination. Of note was the absence of other potential major findings (e.g., corneal edema, anterior chamber cells or flare).

The Phase 2 findings were predictive of the observations in the larger, longer-term Phase 3 studies with regards to conjunctival hyperaemia.

Other biomicroscopic findings with low incidence seen in the netarsudil treatment groups in the Phase 3 studies were lid erythema and lid edema. Corneal staining was observed with similar incidence in the netarsudil and timolol treatment groups. Cornea verticillata, as noted in Section on ADRs, was primarily recorded as “other” and captured as a TEAE, and thus not in these tables.

Thus, other than conjunctival hyperaemia, cornea verticillata, and to a lesser extent, lid edema and lid erythema, chronic treatment with netarsudil QD was similar to timolol in its ocular safety as judged by investigators with biomicroscopic evaluation.

Within each treatment group, similar non-clinically relevant results were observed for the subgroups of age (< 65 years vs ≥65 years), gender (females vs males), ethnicity (white vs other races) and iris color (blue/green/grey vs black/brown vs hazel). Similar results were also observed in the fellow eye.

The pooled Phase 3 analysis showed that higher incidences of conjunctival hyperaemia occurred in the netarsudil QD and BID groups in males versus females (QD: 60.5 vs. 50.0%; BID: 74.8 vs. 67.0%) and in white versus other ethnicities (QD: 61.3 vs. 34.1%; BID: 75.4 vs. 55.1%).

Higher incidences of cornea verticillata occurred in the netarsudil QD and BID groups in elderly (≥65 years) versus non-elderly (<65 years) (QD: 24.8 vs. 15.9%; BID: 30.7 vs. 23.0%), in males versus

females (QD: 24.4 vs. 18.4%; BID: 31.8 vs. 24.2%) and in white versus other ethnicities (QD: 25.6 vs. 7.0%; BID: 32.7 vs. 8.2%).

Results were also similar in terms of biomicroscopic examination in subjects with prior prostaglandin treatment, no prior prostaglandin treatment, and no prior hypotensive treatment.

Table 37 - Maximum Number of Subjects with a Clinically Significant Finding in Biomicroscopy Parameters in the Study Eye at any Treatment Visit in Netarsudil Phase 3 Studies (Pooled Safety Population)

Biomicroscopy Parameters	Pooled Phase 3 Population		
	Netarsudil 0.02% QD PM (N=839) n (%)	Netarsudil 0.02% BID (N=289) n (%)	Timolol 0.5% BID (N=839) n (%)
Lids			
Erythema	9 (1.7)	14 (5.0)	1 (0.3)
Edema	9 (1.7)	5 (1.8)	1 (0.4)
Conjunctiva			
Hyperaemia	74 (10.5)	52 (18.7)	5 (0.6))
Edema	6 (2.2)	11 (4.0))	0
Cornea			5 (0.6)
Staining	6 (2.2)	8 (2.9)	4 (0.5)
Edema	1 (0.3)	2 (0.9)	0
Anterior Chamber			
Cells	0	0	1 (0.1)
Flare	0	0	0
Lens			
Lens opacity (for phakic eyes)	8 (1.2)	4 (2.3)	7 (1.1)

Note: Biomicroscopy findings were determined to be clinically significant based upon an assessment by the Investigator. The N value reflects the total number of subjects in the Safety population. The actual number that had a biomicroscopic examination at any particular visit, may differ slightly as reflected in the percentages in this table.

Ophthalmoscopy

Dilated ophthalmoscopy was performed in the Phases 1, 2 and 3 clinical studies at the screening and post-randomization visits. The examination included an assessment of the retina, macula, choroid, optic nerve, and vitreous humor using a grading scale of normal or abnormal. Changes in ophthalmoscopy parameters were reported as AEs based on the judgment of the investigator. In addition, changes in ophthalmoscopy parameters were identified as clinically significant by the investigator.

For the most part, across all studies, there were relatively few changes in ophthalmoscopy, and the changes were similar across the treatment groups. This is reflected in the low rate of AEs associated with ophthalmoscopy.

Cup-Disc Ratio

Measurement of the vertical cup-disc ratio was performed as part of the dilated ophthalmoscopy examination in all clinical studies at the screening and post-randomization visits. The cup-disc ratio was scored on a scale of 0.1 to 1.0 units in 0.1-unit increments. AEs for any change in this parameter were

reported at the discretion of the investigator. A change from baseline of 0.2 units or more in either eye was defined as a clinically significant change.

Clinically significant changes from baseline in cup-disc ratio were only reported in the Phase 3 studies, with similar numbers reported across all treatment groups in both studies.

In the 12- month Phase 3 study (AR-13324-CS302), the mean cup-disc ratio baseline values were similar in the netarsudil and timolol groups and remained relatively constant over the treatment period. Isolated AEs reflective of changes in the optic nerve were reported but no patterns emerged.

Adverse events reflective of changes in the optic nerve were only reported in the 12-month studies. Study AR-13324-CS302 included 3 reports of optic nerve cup-disc ratio increased in the netarsudil QD (1 report) and BID (2 reports) groups and isolated reports of glaucomatous optic disc atrophy (netarsudil QD group) and optic nerve cupping (timolol group).

In study AR-13324-CS303 there were 3 reports of optic disc hemorrhage in the netarsudil BID (2 reports) and timolol (1 report) groups. Only one subject discontinued test article or study participation due to these events (AR-13324-CS302, netarsudil BID).

Isolated AEs reflective of changes in the optic nerve were reported but no patterns emerged.

Specular Microscopy

Specular microscopy was not performed in the Phase 1 or 2 studies. Specular microscopy was performed in one of the Phase 3 studies (AR-13324-CS302) at the qualifying (baseline) and month 3 visits. This testing was done at selected sites based upon the availability of a specular microscope. Prior to providing any corneal endothelial cell photographs, the study sites were certified by the centralized reading center. During the study, the sites provided 3 images of each eye and the data were submitted electronically via a web portal to the centralized reading center.

The specular microscopy parameters analyzed included endothelial cell density, coefficient of variation (variation in individual cell area; also known as polymegathism), and hexagonality (percentage of 6 sided cells; also known as pleomorphism). The presentation of the specular microscopy results to follow includes an evaluation of these parameters comparing baseline to month 3 values.

The endothelial cell density baseline values were similar in the netarsudil QD (2480 cells/mm2), netarsudil BID (2447 cells/mm2), and timolol (2455 cells/mm2) groups.

The mean changes from baseline to month 3 in cell density were small and not clinically relevant comparing the netarsudil QD (+1.7 cells/mm2), netarsudil BID (+16.8 cells/mm2), and timolol (-1.1 cells/mm2) groups as presented in AR-13324-CS302. Similar results were obtained in the study and fellow eyes.

The variation in individual cell areas was assessed by determining the coefficient of variation (polymegathism). The coefficient of variation values were almost identical at baseline across the netarsudil QD (32.4%), netarsudil BID (32.8%), and timolol (32.6%) groups. The mean changes from baseline to month 3 were very small and not clinically relevant comparing the netarsudil QD (-1.6%), netarsudil BID (-2.0%), and timolol (-1.4%) groups as presented in AR-13324-CS302. Similar results were obtained in the study and fellow eyes.

Finally, the hexagonality was assessed to determine the percentage of endothelial cells that were 6 sided (pleomorphism). The hexagonality values were almost identical at baseline across the netarsudil QD (59.5%), netarsudil BID (59.1%), and timolol (59.2%) groups. The mean changes from baseline to month 3 were very small and not clinically relevant comparing the netarsudil QD (-0.5%), netarsudil BID (-0.8%), and timolol (+0.7%) groups. Similar results were obtained in the study and fellow eyes.

In summary, the changes in endothelial cell density, coefficient of variation, and hexagonality were small and not clinically relevant based upon the 3 month on-therapy time point at which these parameters were assessed.

Pachymetry

Central corneal thickness was measured in both eyes using ultrasound pachymetry at screening in all Phase 2 and 3 studies, and also at follow-up in StudyAR-13324 CS202 (day 28). In this study, no subject experienced a criterion increase (100 µm) in central corneal thickness during the study (AR-13324-CS302).

Intraocular Pressure

Intraocular pressure was measured in the Phase 1, 2 and 3 studies at the screening and/or qualifying, and post-randomization visits. Two consecutive IOP measurements of each eye were obtained at various time points during each visit using a calibrated Goldmann applanation tonometer. Intraocular pressure was evaluated as a safety measure by identifying all on-therapy IOP increases ≥ 10 mmHg in all Phase 1 and 3 studies, and as an efficacy parameter in all of the Phase 2 and 3 studies.

In the 12-month Phase 3 studies, AR-13324-CS302 and AR-13324-CS303, IOP was measured at a single 08:00 hour time point at Months 6, 9 and 12. In study AR-13324-CS304 IOP was measured at 08:00, 10:00 and 16:00 hours throughout the duration of the study. Adverse events for any change in IOP were reported based on the judgment of the investigator.

Phase 1 Studies: No AEs for IOP were reported and there were no IOP increases ≥ 10 mmHg.

Phase 2 Studies:

Study AR-13324-CS201: No AEs for IOP reported.

Study AR-13324-CS202: There were 2 reports of “intraocular pressure fluctuation” and 1 report of “intraocular pressure increased”, all in the netarsudil 0.01% treatment group.

Study AR-13324-CS204: No AEs for IOP reported.

