22 May 2014
EMA/366328/2014
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Simbrinza

International non-proprietary name: Brinzolamide / Brimonidine tartrate

Procedure No. EMEA/H/C/003698/0000

Note
Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.
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<tr>
<td>α 2</td>
<td>Alpha 2</td>
</tr>
<tr>
<td>ADR</td>
<td>Adverse drug reaction</td>
</tr>
<tr>
<td>AE</td>
<td>Adverse event</td>
</tr>
<tr>
<td>AUC</td>
<td>Area under the curve</td>
</tr>
<tr>
<td>BAK</td>
<td>Benzalkonium chloride</td>
</tr>
<tr>
<td>BID</td>
<td>Two times daily (<em>Bis in Die</em>)</td>
</tr>
<tr>
<td>Brinz/Brim</td>
<td>Brinzolamide /Brimonidine 10mg/mL + 2 mg/mL Eye Drops, Suspension</td>
</tr>
<tr>
<td>cAMP</td>
<td>Cyclic AMP</td>
</tr>
<tr>
<td>CA</td>
<td>Carbonic anhydrase</td>
</tr>
<tr>
<td>CAI</td>
<td>Carbonic anhydrase inhibitor</td>
</tr>
<tr>
<td>CHMP</td>
<td>Committee for Medicinal Products for human Use</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>CNS</td>
<td>Central nervous system</td>
</tr>
<tr>
<td>CYP3A4</td>
<td>Cytochrome P450 3A4 a member of the cytochrome P45 mixed-function oxidase system</td>
</tr>
<tr>
<td>EFD</td>
<td>Embryo-foetal development</td>
</tr>
<tr>
<td>eg</td>
<td><em>Exempli gratia</em> (for the sake of an example)</td>
</tr>
<tr>
<td>EMA</td>
<td>European Medicines Agency</td>
</tr>
<tr>
<td>EU</td>
<td>European Union</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>g</td>
<td>Gram</td>
</tr>
<tr>
<td>GTP</td>
<td>Guanosine triphosphate</td>
</tr>
<tr>
<td>H or h</td>
<td>Hour</td>
</tr>
<tr>
<td>i.e.</td>
<td><em>id est</em> (that is)</td>
</tr>
<tr>
<td>IOP</td>
<td>Intraocular pressure</td>
</tr>
<tr>
<td>ITT</td>
<td>Intent-to-treat</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------</td>
</tr>
<tr>
<td>kg</td>
<td>Kilogram</td>
</tr>
<tr>
<td>LD50</td>
<td>Lethal Dose, 50% or median lethal dose</td>
</tr>
<tr>
<td>LSM</td>
<td>Least Squares Mean</td>
</tr>
<tr>
<td>MAA</td>
<td>Marketing Authorisation Application</td>
</tr>
<tr>
<td>MAOIs</td>
<td>Monoamine oxidase inhibitors</td>
</tr>
<tr>
<td>mg</td>
<td>Milligram</td>
</tr>
<tr>
<td>mL</td>
<td>Millilitre</td>
</tr>
<tr>
<td>μg</td>
<td>Microgram</td>
</tr>
<tr>
<td>mmHg</td>
<td>Millimeters of mercury</td>
</tr>
<tr>
<td>min</td>
<td>Minute</td>
</tr>
<tr>
<td>N</td>
<td>Sample size</td>
</tr>
<tr>
<td>ng</td>
<td>Nanogram</td>
</tr>
<tr>
<td>OAG</td>
<td>Open-angle glaucoma</td>
</tr>
<tr>
<td>OHT</td>
<td>Ocular HyperTension</td>
</tr>
<tr>
<td>POC</td>
<td>Proof of concept</td>
</tr>
<tr>
<td>POAG</td>
<td>Primary open-angle glaucoma</td>
</tr>
<tr>
<td>PK</td>
<td>Pharmacokinetics</td>
</tr>
<tr>
<td>PM</td>
<td>In the evening (Post Meridiem)</td>
</tr>
<tr>
<td>QD</td>
<td>Once daily</td>
</tr>
<tr>
<td>qhs</td>
<td>Every night at bedtime (quaque hora somni)</td>
</tr>
<tr>
<td>QID</td>
<td>Four times daily</td>
</tr>
<tr>
<td>SAEs</td>
<td>Serious adverse events</td>
</tr>
<tr>
<td>SAR</td>
<td>Serious adverse reaction</td>
</tr>
<tr>
<td>SE</td>
<td>Standard error</td>
</tr>
<tr>
<td>SmPC</td>
<td>Summary of product characteristics</td>
</tr>
<tr>
<td>SOC</td>
<td>System organ classification</td>
</tr>
<tr>
<td>TCAs</td>
<td>Tricyclic antidepressants</td>
</tr>
<tr>
<td>TID</td>
<td>Three times daily (ter in die)</td>
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1. Background information on the procedure

1.1. Submission of the dossier

The applicant, Alcon Laboratories (UK) Ltd, submitted on 4 June 2013 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Simbrinza, through the centralised procedure under Article 3(2)(b) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 21 February 2013. The eligibility to the centralised procedure under Article 3(2)(b) of Regulation (EC) No 726/2004 was based on demonstration of significant therapeutic innovation.

The applicant initially applied for the following indication:

"Decrease of elevated intraocular pressure in adult patients with open-angle glaucoma or ocular hypertension"

The legal basis for this application refers to:

Article 10(b) of Directive 2001/83/EC – relating to applications for new fixed combination products.

The application submitted is a new fixed combination medicinal product.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) [P/259/2011] on the granting of a (product-specific) waiver.

Information relating to orphan market exclusivity

Not applicable.

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.

Scientific Advice

The applicant received advice from the CHMP in November 2010 (EMA/CHMP/SAWP/686621/2010). The Scientific Advice pertained to the non-clinical and clinical aspects of the dossier.
**Licensing status**

Simbrinza was given a Marketing Authorisation in the U.S. on 19 April 2013, with the three times daily (TID) dosing schedule.

**1.2. Manufacturers**

**Manufacturers responsible for batch release**

Alcon-Couvreur N.V.  
Rijksweg 14  
BE-2870 Puurs  
Belgium

**1.3. Steps taken for the assessment of the product**

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

Rapporteur: Robert James Hemmings  
Co-Rapporteur: Concepcion Prieto Yerro

- The application was received by the EMA on 4 June 2013.
- The procedure started on 24 July 2013.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 11 October 2013. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 11 October 2013.
- PRAC RMP Advice and assessment overview, adopted by PRAC on 7 November 2013.
- During the meeting on 21 November 2013, the CHMP agreed on the consolidated List of Questions to be sent to the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 21 February 2014.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Questions to all CHMP members on 23 April 2014.
- During the CHMP meeting on 25 April 2014, the CHMP agreed on a list of outstanding issues to be addressed by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 30 April 2014.
During the meeting on 22 May 2014, 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 Simbrinza.

2. Scientific discussion

2.1. Introduction

Brinzolamide was approved in the EU as 10 mg/mL eye drops, suspension on 9 March 2000 via the Centralised Procedure as ‘Azopt’. The MAH for Azopt is the same as the applicant for this MAA for Simbrinza.

Brimonidine was first approved within the EU in UK on 18 March 1997 as 2 mg/mL eye drops, solution.

Both products are approved for the treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma (as monotherapy in adult patients unresponsive to beta-blockers or in patients in whom beta-blockers are contraindicated, or as adjunctive therapy to other intraocular pressure lowering medications when the target IOP is not achieved with a single agent).

Both the individual mono-components are licensed in the EU with a posology of two times daily, whilst in the USA they are licensed with a posology of three times daily (TID) administration.

This application concerns a fixed combination medicinal product including both brinzolamide and brimonidine in the same strengths as approved for the mono-component products. The proposed posology with this application was one drop of Simbrinza in the affected eye two times daily, in line with the EU posology of the mono-components.

Glaucma is an optic neuropathy that leads to loss of optic-nerve tissue with an excavation of the ophthalmoscopically visible optic nerve head and consequently, to a progressive loss of vision. Glaucma is the leading cause of irreversible blindness worldwide.

Glaucma is a frequent disease. Up to 10% of people over the age of 40 years have an IOP above 21 mmHg (normal range 10 to 21 mmHg). Those who have such high pressures but no optic-nerve damage are considered to have ocular hypertension. Elevated IOP is a risk factor for its development and reduction of IOP has been demonstrated to protect against further damage to the optic nerve. In medical practice, those patients who have ocular hypertension should be periodically examined (optic nerve, visual field) to determine whether there is evidence of progressive damage which would indicate the need to start with treatment. However, in some cases (e.g. additional risk factors for glaucoma) a high IOP may be treated even in the absence of optic nerve damage.

Chronic pharmacological therapy is required to lower and control IOP and successfully control glaucoma. Pharmacological treatments are based on the decrease of production of aqueous humour produced by the ciliary body but there is also the possibility to increase its outflow by means of surgery or laser. The target pressure is that which is thought to be safe to the optic
nerve, taking into account the amount of optic damage and the pressure at which the damage occurred, but in principle, it should stay below 21 mmHg.

The medical treatment of glaucoma usually starts with a topical beta-blocker that permits a sufficient decline in IOP in most cases. If necessary (in patients poorly controlled on beta-blockers or when beta-blockers are contra-indicated), either other topical drugs can be used or other topical or systemic drugs have to be added to the patient’s regimen. Laser procedures or filtering surgery are usually performed after failure of medical treatment.