Phase 3 Studies

The pooled population included 19 reports of intraocular pressure increased in the netarsudil QD (14 reports), netarsudil BID (2 reports), and timolol (3 reports) groups. With the exception of 1 subject in the netarsudil QD group, these events were mild to moderate in intensity and 17 reports were considered related to test article (netarsudil QD: 12; netarsudil BID: 2; timolol: 3). Fourteen (14) of the subjects (netarsudil QD: 11; netarsudil BID: 1; timolol: 2) discontinued test article or study participation due to this event.

A total of 4 reports (0.5%) of IOP increase ≥10 mmHg at any post-baseline visit were recorded in the study eye for the netarsudil QD treatment group, with no reports in the netarsudil BID or timolol groups. Four fellow eyes of subjects in the netarsudil QD group experienced an IOP increase of ≥ 10 mmHg.

Vital Signs

Blood pressure and heart rate were measured in all Phase 1, 2 and 3 studies at the screening and/or qualifying, and post-randomization visits. Adverse events for any change in vital signs were reported based on the judgment of the investigator.

The presentation of the blood pressure and heart rate results includes an evaluation of the mean changes from baseline values at all on-therapy visits with an emphasis on the maximal changes observed.

Phase 1 and 2 Studies

In these studies, the changes from baseline in systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR) were generally small and not clinically relevant.

In Study AR-13324-CS101, the mean changes from baseline are SBP (+3.2 mmHg), DBP (+3.9 mmHg), and HR (-13.1 bpm). Even though some of the mean HR values were reduced by 10 bpm or more, none of the mean values at any visit fell below 60 bpm which is within the normal range for the healthy subjects that participated in this study.

No AEs consistent with any vital sign changes were reported.

In Study AR-13324-CS102, the mean changes from baseline in SBP (-8.4 mmHg), DBP (-2.0 mmHg), and HR (+2.2 bpm) were small and not clinically relevant. No AEs consistent with any vital sign changes were reported.

-In the Phase 2 studies, the mean changes from baseline in SBP, DBP, and HR were small and similar comparing the treatment groups across all Phase 2 studies. There were no dose-related changes in any of these parameters comparing the netarsudil groups and none of these mean changes were clinically relevant.

-Mean changes in SBP in the netarsudil 0.01% (-3.0 to -2.3 mmHg), 0.02% (-2.2 to 1.9 mmHg), and 0.04% (2.8 mmHg) groups were comparable to changes in the vehicle (-5.1 to -0.3 mmHg) and latanoprost (-2.1 to -0.5 mmHg) control groups.

-Mean changes in DBP in the netarsudil 0.01% (-2.0 to 3.1 mmHg), 0.02% (-2.0 to 1.4 mmHg), and 0.04% (-3.1 mmHg) groups were also comparable to changes in the vehicle (-3.0 to 0.8 mmHg) and latanoprost (-1.1 to -0.2 mmHg) control groups.

-Similarly, mean changes in HR in the netarsudil 0.01% (-1.0 to 3.5 bpm), 0.02% (-2.7 to +1.0 bpm), and 0.04% (-2.5 bpm) groups were comparable to changes in the vehicle (2.9 to 16.0 bpm) and latanoprost (-1.6 to -0.3 bpm) groups.

No AEs consistent with any vital sign changes were reported in the Phase 2 studies.

Phase 3 Studies

The vital sign parameters were assessed across all Phase 3 studies. With respect to the pooled analysis, mean changes over the study in SBP in the netarsudil QD (-3.7 to -0.4 mmHg) and netarsudil BID (-2.4 to +0.6 mmHg) groups were comparable to the timolol group (-2.2 to -0.1 mmHg).

Mean changes in DBP in the netarsudil QD (-1.2 to +0.4 mmHg) and BID (-2.7 to +0.5 mmHg) groups were also comparable to the timolol group (-1.5 to +0.3 mmHg).

Changes in mean HR in the timolol group demonstrated statistically significant reductions from baseline and ranged from -1.5 to -3.0 bpm. In comparison there were no statistically significant reductions in mean HR in the netarsudil groups (QD [-1.3 to +0.9 bpm] and BID [-1.1 to +0.4]) except for a single visit in the netarsudil QD group in AR-13324-CS302 (1.3 bpm) (ISS Table 14.3.6.1).

Several AEs reflective of changes in vital signs were reported across the four Phase 3 studies. These included 12 reports of blood pressure increased across the netarsudil QD (4 reports), netarsudil BID (3 reports), and timolol (5 reports) groups. These events were mild to moderate in intensity and considered not related to test article. Two additional AEs of heart rate irregular were reported in the netarsudil QD group (AR-13324-CS302). These events were mild in intensity and 1 was considered related to test article; neither of these events led to discontinuation of test article or study participation. In addition, there was 1 report of heart rate reduced in the timolol group; this event was moderate in intensity and considered possibly related to test article and the subject was discontinued from the study

Summary

In summary, the mean changes from baseline in SBP, DBP, and HR were generally small and not clinically relevant in subjects treated with netarsudil. In subjects treated with timolol, there was a statistically significant reduction in mean heart rate. One report of heart rate reduced in the timolol group was considered possibly related to test article and the subject was discontinued from the study. Several AEs were reported for blood pressure increased and heart rate irregular; none of the affected subjects discontinued test article or study participation due to either of these events.

Safety in special populations

Intrinsic Factors

All of the safety parameters evaluated in the Phase 3 studies were analyzed based on various intrinsic factors that included age category, race, sex, and iris color. These analyses were conducted after pooling these data from the four netarsudil Phase 3 studies. For the most part, there was no difference between netarsudil ophthalmic solution 0.02% QD and timolol ophthalmic solution 0.5% BID with respect to differences in their safety profiles across demographic groups.

The key findings from these pooled analyses showed some statistically significant but not clinically relevant differences between subgroups as follows:

1. Whites had a higher incidence of both overall adverse events and ocular adverse events when compared to subjects of other ethnicities for both netarsudil and timolol. The comparative incidences (white vs. other races) of ocular events were as follows: netarsudil QD (89.0 vs. 66.8%); netarsudil BID (93.8 vs. 80.8%); timolol (64.2 vs. 50.0%).
2. An analysis of adverse event severity indicated that in the netarsudil treatment groups, white subjects had greater incidences of moderate and severe adverse events compared to subjects of other races.
3. Higher incidences of conjunctival hyperaemia occurred in the netarsudil QD and BID groups in males versus females (QD: 60.5 vs. 50.0%; BID: 74.8 vs. 67.0%) and in white versus other ethnicities (QD: 61.3 vs. 34.1%; BID: 75.4 vs. 55.1%).
4. Higher incidences of cornea verticillata occurred in the netarsudil QD and BID groups in elderly (≥65 years) versus non-elderly (<65 years) (QD: 24.8 vs. 15.9%; BID: 30.7 vs. 23.0%), in males versus females (QD: 24.4 vs. 18.4%; BID: 31.8 vs. 24.2%) and in white versus other ethnicities (QD: 25.6 vs. 7.0%; BID: 32.7 vs. 8.2%).

In addition, there were also no notable differences observed between subjects with no prior ocular hypotensive treatment versus previously treated subjects, and no differences between prior prostaglandin use and no prior prostaglandin use).

An analysis of safety in subjects with concomitant systemic medications was not performed since the systemic exposure to netarsudil has been shown to be negligible.

Extrinsic Factors

The recommended dosage of netarsudil ophthalmic solution 0.02% is 1 drop instilled into the eye QD for all patients. Therapy is not individualized based upon extrinsic factors and thus an analysis of safety by extrinsic factors is not applicable.

Use in Pregnancy and Lactation

There are no adequate or well-controlled studies using netarsudil in pregnant women.

The clinical studies conducted during the development of netarsudil excluded women of childbearing potential who were pregnant, nursing, planning a pregnancy, or not using a medically acceptable form of birth control.

During the clinical development of netarsudil, one pregnancy was reported in a female subject who was enrolled in the Phase 3 Study AR-13324-CS302 and received test article for 87 days with the last dose on 25 February 2015 at which time the subject discontinued from the study due to a protocol violation (failure to use acceptable form of contraception and a positive pregnancy test). The subject had a negative pregnancy test at the screening visit and was using a condom/spermicide as a form of contraception. The outcome of the pregnancy was the delivery of a healthy baby at 37 weeks gestation.

Immunological events

No immunological events were reported.

Safety related to drug-drug interactions and other interactions

No specific drug-drug interaction studies were performed during the clinical development of netarsudil (also due to the lack of systemic absorption of netarsudil after ocular dosing) and none were reported.

Netarsudil ophthalmic solution has been administered safely in conjunction with other ophthalmic medications and diagnostic agents to include antibiotics, anesthetics, cycloplegics, mydriatics, ocular lubricants, and vital dyes. Netarsudil ophthalmic solution was also used in a fixed dosed combination with latanoprost.

The applicant has provided general recommendations in the SmPC relating to the concomitant use of other topically administered ocular preparations, it is noted that these recommendations are largely based on extrapolation from general administration recommendations from other ocular medicines rather than on specific data from netarsudil use. As netarsudil is a new active substance, it would be preferable to further explore this topic and the applicant has agreed to further evaluate this issue through the PASS.

In section 4.2 of the proposed SmPC, the applicant includes specific guidance for HCPs and patients outlining that a period of 5 minutes should be observed before other topical ocular preparations are administered following netarsudil administration. Recommendation with regards to the order of administration of different ocular preparations is also included.