Given that glaucoma and ocular hypertension (OHT) can progress and typically worsen with age, necessitating the use of more than one IOP-lowering treatment in many patients, and that life expectancy of the population is increasing, the potential public health problem and demand for alternative treatments is high. Approximately 40% of open-angle glaucoma patients require 2 or more medications within 5 years of diagnosis. Combination treatments would be expected to reduce treatment burden and potentially improve patient adherence to treatment since more than one active treatment is included in a single formulation.

At the time of this application, all available anti-glaucoma combinations had the beta-blocker timolol as one of the components. Among topical anti-glaucoma agents, beta-blockers tend to have the greatest number of contra-indications due to a number of undesirable systemic effects. Development of a combination treatment such as Brinzolamide/Brimonidine, should benefit patients and physicians by providing an alternative combination choice for treatment of elevated IOP for those patients who cannot use any of the currently available timolol-containing combination medicines.

2.2. Quality aspects

2.2.1. Introduction

The finished product is available as an eye drop suspension containing a fixed combination of 10mg/ml of brinzolamide and 2 mg/ml of brimonidine as active substances.

Other ingredients are: carbomer, sodium chloride, mannitol, propylene glycol, tyloxapol, boric acid, benzalkonium chloride, sodium hydroxide, hydrochloric acid and water.

The medicine is available in 8 ml round opaque low density polyethylene (LDPE) bottles with a LDPE dispensing plug and white polypropylene screw cap (drop-tainer) containing 5 ml suspension as described in section 6.5 of the SmPC.

2.2.2. Active substance

Two active substances are used in this fixed combination product, brinzolamide and brimonidine.

Brinzolamide

Brinzolamide is a white to off-white crystalline powder and the solubility is pH dependent with minimal solubility at neutral pH and increased solubility at acid or more basic pH. It presents one single asymmetric centre being the R-enantiomer the active one. According to the synthetic
process described in this application the active substance is consistently obtained as the R-enantiomer and is routinely controlled by a chiral purity test. Brinzolamide produced by the proposed active substance supplier is a crystalline form. Only one polymorphic form of brinzolamide has been observed and described in the literature.

The chemical name of Brinzolamide is \((R)-4\text{-}(\text{Ethylamino})\text{-}3,4\text{-dihydro}\text{-}2\text{-}(3\text{-methoxypropyl})\text{-}2H\text{-}thieno[3,2-e]\text{-}1,2\text{-thiazine}\text{-}6\text{-sulfonamide}\text{-}1,1\text{-dioxide}\) and has the following structure:

![Chemical structure of Brinzolamide](image)

**Figure 1: Chemical structure of Brinzolamide**

There is no monograph in the Ph Eur or national Pharmacopeia but there is a USP monograph available.

The chemical structure elucidation has been performed by infrared spectroscopy, ultraviolet spectroscopy, \(^1\text{H}\) NMR spectroscopy, \(^{13}\text{C}\) NMR spectroscopy, x-ray diffraction and mass spectrometry. The molecular formula of this active substance is confirmed by elemental analysis.

**Manufacture**

The brinzolamide is sourced from two manufacturers, both manufacturers used the same route of synthesis. The active substance is synthesised in four steps using commercially available and well defined starting materials. The final active substance is purified by crystallisation.

The designation of the starting materials for the synthesis of the active substance has been justified with respect to their impurity profiles, their potential for carry-over into the final active substance, their structural complexity and with respect to their proximity to the final intermediate and the active substance, respectively.

Information provided adequately describes the manufacturing including reactions conditions, quantities of raw materials and yields.

The characterisation of the active substance and its impurities is in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origins and characterised. The carry-over of impurities, reagents, solvents and catalysts from the starting material into the final active substance has been also discussed. The impurity profile of the active substances for both manufactures is identical.
Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediates, starting materials and reagents have been presented.

The active substance is packaged in double polyethylene bag and secured with plastic tie or elastic band, in a rigid opaque plastic, metal or fibreboard drum. The materials in contact with the active substance comply with the EC directive 2002/72/EC and EC 10/2011.

**Specification**

The active substance specification includes tests for appearance, solubility, identification (IR; chiral HPLC), solution colour (Ph Eur), solution clarity (Ph Eur), loss on dying (Ph Eur), heavy metals (Ph Eur), residue on ignition (Ph Eur), impurities (HPLC), assay (HPLC), residual solvents (GC), and microbiological quality (Ph Eur).

A detailed description for all analytical methods was provided. Full method validation data was also provided for the in-house analytical methods in accordance with the relevant ICH Guidelines. The analytical methods proposed are suitable to control the quality of the active substance. The impurity limits are acceptable and there is no concern from the point of view of safety.

Batch analysis data are provided on 5 production batches produced by one manufacture and 8 production batches produced by the second manufacturer. All the batches were manufactured according to the proposed synthetic route, and the batch analysis data show that the active ingredient can be manufactured reproducibly. All results are within the specifications and consistent from batch to batch.

**Stability**

Seven production scale batches of the active substance packed in the intended commercial packaging from the proposed manufacturers were put on stability testing as per ICH conditions: under long term (25°C/60%RH) for up 60 months and accelerated (40°C/75%RH) for up 6 months. The active substance used in the primary stability studies was manufactured according to the commercial process.

The following parameters were tested: appearance, identification (IR; chiral HPLC), loss on dying (Ph Eur), heavy metals (Ph Eur), residue on impurities (HPLC), assay (HPLC) and chiral purity (HPLC).

Forced degradation studies were conducted by exposing the active substance to UV radiation, high temperature, aqueous hydrolysis, acid, base and oxidative conditions. Based on these studies it is observed that the active substance is sensitive to oxidation and hydrolysis conditions.

Photostability testing following ICH guidelines Q1B was performed on one batch of the active substance. The results showed that there are no significant changes for any of the evaluated parameters established for the stability studies.

The stability results indicate that the active substance is stable at controlled room temperature. The results justify the proposed retest period in the proposed container.
**Brimonidine**

Brimonidine tartrate is light tan powder and soluble in water and slightly soluble in methanol. It was noted that the solubility in water increase with the decrease of pH. The substance brimonidine is achiral, but the tartaric acid is used in its L (+) form. The active substance is controlled routinely by specific optical rotation. Brimonidine tartrate produced by the proposed active substance supplier is a crystalline form. Polymorphism has not been observed for active substance.

The chemical name of brimonidine tartrate is 5-Bromo-N-(4,5-dihydro-1H-imidazol-2-yl) quinoxalin-6-amine; (2R,3R)-2,3-dihydroxybutanedioic acid and has the following structure:

![Chemical structure of Brimonidine tartarate](image)

**Figure 2: Chemical structure of Brimonidine tartarate**

The chemical structure elucidation has been performed by infrared spectroscopy, $^1$H NMR spectroscopy, $^{13}$C NMR spectroscopy, mass spectrometry, ultraviolet spectroscopy. The molecular formula of this active substance is confirmed by elemental analysis.

**Manufacture**

The Brimonidine tartrate was planned to be sourced by two independent manufactures that used the same route of synthesis. During the evaluation, the applicant decided to withdraw one of the manufactures of this active substance for commercial reasons.

The active substance is synthesised in four steps using commercially available and well defined starting materials. The final active substance is purified by crystallisation.

The designation of the starting materials for the synthesis of the active substance has been justified with respect to their impurity profiles, their potential for a carry-over into the final active substance, their structural complexity and with respect to their proximity to the final intermediate and the drug substance, respectively.

Information provided adequately describes the manufacturing including reactions conditions, quantities of raw materials and yields.
The characterisation of the active substance and its impurities is in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origins and characterised. The carry-over of impurities, reagents, solvents and catalysts from the starting material into the final active substance has been also discussed. The impurity profile of the active substances for both manufactures is identical.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediates, starting materials and reagents have been presented.

The active substance is packaged in a colourless polyethylene bag with a minimum thickness of 0.06 mm. The bag is then wrapped in a second, identical polyethylene bag that is packed in a rigid opaque container (HDPE or metal drum). The materials in contact with the active substance comply with the EC directive 2002/72/EC and EC 10/2011.

**Specification**

The active substance specification includes tests for appearance, identification (IR, specific optical rotation and HPLC), mp, pH of 1% solution, loss on drying (Ph Eur), residue on ignition (Ph Eur), heavy metals (Ph Eur), clarity of 1% solution, impurities (HPLC), assay (HPLC), residual ethylenediamine (IC) and microbiological quality (Ph Eur).

A detailed description for all analytical methods was provided. Full method validation data was also provided for the in-house analytical methods in accordance with the relevant ICH Guidelines. The analytical methods proposed are suitable to control the quality of the active substance. The impurity limits are acceptable and there is no concern from the point of view of safety.

Batch analysis data are provided on seven production batches produced by the proposed synthetic route, and the batch analysis data show that the active ingredient can be manufactured reproducibly. All results are within the specifications and consistent from batch to batch.

**Stability**

Three production scale batches of the active substance packed in the intended commercial packaging from the proposed manufacturers were put on stability testing as per ICH conditions: under long term (25°C/60%RH) for up 5 years and accelerated (40°C/75%RH) for up 6 months. The active substance used in the primary stability studies was manufactured according to the commercial process.

The following parameters were tested: appearance, identification (IR), solution pH, loss on drying, impurities (HPLC) and assay (HPLC).

Forced degradation studies were conducted by exposing the active substance to UV radiation, high temperature, aqueous hydrolysis, acid, base and oxidative conditions. Based on these studies it is observed that the active substance is sensitive to oxidation.
Photostability testing following ICH guidelines Q1B was performed on one batch of the active substance. The results showed that there are no significant changes for any of the evaluated parameters established for the stability studies.

The stability results indicate that the active substance is stable at controlled room temperature. The results justify the proposed retest period in the proposed container.

### 2.2.3. Finished medicinal product

The pharmaceutical development of this eye drop suspension was based on two other authorised ophthalmic products containing brinzolamide and brimonidine. The concentrations of the active substances in Simbrinza (brinzolamide and brimonidine tartrate) are the same of the respective active substances in the already authorised medicinal products: brinzolamide 10mg/ml eye drops suspension (Azopt) and brimonidine tartrate 2 mg/ml eye drops solution. Brinzolamide is present in the finished product as suspended particles due to its low aqueous solubility, whereas brimonidine is in solution. It was noted that the particle size is tightly controlled and unchanged throughout the shelf life. The qualitative and quantitative composition of excipients in this eye drop suspension are similar to those present in Azopt with the exception of the addition of propylene glycol and boric acid and the exclusion of EDTA. The concentration of benzalkonium chloride was selected at 0.03 mg/mL (0.003%) which is one-third of the concentration in Azopt (0.01%). This lower concentration of benzalkonium chloride still provides an effective level of preservation to meet the Ph. Eur. criteria in the presence of boric acid. It was noted that the selection of excipients was also based on the desired quality attributes of the finished product such as pH, viscosity, tonicity, redispersibility and settling characteristics have been outlined. The pH selected for this formulation was close to neutral (pH 6.5), which is similar to the pH selected for brimonidine tartrate 2 mg/ml eye drops solution (pH 6.4). The concentration of carbomer is the same as in Azopt, in order to achieve the formulation viscosity, similar bioavailability and ocular retention. Based on preliminary stability studies it was confirmed that there are no compatibility issues concerning the excipients selected in this particular formulation.

All the excipients selected are pharmacopeia grade and controlled according with their relevant monographs.

The formulation used during clinical studies is the same that the used for marketing.

The primary packaging is described as stated in the SmPC. The material complies with Ph Eur and EC requirements. The choice of the container closure system has been validated by stability data. This container was selected on the basis of compatibility and container-closure integrity studies and is adequate for the intended use of the medicinal product.

**Adventitious agents**

No excipients derived from animal or human origin have been used.
**Manufacture of the product**

The manufacturing process selected is based upon the approved manufacturing process for other eye drops fixed combination containing brinzolamide and timolol as active substances, approved via the Centralised Procedure. The manufacturing process consists of the following five steps:

1) Autoclaving and aseptic ball milling of brinzolamide;
2) Carbomer/salt preparation and bulk sterilisation;
3) Brimonidine compounding and filter sterilisation;
4) Final compounding and filling;
5) Labelling and packaging.

The sterilisation method is a combination of steam sterilisation, gamma sterilisation, ethylene Oxide sterilisation during the various steps of the manufacturing process. The sterility of the finished product is achieved by employing aseptic techniques and sterile filling at the last steps of the process.

Sterility issues including sterilisation procedures, and aseptic procedures, critical steps and holding times are adequately addressed and justified. The residual content of ethylene oxide and ethylene chlorohydrin will be below the limits specified in the guideline on limitations to the use of ethylene oxide in the manufacture of medicinal products. The milling process and uniformity of the suspension during filling has been justified and documented. It was noted that the critical stages of the manufacturing process have been validated. The validation of the manufacturing process has been evaluated on three consecutive production scale batches. The quality of the production batches was evaluated through the results of in process testing as well as the results of finished product testing. The process validation is supported by batch data on three production scale batches.

**Product specification**

The finished product release specifications include appropriate tests for this kind of dosage form: identification (HPLC and TLC), assay (HPLC), impurities (HPLC), benzalkonium chloride identification (HPLC), benzalkonium chloride assay (HPLC), boric acid identification (HPIC), boric acid assay (HPIC), pH (Ph Eur), osmolality (Ph Eur), appearance (colour and uniformity), viscosity (Ph Eur), redispersibility, particle size (Ph Eur), fill volume and sterility test (Ph Eur).

Batch analysis data of five scale batches of the finished product are provided. The results confirm the consistency of the process and its ability to manufacture a product complying with the product specification.

**Stability of the product**

Stability data of five scale batches for each 5.0 ml and 2.5 ml of finished product stored under long term conditions for 24 months at 25 °C / 60% RH, intermediate conditions for 24 months at 25 °C / 65% RH and for up to six months under accelerated conditions at 40 °C / 75% RH.
according to the ICH guidelines were provided. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for: identification (HPLC and TLC), assay (HPLC), impurities (HPLC), benzalkonium chloride identification (HPLC), benzalkonium chloride assay (HPLC), boric acid identification (HPIC), boric acid assay (HPIC), pH (Ph Eur), osmolality (Ph Eur), appearance (color and uniformity), viscosity (Ph Eur), redispersibility, particle size (Ph Eur), weight change, package condition and sterility test (Ph Eur).

One batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. In addition stress stability studies were performed on one fully representative batch under various extreme conditions including heat, light and freeze. The data demonstrate that the medicinal product is not affected by light and is not susceptible to degradation under heat, light and freeze conditions.

Based on the available stability data, the shelf-life and storage conditions as stated in the SmPC are acceptable.

### 2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The manufacturing flow-chart was provided with suitable in-process controls. The manufacturing process is adequately validated at full scale at the proposed manufacturing site and a validation protocol has been presented.

The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

### 2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. 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. Pharmacology

Primary pharmacodynamic studies
Brinzolamide is a potent and selective inhibitor of carbonic anhydrase-II. Following topical ocular administration, brinzolamide inhibited aqueous humour formation and reduced elevated intraocular pressure (IOP). The topical ocular application of brinzolamide was shown to dose-dependently reduce IOP by up to 30% in ocular hypertensive monkeys and pigmented rabbits.

Brimonidine tartrate is a potent, selective alpha-2 adrenoceptor agonist. The topical ocular application of brimonidine tartrate to cats, rabbits and monkeys reduced IOP and pupil diameter in a dose-related manner. Brimonidine tartrate also reduced IOP in glaucomatous monkeys. In monkeys, the topical ocular treatment with brimonidine tartrate promoted a dose-dependent reduction in aqueous humour flow without affecting total outflow.

Non-clinical primary pharmacology studies with the proposed Brinzolamide/Brimonidine 10 mg/mL + 2 mg/mL eye drops, suspension (Brinz/Brim) have not been conducted as the clinical use of the individual components is well established. This is acceptable.

Secondary pharmacodynamic studies
In tranquilised pigmented rabbits, twice daily topical ocular administration of 20 mg/mL brinzolamide reduced IOP and slightly increased optic nerve head blood flow. Brimonidine was shown to have neuroprotective activity in a variety of neuronal injury animal models. No secondary pharmacology studies with brinzolamide/brominidine were submitted. This was considered to be acceptable.

Safety pharmacology programme
The safety pharmacology of brinzolamide and brimonidine has been characterised in previous regulatory submissions for the Azopt and authorised brimonidine 2 mg/mL eye drops, solution products, respectively, and published literature. In mice and rats intravenously administered brinzolamide, no biologically significant effects were observed except for a small reduction in gastrointestinal propulsion (at 6000 fold the proposed clinical dose of 0.005 mg/kg/day) and minor changes in urine electrolytes and blood gases (at ≥200 the proposed clinical dose). For brimonidine, hypotension and bradycardia were observed in monkeys that received topical ocular administration of the drug. Sedation, reduction in motor activity, reduced gastrointestinal motility and transient hyperglycemia effects were also observed in brimonidine-treated animals.

In a hERG assay conducted with the brinzolamide/brominidine combination, concentrations of up to 3 μg/mL +1 μg/mL produced no inhibition of hERG tail current in HEK293 cells stably transfected with hERG cDNA.
Pharmacodynamic drug interactions

Pharmacodynamic drug interaction studies conducted with brinzolamide and brimonidine alone or in combination were not reported by the Applicant. Acceptable justification for the omission of these studies was provided. Potential interactions of Brinz/Brim with other drugs are included in the proposed SmPC.

2.3.2. Pharmacokinetics

Absorption, distribution, metabolism and excretion: The range and extent of the pharmacokinetics studies conducted with brinzolamide and brimonidine are acceptable.

Brinzolamide: The binding of brinzolamide to carbonic anhydrase in red blood cells and tissues was shown to reduce its plasma concentration, increase the half-life of the drug and result in non-linear pharmacokinetics. These are reported to be known effects of sulfonamide carbonic anhydrase inhibitors. Protein binding of brinzolamide was not high in rat, monkey or human plasma (25, 75 and 60%, respectively). Brinzolamide is absorbed into the eye following topical ocular dosing. In rabbit eyes, the highest concentrations were found in the anterior ocular tissues of the eye (conjunctiva, cornea, aqueous humour and iris-ciliary body) and at lower levels in the posterior tissues (retina and choroid) and the systemic circulation. Distribution of drug into the posterior tissues appeared to be derived from the systemic circulation. The half-lives of brinzolamide in ocular tissues were approximately 30 to 50 days.

The major metabolites of brinzolamide were shown to be N-desethyl brinzolamide, N-desmethoxypropyl brinzolamide, O-desmethyl brinzolamide and an N-propionic acid metabolite. The CYP3A4, CYP2A6, CYP2B6, CYP2C8 and CYP2C9 isoenzymes are involved in the metabolism of brinzolamide. Brinzolamide and N-desethyl brinzolamide did not inhibit the metabolism of the CYP isozymes.

Low levels of brinzolamide are secreted in milk from lactating rats.

Brimonidine: Low plasma levels of brimonidine was detected in rabbits administered topical ocular eye drops of 1.5 mg/mL brimonidine tartrate which rapidly declined with a half-life of 1 hour. Brimonidine was rapidly absorbed into the eye with a high affinity for melanin in pigmented tissues such as iris-ciliary body.