Discontinuation due to adverse events

Phase 1 Studies

All but one subject completed the Phase 1 studies. One subject in the AR-13324-CS102 study discontinued early due to an AE.

Phase 2 Studies

Nearly all subjects in the Phase 2 studies completed their respective study. Only 9 subjects of 209 (4.3%) exposed to netarsudil were discontinued from a Phase 2 study (Table 16), 2 of which (1.0%) discontinued for AEs.

No subjects discontinued early from study AR-1332-CS204, for any reason, including AEs.

Phase 3 Studies

The discontinuation rates in the longer duration Phase 3 studies were higher than in Phase 2. In the Phase 3 studies a greater proportion of subjects in the netarsudil groups compared with the timolol group

discontinued study participation prior to completing the study (15.3% QD vs. 6.2% timolol in AR-13324-CS301; 41.8% QD; 66.1% BID vs. 18.7% timolol in AR-13324-CS302; 52.9% QD; 88.9% BID vs. 17.4% timolol in AR-13324-CS303; and 30.8% QD vs. 12.0% timolol in AR-13324-CS304).

In the pooled population, the majority of discontinued netarsudil QD and BID subjects were discontinued due to AEs (174/264 [65.9%] and 161/198 [81.3%], respectively).

The most frequent reason for discontinuation of timolol subjects was AE and withdrawal of consent, each 26.4% (28/106 subjects) (Table 17). Non-compliance with study medication and lack of efficacy were observed in only small numbers of subjects across treatment groups and studies.

In the pooled analysis of the 4 AR-13324 Phase 3 studies, a total of 575 (68.5%) netarsudil QD, 91 (31.5%) netarsudil BID and 733 (87.4%) timolol BID subjects completed the full study duration. Conversely, a greater proportion of subjects discontinued study participation in the netarsudil groups (31.5% QD, 68.5% BID) compared to timolol (12.6%). The most frequent reason for discontinuation was AE: 65.9% netarsudil QD, 81.4% netarsudil BID, and 26.4% timolol.

Discontinuation for Adverse Events in the Pooled Phase 3 Population

In the pooled analysis, discontinuations of test article due to TEAEs were highest in the netarsudil BID group (54.3%) followed by netarsudil QD group (19.3%,) and timolol group (1.7%).

The majority of discontinuations in the netarsudil QD and BID groups were associated with ocular events, whereas the majority of discontinuations in the timolol groups were associated with non-ocular events.

The most frequently reported (≥5% of subjects) TEAEs associated with test article discontinuation in the netarsudil groups were conjunctival hyperaemia (QD: 5.8%; BID: 26.3%), cornea verticillata (QD: 3.7%; BID: 10.0%), and vision blurred (QD: 1.4%; BID: 6.9%).

In the pooled analysis of the 4 AR-13324 Phase 3 studies, a total of 575 (68.5%) netarsudil QD, 91 (31.5%) netarsudil BID and 733 (87.4%) timolol BID subjects completed the full study duration. Conversely, a greater proportion of subjects discontinued study participation in the netarsudil groups (31.5% QD, 68.5% BID) compared to timolol (12.6%). The most frequent reason for discontinuation was AE: 65.9% netarsudil QD, 81.4% netarsudil BID, and 26.4% timolol.

Post marketing experience

Netarudil ophthalmic solution 0.02% was approved for use in patients with OAG / OHT by the US FDA on 17th December 2017. At the cut-off point 30 April 2018, 5 medical reports of AEs had been received following use of netarsudil.

2.6.1. Discussion on clinical safety

The assessment of the clinical safety data for netarsudil 0.02% was largely based around the phase 2 and phase 3 clinical studies with netarsudil 0.02% once daily versus active comparator timolol. Data on the use of netarsudil 0.02% administered twice daily was also presented although this specific posology is not being pursued.

In general, the sample size and the safety population included in the main studies are considered appropriate for the overall safety analysis.

In several of the clinical studies, the dosage of netarsudil 0.02% ophthalmic solution was administered topically as either a once daily or twice daily administration. There was an increased frequency of AEs with Netarsudil 0.02% when administered twice daily versus once daily.

In this context, 969 patients were exposed to once daily dosing with Netarsudil 0.02% solution in the clinical development for the mono constituent product.

Additional exposure data for netarsudil 0.02% is provided via the parallel clinical development for the FDC product. This is considered supportive data.

Broadly speaking, the studied population is considered representative of the target population that is expected to receive Netarsudil 0.02% solution and this is acceptable.

The demographic characteristics of patients included in the phase III clinical studies for netarsudil 0.02% once daily included patients ranging in age from 14-96 years with a mean age of 64.9 years. In patients treated with netarsudil 0.02% once daily, 55.8% of patients were ⩾65 years, reflective of the target population. Paediatric patients under 18 years were not specifically studied. This is acceptable given the proposed target population.

A higher number of patients treated with netarsudil 0.02% in the phase III safety population had a diagnosis of open-angle glaucoma (64.4%). 35.6 % of patients had a diagnosis of ocular hypertension.

Almost 75% of patients treated with netarsudil 0.02% once daily in the phase III safety population were Caucasian. The applicant clarified that a higher number of Caucasian subjects were enrolled in all netarsudil studies, which is comparable with the distribution of ethnicities enrolled in studies conducted for other approved ocular hypotensive medications. Of note, the incidence of AEs in Caucasians was approximately 1.3-times higher compared to other ethnicities in both the timolol and netarsudil treatment groups so the applicant does not believe that these data represent a safety signal for Caucasians treated with netarsudil.

An update on any evolving data from ongoing studies and post-marketing experience was presented by the applicant and no new safety concerns arise.

Duration of exposure is in general between 6- 12 months. Within the netarsudil treatment group, 361 subjects were exposed to netarsudil 0.02% once daily for a duration of 6 months to 12 months. In addition, a total of 252 subjects completed over 12 months of therapy with netarsudil 0.02% once daily.

The applicant was asked to provide an overview of longer term safety specific to the use of netarsudil 0.02% once daily beyond 12 months. It was highlighted to the applicant that this is a new active substance for the topical treatment of glaucoma, a condition which generally requires chronic long term treatment. In this context, there was a concern that some adverse events either already established or evolving could occur or worsen after several months to years of netarsudil treatment (eg. possible adverse impact of long-term corneal deposition on visual acuity, punctate keratitis, potential for periocular skin hyperpigmentation or discolouration/ iris hyperpigmentation due to possible melanin binding, and adverse changes in cornea due to chronic administration of BAK), the overall duration of exposure of the proposed product is therefore considered somewhat limited in this context. In the responses to the day 120 LoQ, the applicant acknowledged the absence of longer term safety data with netarsudil 0.02% and proposed to address this issue through a PASS to evaluate longer term safety of netarsudil in the proposed indication. This proposal is endorsed.

The majority of AEs reported for either treatment group during the safety clinical trials were local ocular events.

Based on the existing PK data, the potential for systemic absorption following topical ophthalmic administration of Netarsudil in human subjects is low. Therefore, pharmacologically related ADRs with the use of Netarsudil 0.02% Solution are expected to be local ocular effects with a very low chance of systemic ADRs. This is in line with the data from the netarsudil clinical studies.

The most frequent adverse event associated with the use of Netarsudil 0.02% solution is hyperaemia of the eye. Hyperaemia of the eye generally occurs with the onset of use and generally subsides or resolves over time though it can occur sporadically. The majority of cases were mild. The incidence of hyperaemia was dose related. The incidence was reduced when netarsudil was administered as an evening dose versus morning administration. The incidence of conjunctival hyperaemia in phase II studies associated with once daily netarsudil administered in the evening was 38.9% (versus vehicle 4.3% and latanoprost 15.6%).

Non-ocular AEs were rarely reported for netarsudil in the phase II studies.

AEs observed in the pooled Netarsudil safety data from phase 3 studies:

Long-term safety data from clinical trials was provided in the 3, 6 and 12 month Phase 3 studies (AR-13324 CS302, AR-13324-CS303, and AR-13324-CS304) which included a total of 1,556 subjects across the netarsudil QD (636 subjects), BID (289 subjects), and timolol (631 subjects) groups. Within the netarsudil treatment group, 361 subjects were exposed to netarsudil 0.02% once daily for a duration of 6 months to 12 months.

Overall, the majority of adverse drug reactions associated with the use of Netarsudil 0.02% solution have been mild local ocular side-effects that tend to increase in incidence (and sometimes severity) in a dose-dependent manner.

In the pooled Phase 3 safety population, the majority of TEAEs were mild in intensity. It is noted that more patients in the timolol group experienced mild TEAEs (73.3%) versus netarsudil 0.02 % QD group (58.5%). However, a higher percentage of subjects in the netarsudil group (QD: 73.1%) compared to those in the timolol group (42.3%) experienced AEs that were considered treatment related.

Although many of these local ocular side-effects generally improve and resolve over time, a high percentage of cases can also occur sporadically eg. Ocular hyperaemia. This could potentially impact on patient compliance with long term treatment but this has to be balanced against the potential for greater systemic ADRs which are known to occur with other currently approved glaucoma treatments.

As outlined in the above tables, the majority of ADRs reported during the study were for local ocular effects. Exposure to Netarsudil 0.02% once daily versus twice daily resulted in a lower incidence of ADRs.

In the subgroup analyses in the pooled Phase 3 population, white patients had a higher incidence of both overall adverse events and ocular adverse events when compared to subjects of other races. The comparative incidences (white vs. other races) of ocular events were as follows: netarsudil QD (89.0 vs. 66.8%); timolol (64.2 vs. 50.0%). These patients also had a greater incidence of moderate and severe adverse events compared to subjects of other races.

The applicant clarified that a relative difference in the safety profile between sub populations could only be demonstrated if randomization was stratified by sub group, it therefore cannot be concluded that there is true difference between the Caucasian and “Other” ethnicities in the safety profiles for netarsudil as the study design did not apply a stratified randomization schedule based on subgroups Caucasian vs. “Other” ethnicities. A higher number of Caucasian subjects were enrolled in all netarsudil studies, which is comparable with the distribution of ethnicities enrolled in studies conducted for other approved ocular hypotensive medications. Of note, the incidence of AEs in Caucasians was approximately 1.3-times higher in both the timolol and netarsudil treatment groups.

Hyperaemia

The most common ADR reported across all studies in the safety population was hyperaemia of the eye.

A numerically lower incidence of hyperaemia of the eye was reported in the comparator Timolol solution group relative to the Netarsudil 0.02% solution (at both once daily and twice daily dosing) (11.8% and

14.5%, respectively). The severity of conjunctival hyperaemia was similar between the 2 treatment groups as approximately 90% of the reports in each group were assessed as mild. In both the phase II and phase III studies, the incidence of conjunctival hyperaemia was notably higher for once daily netarsudil 0.02% when compared to either latanoprost (netarsudil 38.9% versus latanoprost 15.6%) or timolol (54.4% versus 10.4%).

The ocular tolerability findings associated with netarsudil are reflected in the proposed SmPC and these local ADRs have to be balanced against the point that other approved glaucoma treatments may have greater potential for systemic ADRs or may be contraindicated in the glaucoma population due to co-morbid medical conditions.

Long term safety of netarsudil, including discontinuation rates due to ocular ADRs will be followed up through routine pharmacovigilance and through the proposed PASS.

Conjunctival haemorrhage

The incidence of conjunctival hemorrhage across the four Phase 3 studies appeared to be notably higher in the netarsudil groups (QD: 15.8 to 20.6%) compared to timolol (0.8 to 3.1%). When present, conjunctival hemorrhage was typically reported as mild and was considered treatment-related.

This ADR is reflected in the SmPC and ocular safety will be followed in the planned PASS study for long term treatment with netarsudil.

Corneal verticillata

In the long term studies, corneal verticillata were commonly reported in approximately 20% of patients treated with netarsudil 0.02% QD. By comparison, corneal verticillata were only reported in 0.2% of patients treated with timolol.

The proposed pathophysiology appears to be similar to the established process of drug-induced phospholipoidosis observed with other medicines, most commonly amiodarone. The applicant conducted a Corneal Deposit Observation Study (AR-13324-OBS01) to further evaluate visual function in subjects who developed corneal deposits in the AR-13324-CS301 and -CS302 clinical studies. At the completion of the observational study, there was no clinically meaningful impact of corneal verticillata on visual function as measured by visual acuity, contrast sensitivity, and a visual function questionnaire. Corneal verticillata were noted to have resolved in all but 3 subjects (4 eyes); in these 3 subjects the corneal deposit grade had decreased and the event stabilized by the completion of the study. After study completion, cornea verticillata resolved in 1 of these subjects and had improved in the other 2 subjects (3 out of 4 eyes). It is noted that corneal deposits or verticillata generally resolved on discontinuation of netarsudil.

In view of the chronic nature of glaucoma treatment and since netarsudil is a new active substance, it would be helpful if further clinical experience beyond one year duration of treatment was available in order to further confirm the clinical behaviour of netarsudil-induced corneal deposits with real-world chronic use of netarsudil 0.02% QD.

The applicant was asked to discuss the issue of corneal veticillata further in the context of any additional post-marketing data available since submission of this application and any additional PV measures required for longer term follow-up. In acknowledging the absence of longer term safety data with netarsudil use in the proposed indication, the applicant proposed to conduct a PASS to further evaluate longer term safety of netarsudil in the proposed indication. This is supported.

The applicant also acknowledges that the incidence of corneal verticillata was higher in certain subpopulations (elderly patients (≥65 years), in male patients and in white patients versus other races). This has been reflected in the SmPC.

Data from slit lamp examination from the pooled safety population indicated that higher incidences of corneal verticillata occurred in the netarsudil QD and BID groups in elderly (≥65 years) versus non-elderly (<65 years) (QD: 24.8 vs. 15.9%; BID: 30.7 vs. 23.0%), in males versus females (QD: 24.4 vs. 18.4%; BID: 31.8 vs. 24.2%) and in white versus other ethnicities (QD: 25.6 vs. 7.0%; BID: 32.7 vs. 8.2%).

The difference in the incidence of cornea verticillata between subgroups is statistically significant for Females vs. Males (p=0.0354, netarsudil QD and p=0.0150 for netarsudil QD and BID combined), and highly statistically significant between Caucasian and "Other" ethnicities (p<0.0001 both for netarsudil QD alone and combined with netarsudil BID) and between subgroups of age <65 yr vs. ≥65 yrs (p=0.0017 for netarsudil QD and p=0.0008 for QD and BID combined)

No specific hypothesis is available in relation to these findings. The applicant postulates that the differences observed between the subgroups might be related to differences in the rate of corneal metabolism of netarsudil but there is no robust justification to support this at this time.

The applicant states that in all cases, patients were asymptomatic and visual function was not impacted by the presence of cornea verticillata and argues that the differences between subgroups does not appear to be of clinical significance.

Nevertheless, in view of the remaining uncertainty around unexplained higher rates of verticillata in certain subpopulations and given that this is a new active substance, it is recommended that this issue should be further followed in the PASS in an effort to provide additional insights into these findings.

The applicant acknowledges that the incidence of corneal verticillata was higher in certain subpopulations (elderly patients (≥65 years), in male patients and in white patients versus other races). This has been reflected in the SmPC.

Other ocular AEs

Other ocular AEs of note which were reported at a higher frequency in the netarsudil 0.02% QD group when compared to timolol 0.5% BD were:

Blurred vision: 7.4% (netarsudil) versus 1.4%(timolol)

Increased lacrimation: 7.2% (netarsudil) versus 0.6% (timolol)

Reduced visual acuity: 5.2% (netarsudil) versus 1.5% (timolol)

Although these AEs occur at a lower frequency when compared to the commonly reported AEs of conjunctival hyperaemia, conjunctival haemorrhage and corneal verticillata, these are still considered important in the context of the characterisation of the overall safety profile of netarsudil and in terms of patient compliance with long term treatment which will be followed up in the PASS.

It is noted that a higher percentage of the following AEs of relevance occurred in the netarsudil 0.02% QD population when compared to timolol.

Eyelid erythema: 6.8% (netarsudil) versus 0.7% (timolol)

Eye pruritus: 4.1% (netarsudil) versus 0.8% (timolol)

Eyelid oedema: 3.5% (netarsudil) versus 0.7% (timolol)

Eyelid pruritus: 2.1% (netarsudil) versus 0.2% (timolol)

Allergic conjunctivitis: 2.5% (netarsudil) versus 0.1% (timolol)

It is noted that instillation site pain occurred at a similar frequency across netarsudil 0.02% and timolol treatments (19.9% versus 21.6%).

Benzalkonium Chloride (BAK)

The applicant has highlighted the potential concerns with long term continuous use of BAK in chronic long term use. Nevertheless, it is acknowledged that similar concentrations of BAK are found in other currently approved ocular treatments for glaucoma.

The possible influence of BAK on the higher frequency of ocular ADRs generally observed with netarsudil 0.02% in terms of its contribution to these findings is difficult to quantify. Cases of punctate keratitis n=27, known to be associated with BAK were observed with netarsudil 0.02% QD in the pooled safety population (3.2%). Cases of punctate keratitis were also reported with timolol but at a lesser frequency (1.8%).

The potential effect of BAK on contact lenses is reflected in the proposed SmPC in line with the most recently updated EU Excipient Guidelines.

During the CHMP SA procedure, there were discussions regarding the concentration of BAK in the proposed product and the applicant considered that removal or reduction of the BAK concentration could be feasible going forward. Furthermore, in the responses to the clinical safety query on BAK, the applicant acknowledges the potential for future improvements on the benefit risk profile of the product as regards the concentration of this preservative. While the applicant maintains that the safety of the existing concentration is widely established and in line with other approved products, which is acknowledged, given the ocular tolerability profile of the current formulation and in order to optimise the benefit-risk profile in the proposed indication, the applicant was asked to provide an update on whether work was ongoing to enhance the benefit-risk of netarsudil 0.02% with specific reference to the issue of BAK in the context of the EMA SA advice.

The applicant confirmed that it is actively pursuing the re-formulation aspects of the product and proposals for a revised bridging study based on previous CHMP SA have been submitted. The applicant's general proposals for the re-formulation and for the bridging study are considered broadly acceptable.

Conclusion on ocular AEs

In summary, based on the above findings from the pooled safety data, it is noteworthy that ocular intolerance to Netarsudil 0.02% was notably higher when compared to the timolol treatment group. A higher frequency of local AEs were reported consistently across the pooled clinical safety studies for netarsudil, including at the 0.02% QD posology for the proposed formulation. As outlined above, numerically higher percentages of ocular AEs were reported in the netarsudil 0.02% QD treatment group for the ADRs conjunctival hyperaemia, ocular hyperaemia, conjunctival haemorrhage, corneal deposits, eye irritation, eye pain, eye pruritus, eyelid pruritus, reduced visual acuity, increased lacrimation and blurred vision when compared to timolol.