In vitro studies showed the metabolism of brimonidine to be similar in rats, monkeys and humans. The major metabolites are generated by hepatic aldehyde oxidases. The primary route of brimonidine elimination is by metabolism. Following intravenous administration to rats and monkeys, brimonidine was eliminated with half-lives of 0.8 and 3.8 hours, respectively.

Brinzolamide and brimonidine combined: In rabbits that received topical ocular doses of Brinz/Brim, systemic exposure to brinzolamide, N-desethylbrinzolamide and brimonidine was detected.

Following the topical ocular administration of ophthalmic formulations of brimonidine and brinzolamide alone or in combination, the uptake of both drugs into the aqueous humour, bulbar conjunctiva and iris-ciliary body was demonstrated in F1 pigmented rabbits. After the ocular administration of three brinzolamide/brimonidine combination formulations (up to 10 mg/mL/2 mg/mL), the uptake of brinzolamide into the aqueous humour, bulbar conjunctiva and iris-ciliary body was also demonstrated.
body was similar to or greater than that following the administration of brinzolamide alone. Following 14 days of twice daily topical ocular administration of Brinz/Brim in rabbits, both drugs showed some accumulation in various ocular tissues. Brinzolamide exposure was higher for brinzolamide alone than for the combination in the lens, aqueous humour and iris-ciliary body and N-desethylbrinzolamide was detected in the choroid. Brimonidine AUC_{0-12 \text{ h}} was higher in most ocular matrices following the administration of Brinz/Brim than after brimonidine tartrate 2 mg/mL alone. There appears to be no clinical relevance of the increased ocular exposure of brinzolamide and/or brimonidine following the administration of the combination formulations compared to the individual components. In the clinical trials conducted, the safety profile of the fixed combination was similar to that of the individual components dosed as monotherapy or concomitantly and did not result in additional risk to patients relative to those known of the individual components.

**Pharmacokinetic drug interactions:** The metabolism of brinzolamide involves CYP isoenzymes. The metabolism of brimonidine involves hepatic aldehyde oxidases. The Applicant stated that due to the different metabolic pathways of the individual components in the fixed combination and the lack of extensive plasma protein binding, drug interactions between them would be unlikely. In addition, the results of a clinical pharmacokinetic study showed similar systemic exposure whether the two drugs were administered in the fixed combination or separately as brinzolamide or brimonidine following the administration of the combination formulations compared to the individual components. Potential interactions of brinzolamide/brimonidine with other drugs are outlined in the proposed SmPC.

### 2.3.3. Toxicology

**Single dose toxicity**

In a 1-day topical ocular toxicity study in rabbits that received 20 mg/mL brinzolamide, no significant effects were detected. In mice and rats, the oral LD50 of brinzolamide was estimated to be between 1000 and 2000 mg/kg. In mice and rats, the intravenous and oral LD50 values of brimonidine were 50 and 100 mg/kg, respectively.

**Repeat dose toxicity**

**Brinzolamide:** In repeated-dose topical ocular toxicity studies conducted for up to 6 months in non-pigmented rabbits and 1 year in monkeys, there was no significant irritation of the eye when up to 40 mg/mL brinzolamide was administered 4 times daily; which exceeded the proposed clinical concentration and dosing frequency of Brinz/Brim. No systemic effects were observed. A steady state whole blood concentration was achieved by 1 week post dose, while plasma levels of brinzolamide were below the limits of quantitation.

In repeated-dose oral toxicity studies, the urinary system was established as the primary site of target toxicity, which is consistent with the known effects of carbonic anhydrase inhibitors.
**Brimonidine:** In a 3-month repeated-dose topical ocular toxicity study conducted in pigmented rabbits with brimonidine tartrate 1.5 mg/mL eye drops, solution, the increased serum glucose effects observed were not considered clinically relevant due to the low systemic exposure of brimonidine in humans following ocular administration. In other repeated dose studies in several species, the systemic administration of 2.5 mg/kg/day brimonidine (>500 fold higher than the proposed clinical dose) produced sedation, ataxia, hypoactivity, ptosis, decreased muscle tone, hypotension and bradycardia which were considered to be related to the exaggerated pharmacology of the compound.

**Brinzolamide and brimonidine combined:** Decreased IOP was observed in rabbits that received the Brinz/Brim combination. The increased corneal thickness also observed was considered to be rabbit-specific and not clinically relevant. Sedation, a known pharmacological effect of the α2-receptor agonist class, was also observed and occurred at 13.6 times the estimated human systemic exposure. Additionally, some brimonidine-treated animals showed decreased food consumption which was considered secondary to sedation.

Penile erection and urogenital swelling were observed in animals that received brimonidine alone or the brinzolamide/brominidine combination. Penile erection resolved by approximately 2 hours post dose. These effects are considered related to α2-receptor agonists and not clinically relevant since neither has been reported in humans following clinical use of brimonidine alone or of the Brinz/Brim combination.

Increased serum glucose levels and resulting secondary effects of liver hepatocellular cytoplasmic vacuolisation and/or glycogen accumulation and islet cell hyperplasia of the pancreas were also observed in animals that received the brinzolamide/brominidine combination. These findings are not considered clinically relevant as there have been no reports of their occurrence in humans following topical ocular administration of brimonidine.

**Genotoxicity**

The genotoxic potential of brinzolamide and brimonidine were evaluated in *in vitro* and *in vivo* studies. Neither substance was considered to be genotoxic.

**Carcinogenicity**

In oral carcinogenicity studies up to 2 years in mice and rats, brinzolamide and brimonidine were not shown to be carcinogenic.

**Reproduction Toxicity**

**Brinzolamide:** In rats orally administered up to 18 mg/kg/day brinzolamide, there was no effect on male or female fertility. In embryofetal development (EFD) studies in rats dosed 18 mg/kg/day brinzolamide, an increased incidence of unossified sternebrae or hyoid and reduced ossification of the fetal skull was observed. In rabbits orally administered up to 6 mg/kg/day, there were no effects on fetal development. In a peri- and postnatal development study, reduced body weights were seen in the F1 pups, at the 15 mg/kg/day dose level. These effects are not considered clinically relevant following the topical ocular administration of brinzolamide.

**Brimonidine:** In rats orally administered up to 0.66 mg/kg/day brimonidine, there was no effect on fertility. Body weight changes were observed in the F0 males and F1 pups from the high dose group. However, following weaning no effects were observed in the F1 and F2 generations.
No embryolethal or teratogenic effects were observed in rats and rabbits dosed up to 2.5 mg/kg/day and 5 mg/kg/day brimonidine, respectively.

**Brinzolamide and brimonidine combined:** In view of the topical ocular toxicity studies with the Brinz/Brim combination which showed similar systemic effects and exposures as those observed in studies with the individual components, demonstrating no synergistic toxicity with the combination, the Applicant concluded that in compliance with the ICH M3 (R2) guidance, EFD studies with the brinzolamide/brominidine combination were not considered necessary. This is acceptable. Section 5.3 of the SmPC is considered adequate.

An exemption from studies in paediatric patients was granted by the EMA and therefore, no studies in juvenile animals have been conducted with the proposed combination product.

**Toxicokinetic data**

The systemic exposures of the individual brinzolamide or brimonidine agents following ocular administration were similar to those of the fixed dose brinzolamide/brominidine combination although studies of different durations were compared.

**Local Tolerance**

Topical ocular doses of brinzolamide/brominidine were well tolerated in rabbits.

**Other toxicity studies**

**Antigenicity:** Brinzolamide showed no potential to induce contact sensitisation in a guinea pig maximisation assay. Antigenicity studies with brimonidine or brinzolamide/brominidine formulations were not performed. This was acceptable, as there is no indication that these compounds would induce sensitisation.

**Immunotoxicity, dependence, metabolites:** No studies on immunotoxicity, dependence potential or metabolites were performed with brinzolamide or brimonidine alone or with the combination. This was acceptable, as no related concerns have arisen during their clinical use.

**Impurities:** There are no impurity issues. The proposed product is a fixed combination of brinzolamide and brimonidine that are already licensed and the impurities have previously been qualified.

**Phototoxicity:** Phototoxicity studies with brinzolamide were not conducted as it does not absorb ultra violet light between the 290 to 700 nm wavelengths. Phototoxicity studies with brimonidine alone or combined with brinzolamide are not considered necessary as no concerns have arisen during their clinical use.

**2.3.4. Ecotoxicity/environmental risk assessment**

In accordance with the Guideline on the environmental risk assessment of medicinal products for human use [EMEA/CHMP/SWP4447/00 corr 1*], the Applicant provided an environmental risk assessment for brinzolamide and brimonidine.
The log Kow for brinzolamide and brimonidine were determined according to the OECD-recommended shake-flask method (OECD Guideline 107) and a new report generated (TDOC-0017525 Version 1.0).

For brinzolamide, the log Kow values obtained in this study ranged from -0.83 to -0.81 with an average of -0.82.

For brimonidine, the log Kow values obtained in this study averaged to 0.42.