It is noted that in patients with either ocular hypertension or open-angle glaucoma, pharmacological treatment focuses on reducing intraocular pressure (IOP) in order to delay or prevent the progression of ocular hypertension to glaucoma, and to slow disease progression in glaucoma patients. In both cases, patients require lifelong treatment and follow-up care to preserve vision, so long-term patient compliance and persistence with glaucoma medication is essential since patients who do not continue therapy risk developing elevated IOP levels and, over time, progressing to blindness.

Compliance with treatment depends on many factors, including patient satisfaction with medication, medication costs, ease of medication administration and patient understanding of the importance of taking their medication over the long term, although one of the most important factors is local and systemic side effects. (Honrubia et al, 2009).

Currently, first-line treatment usually consists of monotherapy with a topical hypotensive drug. Although ophthalmologists traditionally have prescribed beta-blockers as first-line ocular hypotensive therapy, due

to the possibility of producing systemic side effects, other therapeutic options are currently preferred, with prostaglandin analogues being one of the most widely used.

The occurrence of conjunctival hyperaemia and other local ocular ADRs at such a high frequency in the netarsudil group when compared to timolol, although usually mild in intensity, is therefore of some concern because this may have a negative impact on whether the patient takes the proposed treatment as directed and complies with long term treatment over time. Nevertheless, the value of netarsudil in the treatment of glaucoma has to be considered in the context of existing treatments some of which have greater potential for systemic side effects. The ocular tolerability associated with netarsudil can be viewed in this context and the local adverse effects experienced with netarsudil can be clearly reflected in the product information. In addition, longer term safety of netarsudil will be followed through the proposed PASS.

Non-ocular ADRs:

When compared to ocular ADRs, non-ocular ADRs with netarsudil were infrequently observed in the clinical studies.

In the phase 2 studies, the most frequently reported nonocular AEs across all netarsudil treatment groups included headache (1.3 to 4.8%) and nasopharyngitis (1.4 to 3.8%) which were reported at similar incidences for the latanoprost groups (1.4 to 2.6%) in these same studies.

In the pooled safety analysis, the most frequently reported non-ocular AEs in the netarsudil treatment groups included upper respiratory infection (QD: 1.8%; BID: 3.1%), headache (QD: 1.5%; BID: 4.5%) and allergic dermatitis (QD: 0.5%; BID: 2.8%). Similarly, low incidences of these events were reported for the timolol group.

Treatment-related non-ocular TEAEs were reported in single subjects within a treatment group with the exception of dermatitis allergic (netarsudil QD: 3 subjects, 0.4%), dermatitis contact (netarsudil QD: 5 subjects, 0.6%), headache (netarsudil QD: 6 subjects, 0.7%, timolol: 2 subjects, 0.2%), dizziness (netarsudil BID: 2 subjects, 0.7%), dysgeusia (timolol: 3 subjects, 0.4%), bradycardia (timolol: 2 subjects, 0.2%), nausea (timolol: 2 subjects, 0.2%), hypersensitivity (netarsudil QD: 2 subjects, 0.2%) and dyspnea (timolol: 3 subjects, 0.4%).

No specific safety concerns arise.

Serious AEs

Serious AEs were infrequently reported and occurred at a similar frequency across the netarsudil and timolol treatment groups. The majority of cases were systemic rather than ocular reports. Based on the available PK data, netarsudil is unlikely to cause systemic effects due to negligible systemic absorption.

Only two SAEs were considered as related to the study drug as reported by the investigator. The first case was a non-ocular case of an exacerbation of coronary artery disease. The case narrative for this SAE report indicates that the case was confounded by multiple co-morbid medical conditions including previous coronary artery disease. The second was a case iridocyclitis reported in the netarsudil 0.02% twice daily treatment group.

No ocular SAE reported was considered related to netarsudil 0.02% at once daily dosage.

Laboratory findings

In the pooled safety population, more patients in the netarsudil treatment groups experienced loss of > 3 lines of vision when compared to timolol. The rate was numerically higher and almost double in the netarsudil 0.02% QD treatment group and notably higher in the netarsudil 0.02% BD group (netarsudil

QD =3.8%, netarsudil BD= 7.3% versus timolol 1.8%) when compared to timolol. However, no specific factors involved in loss of VA >3 lines could be established from the available data. It is recommended that this topic should continue to be routinely monitored.

In the netarsudil treatment groups, 3 cases of corneal oedema were reported on slit lamp examination (1 case in QD dose and 2 in the BD netarsudil treatment groups). No cases of corneal oedema were reported in the timolol group. Corneal staining on slit lamp examination was reported at a higher frequency in both netarsudil treatment groups when compared to timolol (netarsudil 0.02% QD = 2.2%, netarsudil 0.02% BD=2.9% versus timolol 0.5%). This in line with the AEs reports findings.

No safety concerns arise from the data related to Specular microscopy. No data from specular microscopy beyond 3 months duration of netarsudil treatment is available.

The changes in heart rate and blood pressure across the netarsudil and timolol treatment groups were similar. Minor fluctuations in BP and HR did not result in discontinuation from treatment. Unsurprisingly, subjects in the timolol group experienced a statistically significant reduction in heart rate in line with its established mechanism of action. No new safety signals arise at this time.

Safety in pregnancy/lactation

No data on the use of netarsudil in pregnancy is available. One pregnancy case was reported in the clinical studies. No specific safety concerns were identified. This has been reflected in the SmPC.

Drug-drug interactions

No formal drug interaction studies have been performed with netarsudil. Although, the applicant has provided general recommendations in the SmPC relating to the concomitant use of other topically administered ocular preparations, it is noted that these recommendations are largely based on extrapolation from general administration recommendations from other ocular medicines rather than on specific data from netarsudil use. As netarsudil is a new active substance, it would be preferable to further explore this topic and the applicant has agreed to further evaluate this issue through the PASS.

In section 4.2 of the proposed SmPC, the applicant includes specific guidance for HCPs and patients outlining that a period of 5 minutes should be observed before other topical ocular preparations are administered following netarsudil administration. Recommendation with regards to order of administration of the different ocular preparation is also included.

Discontinuation for AE

In the pooled safety population, the overall discontinuation rates were notably higher in the netarsudil treatment groups when compared to timolol (19.3% netarsudil 0.02% QD versus 1.7% for timolol). It was reported in the clinical studies that substantially higher discontinuation rates of over 50% were observed for netarsudil 0.02% when it was administered twice daily. This posology is not being pursued by the applicant.

In relation to the dosage of interest, netarsudil 0.02% QD, discontinuation rates due to ocular AEs were still numerically higher when compared to timolol-5.8% of patients discontinued treatment due to conjunctival hyperaemia compared to none in the timolol group.The overall number of patients that discontinued study participation due to local ocular intolerance of the study medication was higher in the netarsudil group versus the timolol group.

The SmPC adequately reflects data on discontinuation rates with netarsudil. Furthermore, this issue will be evaluated during the PASS.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.6.2. Conclusions on the clinical safety

Based on the safety data for netarsudil 0.02% provided to date, it is clear that ocular ADRs are consistently reported at a higher rate in the netarsudil 0.02% treatment group when compared to timolol, although the greater potential for systemic AEs arising from topical local absorption of timolol should be borne in mind.

The specific ocular ADR arising from corneal deposits or corneal verticillata occurred specifically in the netarsudil treatment group only when compared to timolol. This finding was identified firstly during the long term phase 3 part of the clinical development programme for netarsudil and was further characterised during a follow up observational study in which the vast majority of cases of corneal verticillata resolved spontaneously without an impact on visual acuity. Nevertheless, further longer term data would be helpful in clarifying the longer term safety profile given the potential effects on the cornea associated with netarsudil and separately, the impact of BAK with long term use.

In general, the higher rate of ocular ADRs seen with netarsudil 0.02% in the clinical studies and potential impact of these on discontinuation rates in the netarsudil population when compared to timolol would appear to indicate that there were local tolerability issues with netarsudil 0.02% when compared to timolol.

The applicant has proposed a PASS to further evaluate the longer term safety of netarsudil. This is endorsed.

Systemic ADRs occurred infrequently in the phase 3 studies and at a similar rate between netarsudil and timolol.

It appears from the available clinical safety data that, while the overall ocular ADRs occurring with netarsudil were generally mild or moderate and often resolved spontaneously, the overall acceptability and tolerability of netarsudil could be considered lower when compared to timolol in respect of the notably higher frequency of ocular ADRs and higher discontinuation rates which occurred in the netarsudil 0.02% QD treatment population.

In general, the percentage of patients experiencing ocular ADRs and discontinuations was even higher in the population treated with netarsudil 0.02% twice daily but this posology is not being pursued.

The role of BAK in contributing to the overall nature and frequency of ocular ADRs seen in the netarsudil treatment groups is difficult to quantify. The applicant has outlined proposals to reduce the current concentration of BAK in the proposed product and the applicant has confirmed that the re-formulation is under active review. The current overview provided by the applicant in relation to the timeframe for re-formulation and subsequent clinical study to bridge to the new netarsudil formulation is considered broadly acceptable.