Table 1. Summary of main study results

<table>
<thead>
<tr>
<th>Substance (INN/Invented Name): Brinzolamide</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAS-number (if available):</td>
</tr>
<tr>
<td>PBT screening</td>
</tr>
<tr>
<td>Bioaccumulation potential- log Kow OECD107</td>
</tr>
<tr>
<td>Result -0.82 (pH 10)</td>
</tr>
<tr>
<td>Conclusion Potential PBT - No</td>
</tr>
<tr>
<td>PBT-statement:</td>
</tr>
<tr>
<td>The compound is not considered as PBT nor vPvB</td>
</tr>
</tbody>
</table>

Phase I

<table>
<thead>
<tr>
<th>Calculation</th>
<th>Value</th>
<th>Unit</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEC_surfacewater, default or refined (e.g. prevalence, literature)</td>
<td>$7 \times 10^{-3}$</td>
<td>$\mu g/L$</td>
<td>$&gt; 0.01$ threshold No</td>
</tr>
<tr>
<td>Other concerns (e.g. chemical class)</td>
<td></td>
<td></td>
<td>No</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Substance (INN/Invented Name): Brimonidine</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAS-number (if available):</td>
</tr>
<tr>
<td>PBT screening</td>
</tr>
<tr>
<td>Bioaccumulation potential- log Kow OECD107</td>
</tr>
<tr>
<td>Result 0.42 (pH 9)</td>
</tr>
<tr>
<td>Conclusion Potential PBT No</td>
</tr>
<tr>
<td>PBT-statement:</td>
</tr>
<tr>
<td>The compound is not considered as PBT nor vPvB</td>
</tr>
</tbody>
</table>

Phase I

<table>
<thead>
<tr>
<th>Calculation</th>
<th>Value</th>
<th>Unit</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEC_surfacewater, default or refined (e.g. prevalence, literature)</td>
<td>$1.4 \times 10^{-3}$</td>
<td>$\mu g/L$</td>
<td>$&gt; 0.01$ threshold No</td>
</tr>
<tr>
<td>Other concerns (e.g. chemical class)</td>
<td></td>
<td></td>
<td>No</td>
</tr>
</tbody>
</table>

Therefore, based on the lower than 4.5 log Kow value obtained (-0.82) and the PEC_surfacewater value ($7 \times 10^{-3}$) which is lower than the action limit (0.01 $\mu g/L$), brinzolamide 10 mg/mL in the
combination product Simbrinza is considered unlikely to represent a risk for the environment following its prescribed use.

In addition, based on the lower than 4.5 log $K_{ow}$ value obtained (0.42) and the $PEC_{\text{surfacewater}}$ value (1.4 x $10^{-3}$) which is lower than action limit (0.01 μg/L), brimonidine 2 mg/mL in the combination product Simbrinza is considered unlikely to represent a risk for the environment following its prescribed use.

These results indicate that further environmental studies are not required.

2.3.5. Discussion on non-clinical aspects

The non-clinical assessment of the Simbrinza (Brinzolamide/Brimonidine 10mg/mL + 2 mg/mL Eye Drops, Suspension) is mainly based upon the established non-clinical profiles of the individual approved active drug substances. Evaluation of the Brinzolamide/Brimonidine combination product, especially in relation to ocular safety and local tolerance has also been appropriately performed by the Applicant.

2.3.6. Conclusion on the non-clinical aspects

Overall, the non-clinical data presented is considered acceptable to support the clinical use of Simbrinza (Brinzolamide /Brimonidine 10mg/mL + 2 mg/mL Eye Drops, Suspension) for the treatment of elevated intraocular pressure in adult patients with open-angle glaucoma or ocular hypertension.

2.4. Clinical aspects

2.4.1. Introduction

Good Clinical Practice (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 were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies
### 2.4.2. Pharmacokinetics

As mentioned above, the posology approved in the US (thrice a day, TID) is different to the one in the EU (twice a day, BID) for both Brinzolamide and Brimonidine. Therefore Simbrinza, fixed dose combination of Brinzolamide/Brimonidine, was developed in two separate clinical development plans – BID programme and the TID programme. As the proposed posology for authorisation in the EU is twice a day (BID) dosing, the BID programme is relevant for this report, although the data from the TID programme offers supportive safety data.
Overall (BID + TID programmes), data from seven studies were submitted. The BID programme included three studies: a Phase 1 pharmacokinetic study with BID and TID dosing (C-10-010) and two Phase 3 confirmatory studies with BID dosing (C-10-040 and C-10-041).

**PK study (C-10-010)**

The pharmacokinetic study C-10-010 used an open-label design and enrolled healthy adults. The overview of this study is given in the table below.

<table>
<thead>
<tr>
<th>Safety / Clinical Pharmacology Studies (BID and TID programs)</th>
<th>Healthy male or female subjects 18 years of age or older</th>
<th>Brinzolamide/Brimonidine</th>
<th>23</th>
<th>1 drop in each eye 2 or 3 times daily</th>
<th>13 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-10-010/Phase 1 Randomized, parallel-group, open-label pharmacokinetic study</td>
<td>Brinzolamide</td>
<td>23</td>
<td>12</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Brimonidine</td>
<td>24</td>
<td>15</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

It was a randomized, multicenter, parallel-group, 13 week, pharmacokinetic study in 142 healthy subjects of at least 18 years of age. The primary objective was to compare the steady-state pharmacokinetics of Brimonidine in plasma and RBC saturation of Brinzolamide and N-desethyl brinzolamide following topical ocular administration of Brinzolamide/Brimonidine dosed TID or BID to the PK following administration of the individual components (Brinzolamide or Brimonidine) in healthy subjects.

The study was conducted in 2 phases, an oral treatment phase and a topical ocular treatment phase. The 14 day oral regimen with 1 mg brinzolamide BID allowed saturation of RBC carbonic anhydrase to be achieved in a reasonable time frame compared to topical ocular administration alone. Subjects were randomized to one of the 6 treatment arms. Subjects in the treatment arms 1, 2, 4, and 5 received 14 days of oral brinzolamide 1 mg, twice daily (BID). Subjects in the treatment arms 3 and 6 received no medication from Day 1 to Day 14. From Day 15, the administered investigational product and control article were as follows:

- **Brimonidine Tartrate 2 mg/mL Eye Drops. Solution** (dosed TID in Treatment Arm 3 or dosed BID in Treatment Arm 6) for Days 15 - 21.

Treatment arms 1, 2 and 3 evaluated the fixed dose and the mono-components at the TID dose regimen, while the treatment arms 4, 5 and 6 evaluated the BID dose regimen.

Subjects in treatment arms 1 to 5 were administered eye drops until Day 107, while subjects in treatment arm 6 were administered eye drops until Day 21.
Samples for PK measurement of Brinzolamide and N-desethyl Brinzolamide (in treatment arms 1, 2, 4 and 5) were taken at pre-dose on study day 1, 15, 21 and 107.

Samples for PK measurement of Brimonidine (in treatment arms 1, 3, 4 and 6) were at pre-dose on study day 15, 21 and 107 respectively. In addition, serial plasma sampling occurred post-dose for PK measurements of Brimonidine on Study Days 21 and 107 at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 8 hours and 12 hours (treatment arms 1, 4 and 6), respectively.

**Results:**

**Day 107 – RBC – Brinzolamide and N-desethyl brinzolamide**

Least Squares Mean ratio comparisons of whole blood concentration and corresponding 90% confidence intervals of the comparisons of Day 107 after TID and BID dosing are shown below.

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Least Squares Means</th>
<th>Least Squares Mean Ratio</th>
<th>Lower 90% CI</th>
<th>Upper 90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brinzolamide</td>
<td>TID 12.1</td>
<td>TID 15.3</td>
<td>0.789</td>
<td>0.597</td>
</tr>
<tr>
<td>N-Desethyl Brinzolamide</td>
<td>TID 1.32</td>
<td>TID 1.30</td>
<td>1.02</td>
<td>0.753</td>
</tr>
</tbody>
</table>

Brinz/Brin TID = Brinzolamide /Brimonidine 10 mg/mL + 2 mg/mL Eye Drops, Suspension, 3 times a day dosing
Brinzolamide TID = Brinzolamide 10 mg/mL Eye Drops, Suspension, three times a day dosing
ANOVA performed on ln-transformed data to calculate least squares means
RBC concentration (μM) derived from whole blood concentration data
Day 107 - Plasma – Brinzolamide

LSM and LSM ratio comparisons of Day 107 brinzolamide plasma concentrations after TID and BID administration are shown in the table below.

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Least Squares Means</th>
<th>Least Squares Mean Ratio</th>
<th>Lower 90% CI</th>
<th>Upper 90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brinzolamide</td>
<td>14.2</td>
<td>11.5</td>
<td>1.24</td>
<td>0.996</td>
</tr>
<tr>
<td>N-Desethyl Brinzolamide</td>
<td>1.56</td>
<td>1.44</td>
<td>1.08</td>
<td>0.772</td>
</tr>
</tbody>
</table>

Brinz/Brim BID = Brinzolamide /Brimonidine 10mg/mL + 2 mg/mL Eye Drops, Suspension, two times a day dosing
Brinzolamide BID = Brinzolamide 10 mg/mL Eye Drops, Suspension, two times a day dosing
ANOVA performed on ln-transformed data to calculate least squares means

Day 107 - Plasma – Brinzolamide

Plasma N-desethyl brinzolamide was not detectable (Limit of detection 1ng/ml) across all treatments (fixed combination or mono-component) and regimens (BID or TID).

Brimonidine PK data:

The results of the LSM ratio comparisons (AUC0-t and Cmax) for the comparison between the Brinz/Brim and Briminodine alone after BID and TID administration are presented in the tables below.
The results for Cmax and AUC of Briminodine after BID and TID administration of the fixed dose combination when compared against the mono-components were all comparable except for the Day 21 steady state systemic exposure of Brimonidine. Following BID administration of the combination product Brinz/Brim the systemic exposure (0.174) was less than the systemic exposure of Brimonidine administered alone (0.227) with the upper 90% confidence limit of the ratio falling slightly below unity (0.954).