The CHMP considers the following measures necessary to address issues related to safety:

The applicant should conduct a PASS as detailed in the RMP to:

- Obtain estimates of the incidence and duration of specific adverse events (e.g. cornea verticillata, conjunctival haemorrhage and conjunctival hyperaemia) with long term use of Rhokiinsa;
- Determine whether specific events remain stable or progress with continued Rhokiinsa use
- Compare the incidence, severity and duration of specific adverse events following long-term

use with Rhokiinsa to the incidence following treatment with a PGA in this study

- Review the overall safety profile of netarsudil compared to the PGAs with long term use of the medications.

The applicant is recommended to develop a new formulation with a reduced concentration of BAK and provide an update annually on the progress.

2.7. Risk Management Plan

Safety concerns

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	• No Important identified risks
Important potential risks	• Damage to the corneal and conjunctival epithelium due to use of eye drops containing preservatives
Missing information	• Use in Pregnant Women • Use by lactating/breastfeeding women • Long term safety of netarsudil (beyond 12 months) • Use in patients with compromised corneal epithelium

Pharmacovigilance plan

Table III.3 Summary Table of additional Pharmacovigilance activities

Study / Status	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 3 - Required additional pharmacovigilance activities				
Observational cohort study Planned	To investigate long term safety of netarsudil beyond 12 months' treatment	- Absence of long-term data (beyond 12 months) - Potential drug interactions (including local reactions and excessive absorption of concomitantly administered topical ocular treatments due to netarsudil's vasodilatory effects), where possible - Safety in patients with compromised corneal epithelium - Longer term (i.e. >12 months) safety profile of netarsudil in elderly (65+ years) patients.	Protocol submission	TBC[1]
			Final Report	TBC [1]

Study / Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
		- Patient discontinuation of treatment rates arising from, in particular, the ocular ADRs known to occur with netarsudil. - Further characterise cornea verticillata in certain subpopulations by age and ethnic background - Safety profile in patients with higher IOPs (30 – 36 mmHg) - Potential phototoxicity adverse events		

[1] it is proposed the study begin 12-18 months after launch in first member state

Risk minimisation measures

Table Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important Potential Risks		
Damage to the corneal and conjunctival epithelium due to use of eye drops containing preservatives	Routine risk minimisation measures: *SmPC section 4.4 Special warnings and precautions for use (guidance with respect to the potential effects of benzalkonium chloride)* *Patient Information Leaflet Section 2 What you need to know before you use Rhokiinsa (guidance with respect to the potential effects of benzalkonium chloride)* Legal status: Restricted medical prescription. There are no additional risk minimisation measures.	There are no routine pharmacovigilance activities beyond adverse reactions reporting and signal detection. There are no planned additional pharmacovigilance activities

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Missing Information		
Use in Pregnancy and lactating/breastfeeding women	Routine risk minimisation measures: *SmPC section 4.6 Fertility, Pregnancy and Lactation (guidance with respect to the lack of data in pregnancy and breastfeeding)* *Patient Information Leaflet Section 2 What you need to know before you use Rhokiinsa (guidance with respect to the lack of data in pregnancy and breastfeeding)* Legal status: Restricted medical prescription. There are no additional risk minimisation measures.	There are no routine pharmacovigilance activities beyond adverse reactions reporting and signal detection. There are no planned additional pharmacovigilance activities
Long term safety of netarsudil	Routine risk minimisation measures: *SmPC section 4.4 Special warnings and precautions for use (guidance with respect to lack of data beyond 12 months)* Legal status: Restricted medical prescription. There are no additional risk minimisation measures.	There are no routine pharmacovigilance activities beyond adverse reactions reporting and signal detection. Additional pharmacovigilance activities: Post-authorisation safety study: observational cohort study.
Use in patients with compromised corneal epithelium	Routine risk minimisation measures: *SmPC section 5.1 Pharmacodynamic properties (guidance with respect to lack of data in patients with compromised corneal epithelium)* Legal status: Restricted medical prescription. There are no additional risk minimisation measures.	There are no routine pharmacovigilance activities beyond adverse reactions reporting and signal detection. Additional pharmacovigilance activities: Post-authorisation safety study: observational cohort study.

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.0 (dated 19 September 2019) is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 18.12.2017. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points

2.9. New Active Substance

The CHMP, based on the available data, considers netarsudil to be a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.

2.10. Product information

2.10.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.10.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Rhokiinsa (netarsudil) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The claimed indication for Rhokiinsa (netarsudil 0.02%) is for the reduction of elevated intraocular pressure in open angle glaucoma or raised intraocular pression.

Glaucoma is a progressive optic neuropathy that causes characteristic loss of visual fields and can eventually lead to blindness due to progressive degeneration of retinal ganglion cells and resulting changes in the head of the optic nerve. It is a leading cause of blindness in Europe.

Primary open angle glaucoma accounts for approximately 74% of all glaucoma cases worldwide. In Europe the population prevalence of primary open angle glaucoma was estimated to be 2% in the population aged over 40 years in 2015.

The objective of current therapy for open angle glaucoma is to reduce intraocular pressure (IOP). The target IOP is determined for each individual with the aim of achieving a pressure at which no further damage is likely to occur to the eye. Those with evidence of nerve damage or visual field impairment are likely to require a lower target IOP.

There is evidence that IOP reduction reduces rate of progression in glaucoma (including those with normotensive glaucoma) and the incidence of glaucoma in those with intraocular hypertension.

3.1.2. Available therapies and unmet medical need

First line treatment for primary open angle glaucoma is usually topical pharmacological therapy. These products work either by decreasing aqueous fluid production (e.g. beta blockers, alpha adrenergic agonists) or increasing aqueous outflow (e.g. prostaglandins). Prostaglandins are the usual first line therapy to treat primary open angle glaucoma. A proportion of patients will fail to respond sufficiently to monotherapy and may require combination therapy of different drug classes to achieve their target IOP.

Primary open angle glaucoma may also be treated with laser or surgical therapy in particular when pharmacological therapy has been insufficient.

3.1.3. Main clinical studies

The applicant submitted five efficacy studies. 2 phase II and 3 phase III studies. All of the phase III studies and one phase II study were non-inferiority active controlled randomised trials. The first comparative controlled trials phase II study (CS202) used latanoprost as a comparator, given that this is first line pharmacological therapy for glaucoma this is deemed appropriate. Subsequent trials used Timolol as a control.

The populations included in the phase III trials were broadly similar but not representative of the overall open angle glaucoma population in that no patients were included in the pivotal study with a maximum baseline IOP at or above 30mmHg and in the two other phase III trials the maximum baseline IOP had to be < 27 mmHg. In addition, patients who make up the majority of those with secondary open angle glaucoma i.e. those with pseudo-exfoliative or pigmentary glaucomas were excluded from all of the studies. Overall it would appear that included patients in the studies had either primary open angle glaucoma or ocular hypertension.

The study providing the main evidence of efficacy (CS304) was a multicentre randomised controlled non-inferiority study comparing netarsudil 0.02% (n = 351) with Timolol (n = 357) conducted in the US

(Δ =1.5). The primary endpoint was evaluated in a smaller population (i.e. the PP population with maximum baseline IOP < 25mmHg) where n =186 in each treatment arm.

3.2. Favourable effects

In the primary efficacy population (per protocol population with maximum baseline IOP < 25mmg Hg) both treatments showed reduction from baseline in IOP at all of the post baseline time points assessed. Overall reduction from baseline was slightly greater from baseline for Timolol 0.5% than Netarsudil 0.02%.

In the Netarsudil 0.02% group mean reduction from baseline at the nine time points assessed ranged from 3.88mmHg to 4.74mmHg and for Timolol 0.5% from 3.77mmHg to 5.17mmHg.

The upper limit of the 95% confidence intervals for the difference in IOP reduction between Netarsudil 0.02% and Timolol 0.5% was < 1.5 mmHg at all-time points and < 1 mmHg at 8 out of 9 time points thereby demonstrating non-inferiority of Netarsudil 0.02% QD to Timolol 0.5% BID.

Non-inferiority to timolol in a similar population (maximum baseline IOP < 25mmHg) was also demonstrated in CS301.

Reports of treatment-related non-ocular AEs were minimal.

3.3. Uncertainties and limitations about favourable effects

In the pivotal study (CS304), netarsudil met the primary endpoint and demonstrated non-inferiority to timolol in the population with baseline IOP < 25mmHg. However, netarsudil was not statistically non-inferior to timolol in the total study population (Baseline IOP < 30 mmHg) with the upper 95% CI for one of the nine time points assessed just outside the non-inferiority margin of 1.5 (1.52). Whilst this from a strictly statistical point of view makes netarsudil not non-inferior to timolol in the per-protocol population with an IOP < 30mmHg, it is of lesser importance from a clinical point of view. It is also acknowledged that non-inferiority was demonstrated in the Per-Protocol population when using an ANCOVA model using treatment as a factor and baseline as a covariate.

The applicant has provided further data on efficacy in the population with baseline IOP ≥ 25 and < 30 mmHg (from the phase III registration studies) and baseline IOP ≥ 30 and < 36mmHg (from PG324 studies conducted with a fixed dose combination of netarsudil and latanoprost). The data from the AR-13324 Phase III studies and the supporting PG324 studies demonstrate that netarsudil lowers mean diurnal IOP by approximately 4 to 6 mmHg in subjects with baseline pressures ≥25 to <36 mmHg. This is broadly similar to the lowering effect in the < 25mm Hg baseline population in the pivotal study.