**Conclusion**

The results showed the steady-state systemic exposure of brinzolamide, N-desethyl brinzolamide, and brimonidine following topical ocular administration of fixed combination Brinz/Brim dosed three times daily (TID) or two times daily (BID) was not meaningfully different compared to that observed following topical ocular administration of the individual active components, Brinzolamide or Brimonidine alone.
2.4.3. Pharmacodynamics

Mechanism of action
Brinzolamide is a carbonic anhydrase inhibitor (CAI). CAIs exert a direct antagonist activity on carbonic anhydrase within the ciliary epithelium, thereby reducing the production of bicarbonate ions which are critical for active ion and fluid transport across the ciliary epithelium. Additionally, when given systemically, CAIs also produce a generalized acidosis, which reduces aqueous humour formation. In order to lower IOP by sufficiently decreasing the amount of aqueous humour formed, the enzyme activity in the ciliary epithelium must be inhibited by at least 90%. IOP lowering effect has been shown to be in the range of 4 to 5 mm Hg in patients with POAG or OHT. When dosed appropriately, CAI treatment can maintain IOP control throughout a 24 hour period. Brinzolamide is approved for use 3 times daily (TID) in the US, although the IOP-lowering efficacy is only marginally better than twice daily (BID) dosing, which is approved elsewhere in most of the rest of the world including EU.

Brimonidine is an alpha 2-adrenergic agonist, highly selective for the alpha 2 receptor, specifically developed for glaucoma treatment. Alpha agonists reduce IOP by decreasing aqueous humour production. With chronic use they also increase uveoscleral outflow. Brimonidine targets the alpha 2-adrenergic receptor in the ciliary epithelium, leading to inhibition of adenylyl cyclase by activation of GTP-binding protein. Inhibiting adenylyl cyclase results in a decrease in cAMP levels intracellularly, ultimately resulting in suppression of aqueous humour production. The mechanism of action by which Brimonidine increases uveoscleral outflow is only poorly understood, but IOP-lowering in the region of 4 to 6 mmHg with Brimonidine treatment is commonly reported.

As the mechanism of Brimonidine and Brinzolamide differ, it can be expected that the combination would complement each other and obtain a better IOP lowering effect than either agent alone.

No additional pharmacodynamic studies have been conducted with the combination.

2.4.4. Discussion on clinical pharmacology

The proposed combination of Brinz/Brim is a novel fixed dose combination of two known active substances (Brinzolamide and Brimonidine) which are individually licensed and the clinical utility of which are well established. The PK characteristics of Brinzolamide and Brimonidine were reviewed and accepted as adequate during the assessment of the MAAs of the individual components. Therefore, the applicant’s approach for this application was to compare the PK/systemic exposure of both Brinzolamide and Brimonidine after administration as the combination (Brinz/Brim) and the mono-components (Brinz alone and Brim alone).

The results from both the BID and TID dosing are relevant as they characterise the PK of the active substances. For the comparison of Brinz/Brim and Brinz alone (both after BID and TID dosing), it was seen that

- Trough RBC levels of Brinz and N-Desethyl Brinz were broadly comparable
- Trough Plasma levels of Brinz were broadly comparable
For the comparison of Brinz/Brim and Brim alone it was seen that
- the 90% C.I for Cmax of Brim included unity both after BID and TID dosing - suggesting comparability
- the 90% C.I for AUC of Brim included unity only after TID dosing. After BID dosing the 90% CI for AUC ratio after Brinz/Brim compared to Brim alone was 0.614-0.954 - suggesting either comparable exposure (depending on results of TID dosing) or lower exposure with the combination (based on BID results)

The PK study shows that generally the PK/systemic exposure of the fixed dose is comparable to the PK/systemic exposure of the individual active constituent, although there are some differences as described above. However, it was agreed that these differences were acceptable, as they are not likely to be clinically significant, especially as a clinical study has been conducted to demonstrate non-inferiority of the combination of Brinz/Brim as compared to Brinz and Brim administered concomitantly. Additionally, the results of these studies support the inference that the PK of both Brinz and Brim are not significantly affected when they are administered as a Brinz/Brim combination. For a fixed dose combination of two known substances the PK of which are well-characterised, the presented PK study results was considered adequate.

No new clinical pharmacodynamic studies have been conducted with the combination of Brinz/Brim. Brinz belongs to a well-known class of carbonic anhydrase inhibitors whose pharmacodynamic properties are reasonably well characterised. Similarly, Brim belongs to the well-known class of alpha 2-adrenergic agonists whose pharmacodynamic properties are well established. The clinical utility and the safety profiles of these two classes of compounds in the treatment of open-angle glaucoma and ocular hypertension are also well established.

In clinical practice, both these products are used concomitantly in the same patient and the applicant has provided literature, discussion and evidence from previous medication history of the patients included in the pivotal studies to support this assertion.

As these products have different mechanisms of action, an additional ocular pressure lowering effect can be anticipated with the combination. Both products are recommended for administration twice a day. Therefore, the rationale for the development of this combination of Brinz/Brim was adequate.

2.4.5. Conclusions on clinical pharmacology

The results of the comparative PK study between Brinz/Brim, Brinz alone and Brim alone (C-10-010) is considered adequate and acceptable to support the application, as the PK of Brinz alone and Brim alone have been characterised and evaluated previously in the authorisation of the individual products.

The PK study shows that generally the PK/systemic exposure of the fixed dose is comparable to the PK/systemic exposure of the individual products.
2.5. **Clinical efficacy**

Seven clinical trials were submitted in support of this application. Five (C-10-010; C-09-038; C-10-033; C-10-039 and C-11-002) of which have been conducted in the USA and two studies (C-10-040 & C-10-041) were conducted across different countries, including many from the EU. Of these, only three studies (C-10-010; C10-040 and C-10-041) are central to the present application of BID dosing regimen.

As Brinzolamide/Brimonidine is a combination of two well-known treatments with established safety and efficacy, the dossier did not include the controlled trials that supported the development of the individual components and consequently these are not discussed in this report. The clinical development of the combination Brinzolamide/Brimonodine had two distinct parts; one part addressing the development for the EU posology of BID dosing for the components and the other part covering the US posology of TID dosing for the components.

The BID dosing development consisted of three clinical studies, including one pharmacokinetic study (C-10-010) and two Phase 3 studies (C-10-040 and C-10-041). These are the main studies supporting this application and discussed in detail in this report.

The TID dosing development consisted of five clinical studies, including one pharmacokinetic study (C-10-010), one POC study (C-09-038), one ocular comfort study (C-11-002), and two Phase 3 studies (C-10-033 and C-10-039). The results of the proof of concept study and ocular comfort study with TID dosing can be extrapolated to the BID dosing as well and are discussed under dose-finding and safety, respectively. The two phase 3 studies are discussed briefly below under supportive studies for efficacy as the efficacy results are not directly relevant to the BID dosing. The safety information from these studies relevant to the BID dosing are discussed under the safety section of this report.

Below is a brief description of the seven studies in this report:

- One pharmacokinetic study (C-10-010) – which compared the steady state PK of the combination of Brinzolamide/Brimonidine with that of the individual components. This study evaluated both the BID and TID dose regimens and has been discussed above under Pharmacokinetics;

- One proof of concept study (C-09-038) – which compared the efficacy of the Brinzolamide/Brimonidine combination with the mono-components using the TID regimen. However, it was accepted that this study will allow the proof-of-concept to be extrapolated to the BID regimen as well;

- Two main efficacy studies (C-10-040 & C-10-041), whereby C-10-040 aimed at demonstrating the superiority of the Brinzolamide/Brimonidine combination as compared to the mono-components, while C-10-041 aimed at demonstrating the non-inferiority of Brinzolamide/Brimonidine combination as compared to the mono-components administered concomitantly. These studies evaluated the BID regimen and hence are of key relevance to this application and discussed under 'main studies';

- Two other efficacy studies (C-10-033 and C-10-039) were similar to the two main efficacy studies above but evaluated the TID dosing regimen. Therefore, albeit in a different dosing regimen, they provide additional supportive information on the efficacy
of the combination. They are discussed briefly under ‘Supportive studies’. These studies also provide additional safety information for the combination.

- One local tolerability/comfort study (C-11-002), evaluating the TID dose regimen. However, its conclusions on tolerability are also applicable to the BID dosing regimen and therefore this study is discussed under ‘safety’.

2.5.1. Dose response studies

No dose-response studies were conducted with the combination. The dose-strength in the Brinz/Brim combination was the same as the approved dose-strengths of Brinz alone and Brim alone, respectively. This approach was supported by the results of the PK study and is a direct reflection of the way these two drugs are used concomitantly in clinical practice. A proof-of-concept study (study C-09-038) was conducted with the combination of Brinz/Brim comparing against Brinz alone, Brim alone and Brinz+Brim administered concomitantly. Study C-09-038 was conducted to investigate the hypothesis that the combination of Brinzolamide/Brimonodine would be more efficacious than the individual components and would not be inferior to the two drugs administered concomitantly. This study evaluated the TID dose regimen, but it was accepted that the inferences from this study could reasonably be extrapolated to the BID dose regimen.

Proof of concept STUDY C-09-038

This was a randomized, observer-masked, parallel-group, active-controlled study to evaluate the safety and IOP-lowering efficacy of the combination of Brinzolamide/Brimonodine fixed combination ophthalmic suspension in patients with open-angle glaucoma and/or ocular hypertension in comparison to the individual active constituents instilled either individually or concomitantly.

Enrolled patients were randomized to one of four study groups:

- Brinzolamide/Brimonodine and Vehicle in both eyes
- Brinzolamide and Brimonodine concomitantly administered to both eyes
- Brinzolamide and Vehicle in both eyes
- Brimonodine and Vehicle in both eyes

Adult patients diagnosed with open-angle glaucoma and/or ocular hypertension with mean IOP measurement in at least one eye of greater than or equal to 24 mmHg at the 8 AM time point and greater than or equal to 21 mmHg at the 10 AM time point at both eligibility visits prior to randomization were eligible.

Patients instilled their assigned study medications TID for 6 weeks and were evaluated for safety and efficacy at fixed times (8 AM, + 2 hrs, + 7 hrs, and + 9 hrs) at Week 2 and Week 6.

The primary efficacy endpoint was the mean change in IOP from baseline to each of the assessment time points (8 AM, + 2 hrs, + 7 hrs, and + 9 hrs) at Week 6.

In this study, 170 patients were enrolled and analysed.
Based on the 95% confidence interval around the mean differences at Week 6, Brinz/Brim was superior to Brinz at + 2 hrs, + 7 hrs, and + 9 hrs (Table 2-2) and was superior to Brim at both + 2 hrs and + 7 hrs (Table 2-3).

### Table 2-2:
**Comparison of Mean IOP Change (mmHg) from Baseline: Brinz/Brim versus Brinz (Intent-to-Treat Data)**

<table>
<thead>
<tr>
<th>Time</th>
<th>Points</th>
<th>N</th>
<th>Mean (SE)</th>
<th>N</th>
<th>Mean (SE)</th>
<th>Difference</th>
<th>(95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 6</td>
<td>8 AM</td>
<td>40</td>
<td>-5.5 (0.51)</td>
<td>44</td>
<td>-5.7 (0.48)</td>
<td>0.1</td>
<td>(-1.2, 1.5)</td>
</tr>
<tr>
<td></td>
<td>+2HRS</td>
<td>40</td>
<td>-8.5 (0.51)</td>
<td>44</td>
<td>-8.7 (0.48)</td>
<td>-3.8</td>
<td>(-5.2, -2.4)</td>
</tr>
<tr>
<td></td>
<td>+7HRS</td>
<td>39</td>
<td>-5.4 (0.51)</td>
<td>44</td>
<td>-2.8 (0.48)</td>
<td>-2.5</td>
<td>(-3.9, -1.1)</td>
</tr>
<tr>
<td></td>
<td>+9HRS</td>
<td>39</td>
<td>-6.8 (0.51)</td>
<td>44</td>
<td>-3.9 (0.48)</td>
<td>-2.9</td>
<td>(-4.3, -1.5)</td>
</tr>
</tbody>
</table>

*Brinz/Brim = brinzolamide 1%/brimonidine tartrate 0.2% ophthalmic suspension TID
Brinz = brinzolamide ophthalmic suspension, 1% TID
SE = Standard Error
Estimates based on least squares means using repeated measures analysis of variance.*

Overall, the frequentist analysis generally demonstrated that the combination product is superior to each of its active components in regard to the mean IOP change from baseline to Week 6.

### Table 2-3:
**Comparison of Mean IOP Change (mmHg) from Baseline: Brinz/Brim versus Brim (Intent-to-Treat Data)**

<table>
<thead>
<tr>
<th>Time</th>
<th>Points</th>
<th>N</th>
<th>Mean (SE)</th>
<th>N</th>
<th>Mean (SE)</th>
<th>Difference</th>
<th>(95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 6</td>
<td>8 AM</td>
<td>40</td>
<td>-5.5 (0.51)</td>
<td>41</td>
<td>-4.1 (0.50)</td>
<td>-1.4</td>
<td>(-2.8, 0.0)</td>
</tr>
<tr>
<td></td>
<td>+2HRS</td>
<td>40</td>
<td>-8.5 (0.51)</td>
<td>40</td>
<td>-5.3 (0.51)</td>
<td>-3.2</td>
<td>(-4.6, -1.8)</td>
</tr>
<tr>
<td></td>
<td>+7HRS</td>
<td>39</td>
<td>-5.4 (0.51)</td>
<td>40</td>
<td>-3.0 (0.51)</td>
<td>-2.4</td>
<td>(-3.8, -1.0)</td>
</tr>
<tr>
<td></td>
<td>+9HRS</td>
<td>39</td>
<td>-6.8 (0.51)</td>
<td>40</td>
<td>-5.9 (0.51)</td>
<td>-0.9</td>
<td>(-2.3, 0.5)</td>
</tr>
</tbody>
</table>

*Brinz/Brim = brinzolamide 1%/brimonidine tartrate 0.2% ophthalmic suspension TID
Brim = brimonidine tartrate ophthalmic solution, 0.2% TID
SE = Standard Error
Estimates based on least squares means using repeated measures analysis of variance.*

The mean IOP changes from baseline to Week 6 were similar at all 4 time points in the Brinz/Brim, Brinz + Brim groups. Specifically, the differences between study drug groups ranged from -0.22 to +0.03 mmHg and the respective 95% credible intervals had upper bounds ranging from 0.57 to 0.82 (all demonstrating non-inferiority, given the non-inferiority margin of 1.5 mmHg) (Table 2-4).
2.5.2. Main studies

There are two main phase 3 clinical studies (C-10-040 and C-10-041) that are supportive of the efficacy of the combination with BID dosing. A brief outline of these studies is provided below, before describing them in details individually.

**Study design**

Both Phase 3 confirmatory studies (C-10-040 and C-10-041) were double-masked and conducted in patients who were diagnosed with ocular hypertension (OHT) or open-angle glaucoma (OAG), with or without pseudo-exfoliation or a pigment dispersion component.

Both C-10-040 and C-10-041 were randomized, double-masked, parallel group, active-controlled studies. Both were with BID dosing.

**Objectives**

C-10-040 was designed to demonstrate the superiority of the Brinzolamide/Brimonidine fixed combination to each of its individual components whereas C-10-041 was designed to demonstrate the non-inferiority of Brinzolamide/Brimonidine compared to the individual components administered concomitantly (Brinzolamide+Brimonidine). Both studies were designed in accordance with ICH E9 (Statistical Principle for Clinical Trials, CPMP/ICH/363/96).

**Endpoints**

Primary efficacy for both studies was based on mean diurnal IOP change from baseline at 3 months, with supportive safety and efficacy evaluated through to 6 months.

**Treatments**

Study C-10-040 compared Brinz+Brim, Brinz alone and Brim alone in three parallel groups, while Study C-10-041 compared Brinz+Brim with Brinz and Brim concomitantly administered 10 minutes apart. In both studies patients instilled 1 drop of their assigned study medications in both eyes BID at 9 AM and 9 PM for 6 months.

<table>
<thead>
<tr>
<th>Visit</th>
<th>Time Points</th>
<th>Brinz/Brim Post Mean</th>
<th>95% Credible Interval</th>
<th>Brinz+Brim Post Mean</th>
<th>95% Credible Interval</th>
<th>Difference Post Mean</th>
<th>95% Credible Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 6</td>
<td>8 AM</td>
<td>-6.09 (-6.66, -5.53)</td>
<td>-6.12 (-6.67, -5.56)</td>
<td>0.03 (-0.76, 0.82)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>+2 HRS</td>
<td>-7.68 (-8.24, -7.12)</td>
<td>-7.67 (-8.23, -7.11)</td>
<td>-0.02 (-0.81, 0.77)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>+7 HRS</td>
<td>-6.14 (-6.70, -5.58)</td>
<td>-5.92 (-6.48, -5.36)</td>
<td>-0.22 (-1.01, 0.57)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>+9 HRS</td>
<td>-6.81 (-7.36, -6.25)</td>
<td>-6.78 (-7.34, -6.22)</td>
<td>-0.02 (-0.81, 0.77)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Brinz/Brim = brinzolamide 1%/brimonidine tartrate 0.2% ophthalmic suspension TID
Brinz + Brim = brinzolamide ophthalmic suspension, 1%, and brimonidine tartrate ophthalmic solution, 0.2% administered TID concomitantly
Difference=Brinz/Brim – Brinz + Brim
Post Mean=Posterior Mean
**Study Participants**

Both C-10-040 and C-10-041 enrolled adult patients aged 18 years and older, including elderly, diagnosed with primary open-angle glaucoma and/or ocular hypertension, who in the opinion of the investigator were insufficiently controlled on monotherapy or were already taking multiple IOP-lowering medications.

The inclusion criteria are summarized below:
- Diagnosed with open-angle glaucoma or ocular hypertension, who in the opinion of the Investigator, were insufficiently controlled on monotherapy or were already on multiple IOP-lowering medications (subjects 18 years or older)
- Mean IOP measurements in at least 1 eye, the same eye(s), must have been:
  - ≥ 24 mmHg and ≤ 36 mmHg at the 9 AM time point, and
  - ≥ 21 mmHg and ≤ 36 mmHg at the 11 AM time point at both the Eligibility 1 and Eligibility 2 visits following washout of any IOP-lowering medication
- Mean IOP must not have been > 36 mmHg in either eye at any time point.
- Should have been able to understand and sign an informed consent that had been approved by an Institutional Review Board/Independent Ethics Committee

The exclusion criteria are summarized as follows:
- Women of childbearing potential if pregnant, test positive for pregnancy at Screening Visit, breastfeeding, or not in agreement to use adequate birth control methods to prevent pregnancy throughout the study.
- Severe central visual field loss.
- Best corrected visual acuity (BCVA) score worse than 55 ETDRS letters (20/80 Snellen equivalent).
- Chronic, recurrent or severe inflammatory eye disease.
- Ocular trauma within the preceding 6 months.
- Ocular infection or ocular inflammation within the preceding 3 months.
- Clinically significant or progressive retinal disease.
- Other ocular pathology.
- Intraocular surgery within the 6 months prior to entry.
- Ocular laser surgery within the 3 months prior to entry.
- Any abnormality preventing reliable applanation tonometry.
- Any other conditions, including severe illness, which would make the subject, in the opinion of the Investigator, unsuitable for the study.
- Recent use of high-dose (>1 gram daily) salicylate therapy.
- Recent, current, or anticipated treatment with any medication that augments adrenergic responses, or precludes use of an alpha-adrenergic agonist.
- Concurrent use of glucocorticoid medications administered by any route.