There is very limited data on efficacy of netarsudil in those with pseudo-exfoliative or pigmentary glaucomas. This data is insufficient to support the inclusion of patients with seconday glaucoma such as pseudo-exfoliative or pigmentary in the overall, broad indication.

3.4. Unfavourable effects

Across the pooled clinical safety studies, the following three ocular ADRs were consistently reported for netarsudil 0.02%: i) conjunctival hyperaemia, ii) corneal verticillata (deposits) and iii) conjunctival haemorrhage.

While many of these ADRs were generally considered mild-moderate in intensity and many resolved spontaneously over time (though others occurred sporadically), the frequency of the three most commonly observed ocular ADRs in general was consistently found to be notably higher for netarsudil 0.02% once daily when compared to the active comparator timolol. Ocular ADRs and discontinuation

rates increased further in patients treated with netarsudil 0.02% twice daily when compared to once daily dosing, although the twice daily dosing regimen for netarsudil 0.02% is not being sought by the applicant.

Data from nonclinical studies indicated that the corneal deposits commonly observed in the clinical studies (in approximately 20% of patients treated with netarsudil) were reflected in a similar way in the nonclinical studies. The underlying process involved is understood to be phospholipidosis which is known to occur with other authorised medicines, most commonly amiodarone. Clinical data from an observational study on 45 patients who developed corneal deposits during netarsudil treatment in the phase 3 studies found that the majority of these cases resolved upon discontinuation of treatment and the presence of corneal verticillata did not generally impact on visual acuity. While this data is broadly reassuring, there is a concern about the absence of longer term data in these patients especially in the context of the proposed indication in glaucoma where longer term treatment with netarsudil would be anticipated. This will be addressed by the applicant through the proposed PASS and this is acceptable.

There is some evidence from nonclinical studies that corneal erosion can occur with netarsudil treatment. In rabbit ocular studies, degeneration or erosion of the cornea was observed with netarsudil concentrations of 0.04% and above (twice daily administration). In one study these effects are described as corneal lesions consisting of peripheral vascularization, mixed cell inflammation, attenuation of the overlying corneal epithelium.

While findings related to corneal erosion were not commonly observed in the clinical studies, a number of sporadic cases of corneal oedema and increased corneal staining were noted in the pooled safety data. The possible clinical relevance of the nonclinical findings is unclear especially in the context of longer term treatment with netarsudil and this can be further addressed through the PASS.

Following the assessment of the applicant's responses to non-clinical questions, a new point has been raised in relation to clinical safety following the review of nonclinical data which indicates a potential signal for phototoxicity arising from netarsudil use. The applicant discussed that possible clinical implications arising from this are unlikely but agreed to evaluate further through the PASS.

In relation to the use of BAK in the proposed netarsudil product, the applicant has further discussed the proposed concentration of BAK and the rationale behind its inclusion in netarsudil 0.02%. In view of clinical concerns relating to long term use of BAK, the applicant has considered the potential impact of BAK on the overall benefit-risk of the product, particularly in the context of the need for continuous long term therapy in glaucoma patients. In this context, the applicant has outlined proposals to reduce/remove BAK in line with previous CHMP SA. The applicant has submitted a proposal for a revised bridging study using the new formulation based on previous SA. This is broadly acceptable.

The discontinuation rates in the longer duration Phase III studies were higher than in Phase II. In the Phase III studies a greater proportion of subjects in the netarsudil groups compared with the timolol group discontinued study participation prior to completing the study (15.3% QD vs. 6.2% timolol in AR-13324-CS301; 41.8% QD; 66.1% BID vs. 18.7% timolol in AR-13324-CS302; 52.9% QD; 88.9% BID vs. 17.4% timolol in AR-13324-CS303; and 30.8% QD vs. 12.0% timolol in AR-13324-CS304).

In the pooled population, the majority of discontinued netarsudil QD and BID subjects were discontinued due to AEs (174/264 [65.9%] and 161/198 [81.3%], respectively).

The most frequent reason for discontinuation of timolol subjects was AE and withdrawal of consent, each 26.4% (28/106 subjects). Non-compliance with study medication and lack of efficacy were observed in only small numbers of subjects across treatment groups and studies.

In the pooled analysis of the 4 AR-13324 Phase 3 studies, a total of 575 (68.5%) netarsudil QD, 91 (31.5%) netarsudil BID and 733 (87.4%) timolol BID subjects completed the full study duration. Conversely, a greater proportion of subjects discontinued study participation in the netarsudil groups

(31.5% QD, 68.5% BID) compared to timolol (12.6%). The most frequent reason for discontinuation was AE: 65.9% netarsudil QD, 81.4% netarsudil BID, and 26.4% timolol.

In the pooled analysis, discontinuations of test article due to TEAEs were highest in the netarsudil BID group (54.3%) followed by netarsudil QD group (19.3%,) and timolol group (1.7%).

The majority of discontinuations in the netarsudil QD and BID groups were associated with ocular events, whereas the majority of discontinuations in the timolol groups were associated with non-ocular events.

The most frequently reported (≥5% of subjects) TEAEs associated with discontinuation in the netarsudil groups were conjunctival hyperaemia (QD: 5.8%; BID: 26.3%), cornea verticillata (QD: 3.7%; BID: 10.0%), and vision blurred (QD: 1.4%; BID: 6.9%).

In the pooled safety analysis, non-ocular ADRs were infrequently reported. The most frequently reported non-ocular AEs in the netarsudil treatment groups included upper respiratory infection (QD: 1.8%; BID: 3.1%), headache (QD: 1.5%; BID: 4.5%) and allergic dermatitis (QD: 0.5%; BID: 2.8%). Similarly, low incidences of these events were reported for the timolol group.

Serious AEs with netarsudil were very uncommon. One serious ocular AE reported with netarsudil occurred at the twice daily dosage which is not being pursued with the application.

Long-term safety data was provided in the 3, 6 and 12-month Phase 3 studies (netarsudil QD (636 subjects) and timolol (631 subjects). Within the netarsudil treatment group, 361 subjects were exposed to netarsudil 0.02% once daily for a duration of 6 months to 12 months. In addition, a total of 252 subjects completed over 12 months of therapy with netarsudil 0.02% once daily.

3.5. Uncertainties and limitations about unfavourable effects

Based on the safety data for netarsudil 0.02% provided to date, it is clear that the previously identified ocular ADRs are consistently reported at a higher rate in the netarsudil 0.02% treatment group when compared to timolol.

The ocular ADR arising from corneal deposits or corneal verticillata, occurred specifically in the netarsudil treatment group when compared to timolol. This finding was identified firstly during the long term phase III part of the clinical development programme for netarsudil and was further characterised during a follow up observational study in which the vast majority of cases of corneal verticillata resolved spontaneously without an impact on visual acuity. Nevertheless, further longer term data would be helpful in clarifying the longer term safety profile given the potential effects on the cornea. This issue can be addressed further through the proposed PASS to assess longer term safety of netarsudil 0.02% once daily administration in the treatment of glaucoma.

In general, the higher rate of ocular ADRs observed with netarsudil 0.02% in the clinical studies and potential impact of these on discontinuation rates in the netarsudil population when compared to timolol would appear to indicate that there were local tolerability issues with netarsudil 0.02% when compared to timolol.

Systemic ADRs occurred infrequently in the phase III studies and at a similar rate between netarsudil and timolol.

It appears from the available clinical safety data that, while the overall ocular ADRs occurring with netarsudil were generally mild or moderate and often resolved spontaneously, the overall acceptability and tolerability of netarsudil was lower when compared to timolol in respect of the notably higher

frequency of ocular ADRs and higher discontinuation rates which occurred in the netarsudil 0.02% QD treatment population.

In general, the percentage of patients experiencing ocular ADRs and discontinuations was even higher in the population treated with netarsudil 0.02% twice daily but this posology is not being pursued.

The role of BAK in contributing to the overall nature and frequency of ocular ADRs seen in the netarsudil treatment groups is unclear. However, BAK can disrupt the epithelial layers of the cornea and conjunctiva, decrease the goblet cell numbers within the conjunctiva and alter the permeability of cell membranes therefore, it cannot be excluded that both efficacy and safety are influenced by the difference in the BAK concentration. The current Rhokiinsa formulation contains 0.015% benzalkonium chloride (BAK). The concentration of BAK included in the proposed formulation is similar to approved products in Europe.

The BAK issue was discussed in previous SA procedures (EMA/CHMP/SAWP/432860/2017) and clarification advice (EMA/520545/2017. EMA CHMP SA conclusion endorsed the approach to decrease BAK concentration in an effort to improve safety. The need for a bridging study and scientific justification to support future re-formulation would in principle address this and this was discussed during the SA procedure.In the responses to the clinical safety query on BAK, the applicant acknowledged the potential for future improvements on the benefit risk profile of the product as regards the concentration of this preservative. While the applicant maintains that the safety of the existing concentration is widely established and in line with other approved products, which is acknowledged, given the ocular tolerability profile of the current formulation, the applicant was asked to further discuss and update on the feasibility of enhancing the benefit-risk of netarsudil 0.02% by specifically reviewing the issue of BAK in the context of the EMA SA advice, in order to optimise the benefit-risk profile in the proposed indication, especially in the context of long term treatment of OAG/OHT. In this context, the applicant is actively reviewing the situation with respect to BAK concentrations in the current formulation. An overview of the applicant's proposals to re-formulate and conduct a bridging study following on from previous CHMP SA recommendations has been presented and is broadly endorsed.

Since netarsudil is a new active substance for the topical treatment of glaucoma, a condition which generally requires chronic long term treatment, there is a concern that some adverse events either already established or evolving could occur or worsen after several months to years of dosing (eg. possible adverse impact of long-term corneal deposition on visual acuity, punctate keratitis, potential for periocular skin hyperpigmentation or discolouration/ iris hyperpigmentation due to possible melanin binding, and adverse changes in the cornea due to chronic administration of BAK), therefore the overall duration of exposure to the proposed product is considered somewhat limited in the context of the proposed indication in glaucoma. The applicant acknowledges the absence of longer term data with netarsudil treatment in glaucoma and has proposed to conduct a PASS to address this issue. This is agreed.

3.6. Effects Table

Table 38 - Effects Table for netarsudil 0.02% ophthalmic solution

Effect	Short Description	Unit	Treatment	Control	Difference between treatment and control (95% CI)	Uncertainties / Strength of evidence	References
	Favourable Effects						
IOP population with baseline IOP < 25 mmHG	Reduction in IOP from baseline	mmHg	Netarsudil	Timolol			CS304
PP popn with baseline IOP < 25 mmHG	D15 08:00 D15 10:00 D15 16:00 D43 08:00 D43 10:00 D43 16:00 D90 08:00 D90 10:00 D90 16:00		4.74 4.51 4.37 4.55 4.27 4.09 4.52 4.1 3.88	4.94 4.55 3.77 4.85 4.29 4.01 5.17 4.56 3.89	0.17 (-0.43, 0.77) -0.16 (-0.73, 0.41) -0.6 (-1.16, -0.04) 0.25 (-0.34, 0.83) -0.22 (-0.82, 0.37) -0.1 (-0.66, 0.46) 0.56 (-0.02, 1.15) 0.21 (-0.37, 0.79) -0.07 (-0.68, 0.55)		CS304
PP popn baseline IOP < 30 mmHG	D15 08:00 D15 10:00 D15 16:00 D43 08:00 D43 10:00 D43 16:00 D90 08:00 D90 10:00 D90 16:00		4.74 4.74 4.39 4.45 4.47 4.2 4.52 4.13 3.95	5.3 4.97 4.19 5.37 4.87 4.14 5.52 5.11 4.27	0.6 (0.02, 1.17) 0.13 (-0.42, 0.691) -0.09 (-0.62, 0.44) 0.93 (0.35, 1.52) 0.23 (-0.31, 0.78) 0.01 (-0.54, 0.56) 0.89 (0.3, 1.49) 0.7 (0.13, 1.27) 0.36 (-0.02, 0.93)		CS 304
	Unfavourable Effects						
Conjunctival hyperaemia	Incidence of ocular hyperaemia	%	54.4	10.4			Pooled safety studies
Corneal verticillata	Incidence	%	20% approx	0.2			Pooled safety studies
Conjunctival haemorrhage	Incidence	%	15-20%	0.8-3.1			Pooled safety studies
Loss of >3 lines vision	Incidence	%	3.8	1.8		Higher rates were noted again when netarsudil was administered BD (7.3%)	Pooled safety population
Blurred vision	Incidence	%	7.4	1.4			Pooled safety studies
Increased lacrimation	Incidence	%	7.2	0.6			Pooled safety studies

Effect	Short Description	Unit	Treatment	Control	Difference between treatment and control (95% CI)	Uncertainties/ Strength of evidence	References
Reduced visual acuity	Incidence	%	5.2	1.5			Pooled safety studies
Punctate keratitis	Incidence	%	3.2	1.8		Cases of punctate keratitis were also reported with timolol but at a lesser frequency (1.8%)	Pooled safety population
Eyelid erythema	Incidence	%	6.8	0.7			Pooled safety studies
Eyelid pruritus	Incidence	%	4.1	0.8			Pooled safety studies
Eyelid oedema	Incidence	%	3.5	0.7			Pooled safety studies
Allergic conjunctivitus	Incidence	%	2.5	0.1			Pooled safety studies
Instillation site pain	incidence	%	19.9	21.6		Instillation site pain was broadly similar between netarsudil and timolol	Pooled safety population

Notes: *In favourable effects table "difference between treatment and control", positive results favour timolol and negative results favour netarsudil. Difference from Timolol 0.5% and two-sided CIs and p-values are based on 2-sample t-tests comparing Netarsudil 0.02% QD vs Timolol 0.5%.*

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Netarsudil is a new topical anti-glaucoma medicinal product with a different mode of action to previously authorised topical products and as such provides an alternative treatment option.

Netarsudil has demonstrated similar IOP lowering effects in clinical studies across a range of baseline IOPs (< 25mmgHg, ≥ 25 and < 30 mmHg, ≥ 30 and < 36mmHg). It is acknowledged that non-inferiority to timolol was only demonstrated in a population with baseline IOP < 25 mmHg, though failure to demonstrate non-inferiority in the overall study population (<30mmHg at baseline) was marginal, and data in the population without IOP ≥ 30 and < 36mmHg has been obtained from studies for a fixed dose combination of netarsudil and latanoprost.

Whilst a broad indication for open angle glaucoma is sought, patients with pseudoexfoliative or pigmentary glaucoma were excluded from all of the phase 2 and 3 studies submitted in this application, therefore there is extremely limited data to support use in this population. Therefore, the applicant has agreed to a revised indication wording to reflect the available data.

Unfavourable effects reported in the safety population mostly relate to ocular ADRs. Although frequently mild-moderate in intensity, these ocular ADRs occurred in a notably higher percentage of patients treated with netarsudil 0.02% once daily when compared to timolol. Rates of discontinuation were in general higher in the netarsudil 0.02% treatment group also. These topics have been reflected in the final netarsudil product information.

There was a concern that the unfavourable effects observed in the netarsudil treatment group could impact on overall tolerability of netarsudil in the long term and this may have implications for long term compliance with treatment, which is crucial given the target indication in glaucoma.

Therefore, the applicant has agreed to further evaluate the issue of long term safety of netarsudil, including the impact of ocular ADRs on continuation of treatment longer term, during the PASS which will be conducted post-approval.

Potential unfavourable effects arising from the long term use of BAK as part of netarsudil treatment are also noted. The applicant is actively reviewing this issue and has presented plans to re-formulate the product to remove or reduce BAK concentration as a post-approval measure, in line with previous CHMP SA recommendations. This is endorsed.

3.7.2. Balance of benefits and risks

Netarsudil has a different mode of action to already authorised topical anti-glaucoma products and provides another treatment option. The initiation of the treatment is therefore restricted to ophthalmologists or healthcare professionals qualified in ophthalmology. Efficacy has been demonstrated across a range of baseline IOPS though other products such as timolol and latanoprost show greater efficacy at higher baseline IOPs than netarsudil. Nevertheless, the applicant has demonstrated that some patients with higher baseline IOP levels demonstrated substantial reduction in baseline IOP (> 7mmHg).

There is minimal data on efficacy in those with pseudoexfoliative or pigmentary glaucoma as those patients were excluded from clinical studies; therefore the inclusion of these patients in the sought indication is not supported. The applicant has agreed to reflect this in the final wording for the indication.

The overall safety profile of netarsudil 0.02% was dominated by ocular ADRs. The key findings related to three ocular ADRs which were commonly reported with netarsudil-conjunctival hyperaemia, corneal verticillata and conjunctival haemorrhage.

Whilst these ADRs were in general mild-moderate in intensity and often resolved spontaneously, they occurred at a notably higher frequency when compared to timolol.

There is a concern that the unfavourable effects observed in the netarsudil treatment group could impact on overall tolerability of netarsudil and this may have implications for long term compliance with treatment. This issue should be considered in view of the proposed treatment in glaucoma and the importance of compliance with chronic treatment. Nevertheless, it is considered that this concern is adequately reflected in the SmPC/label and will be further followed in the proposed PASS to further evaluate longer term safety of netarsudil in the proposed indication.

Also, the less favourable ocular tolerability profile associated with netarsudil in the clinical studies has to be balanced against the potential for systemic ADRs which can be associated with other ocular treatments for glaucoma but are less likely with netarsudil in view of its negligible systemic absorption.

Potential unfavourable effects arising from the long term use of BAK as part of netarsudil treatment are noted. This topic was the discussed in detail during the previous CHMP SA on netarsudil, however as the current BAK concentration is in line with other authorised topical ocular products, this was not seen as barrier to authorisation. Nevertheless, the applicant acknowledged the previous SA recommendations to

consider reducing BAK concentration in netarsudil. In this context, the applicant confirmed that the issue of BAK concentration reduction is under active review. It is acknowledged that the applicant plans to re-formulate to remove or reduce the BAK concentration are progressing and an outline of the recommended clinical study to bridge to the re-formulated product has been presented. This is considered broadly acceptable. It is recommended that the applicant provides an update to the Rapporteur on an annual basis in relation to how the re-formulation to reduce/remove BAK concentration is progressing.

3.8. Conclusions

The overall B/R of Rhokiinsa is positive for the *reduction of elevated intraocular pressure (IOP) in adult patients with primary open-angle glaucoma or ocular hypertension*.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Rhokiinsa is favourable in the following indication:

Rhokiinsa is indicated for the reduction of elevated intraocular pressure (IOP) in adult patients with primary open-angle glaucoma or ocular hypertension.
The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription.

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of

an important (pharmacovigilance or risk minimisation) milestone being reached.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that netarsudil is a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.