Following washout of previous IOP-lowering medications, patients had to have an IOP between 24 and 36 mmHg at 8 AM and between 21 and 36 mmHg at 10 AM on each of 2 eligibility visits. The same eye was required to qualify at each time-point. The Eligibility 2 Visit was conducted 3 to 8 days after the Eligibility 1 Visit.

In both pivotal studies, randomization was stratified into 2 groups of patients, according to their baseline IOP (low: 24 to 27 mmHg, and high: 28 to 36 mmHg).

**In-Study Assessments**

During the treatment phase, visits were performed at Week 2 (i.e. 14 ± 3 day), Week 6 (i.e. 42 ± 3 days), Month 3 (i.e. 90 days ± 7 days), and Month 6 (i.e. 180 days ± 7 days) after the second Eligibility Visit.
For C-10-040 IOP measurements were taken once at screening and at 3 time points during all other post-screening visits at 9AM, 11 AM (+2 h) and 4PM (+7h). Patients at selected investigational centres underwent additional IOP measurements at 7 PM (+ 10 h) as well.

For C-10-041, IOP measurements were taken once at screening and 2 times at all other post-screening visits: at 9 AM and 11 AM (+2 h).

In each study, the baseline IOP measurement for each eye and time point was estimated as the mean IOP obtained during each of the 2 eligibility visits.

The safety assessments included adverse events, pachymetry, automated perimetry, pulse/blood pressure, fundus parameters ( vitreous, retina/macula/choroid and optic nerve), best-corrected visual acuity (BCVA) and slit-lamp examination (cornea, iris/anterior chamber, lens, eyelids and conjunctiva).

**STUDY C-10-040**

**Methods**

- **Statistical methods**

**Analysis Populations**

The intent-to-treat (ITT) analysis set included all patients who received study drug and completed at least one scheduled on-therapy study visit. The per protocol (PP) analysis set included all patients who satisfied pre-randomization inclusion/exclusion criteria, received study drug, and completed at least one scheduled on-therapy study visit. In addition, individual patient visits and data points that did not satisfy the protocol criteria may have been excluded from the PP analysis set. The ITT analysis set provided primary inference for the primary and supportive efficacy analyses, while the PP analysis set was considered supportive. The safety analysis set included all patients who received study drug. Evaluability for inclusion of patients (and where applicable, individual study visits) in the ITT, PP, and safety analysis sets was determined prior to locking the database and breaking the code for the masked study drug.

One eye from each patient was chosen as the study eye and only data for the study eye were used for the efficacy analyses. In cases where a patient dosed only 1 eye during the study, the dosed eye was selected as the study eye. If both eyes were dosed during the study, the worse evaluable eye was selected as the study eye. The worse eye was defined as the eye with the higher IOP at 9 AM averaged across the 2 eligibility visits. If both eyes had equal IOP measurements at the specified time point, then the worse eye was defined as the eye with the higher IOP at 11 AM averaged across the 2 eligibility visits. If both eyes had equal IOP measurements at the specified time point, then the right eye was selected for analysis.

**Primary Efficacy Endpoint**

The superiority of Brinzolamide/Brimonidine to each of its individual active components (Brinzolamide and Brimonidine) with respect to treatment group differences in the mean diurnal IOP change from baseline was determined using pairwise tests at each on-therapy study visit.
In addition, the mean diurnal IOP change from baseline was summarized using descriptive statistics for each on-therapy visit up to Month 3 (Week 2, Week 6, Month 3) and at Month 6 (the IOP assessments were collected at this visit for patient safety). Similarly, descriptive statistics by visit were also presented for the diurnal IOP change from baseline using IOP change measurements averaged over the assessment time points at 9 AM, + 2 h, + 7 h, and + 10 h in those investigational centres that were selected to perform an assessment of IOP at +10 h (of note, the +10 h collection time point was not performed at Week 2).

The primary efficacy endpoint was analysed on an observed-case basis. For this analysis, the statistical model and associated analyses used were robust for data missing at random. A sensitivity analysis was performed in which the last observation carried forward (LOCF) method was used to impute values for dropouts and for missing IOP values at Month 3. If a patient missed a visit, the most recently measured IOP for the same time of day was used to impute the IOP at the missed Month 3 visit. Similarly, if a patient was discontinued from the study, the last IOP measurement for each time of day was carried forward to replace the IOP measurements for the Month 3 visit. Treatment group differences in mean IOP were determined using pairwise, 2-sample t-tests for each time point at the Month 3 visit.

**Supportive Efficacy Endpoints**

Pairwise tests were performed using the least squares means derived from a statistical model that accounted for correlated IOP measurements within patient where investigational centre and actual baseline 9 AM IOP stratum were included in the model. Differences between treatment groups in the percentage of patients with IOP measurements less than 18 mmHg at each on-therapy study visit were investigated across strata (investigational centre and 9 AM baseline IOP category) using a Cochran-Mantel-Haenszel test. The IOP values, the absolute and percent changes in IOP values from baseline, and the percentage of patients with IOP values less than 18 mmHg were summarized using descriptive statistics at each on-therapy visit and time point.

**Results**

- **Participant flow**

Overall, 560 patients were randomized in the study, including 193 in the Brinzolamide/Brimonidine group, 192 in the Brinzolamide group, and 175 in the Brimonidine group. The same percentage of patients in the Brinzolamide/Brimonidine and Brimonidine groups discontinued early from the study (17.1%); this percentage was greater than the percentage of patients in the Brinzolamide group who discontinued early from the study (7.3%).
The most commonly reported reason for discontinuation was an adverse event (AE). This was highest in the Brinzolamide/Brimonidine arm (11.9%) followed by the Brimonidine (8.6%) and Brinzolamide (0.5%) groups. The second most common reason for discontinuation was inadequate control of IOP, which was highest in the Brimonidine arm and lowest with the Brinzolamide/Brimonidine combination.
Baseline data

The patients were primarily 65 years of age and older (54.0%), female (55.3%), and White (70.5%). The majority of patients also had brown eyes (60.3%) and a diagnosis of open-angle glaucoma (75.3%). No clinically meaningful differences were observed between study drug groups in regard to any demographic parameter. The mean diurnal IOP at baseline was similar for the Brinzolamide/Brimonidine (25.9 mmHg), Brinzolamide (25.9 mmHg), and Brimonidine (26.0 mmHg) groups. The mean baseline IOP measurements in all 3 study drug groups were similar at each of the 3 assessment time points (approximately 27 mmHg at 9 AM, approximately 26 mmHg at 11 AM, and approximately 25 mmHg at 4 PM); no important differences were noted in the mean baseline IOP measurements (average of Eligibility 1 and 2 visits for each time point) among the study drug groups at any of the assessment time points. Within the ITT analysis set most patients (70.1%) had a baseline IOP within the 24 to 27 mmHg stratum.

The mean corneal thickness at baseline was approximately 0.55 mm in each study drug group. No meaningful differences in baseline corneal thickness measurements were observed between study drug groups or between the ITT and PP analysis sets. More than 90% of the patients in each study drug group had corneal thickness measurements of 0.60 mm or less.

The base-line IOP lowering medications prior to study entry were comparable across treatment groups and were consistent with choice of IOP lowering agents in clinical practice.

Outcomes and estimation

PRIMARY ENDPOINT

The mean diurnal IOP reduction from baseline at Month 3 was greater for patients in the Brinzolamide/Brimonidine group (7.9 mmHg) than for patients in the Brinzolamide (6.5 mmHg) and the differences in mean diurnal IOP change from baseline significantly favoured Brinzolamide/Brimonidine relative to Brinzolamide (-1.4 mmHg; p < 0.0001) as shown in the table below.
Comparison of Brinz/Brim combination versus Brinz monotherapy:

Primary analysis (not true ITT):

<table>
<thead>
<tr>
<th>Visit</th>
<th>Brinz/Brim BID Mean (SE)</th>
<th>Brinz BID Mean (SE)</th>
<th>Mean Differenceb (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Month 3</td>
<td>176 -7.9 (0.22)</td>
<td>182 -6.5 (0.23)</td>
<td>-1.4 (-1.9, -0.8)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Comparison of Brinz/Brim combination versus Brim monotherapy:

The mean diurnal IOP reduction from baseline at Month 3 was greater for patients in the Brinzolamide/Brimonidine group (7.9 mmHg) than for patients in the Brimonidine groups (6.4 mmHg), and the differences in mean diurnal IOP change from baseline significantly favored Brinzolamide/Brimonidine relative to Brimonidine (-1.5 mmHg; p < 0.0001) as shown in the table below.

Primary analysis (not true ITT):

<table>
<thead>
<tr>
<th>Visit</th>
<th>Brinz/Brim BID Mean (SE)</th>
<th>Brim BID Mean (SE)</th>
<th>Mean Differenceb (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Month 3</td>
<td>176 -7.9 (0.22)</td>
<td>161 -6.4 (0.24)</td>
<td>-1.5 (-2.0, -0.9)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

For the primary endpoint, the applicant also submitted 4 types of analyses for handling the missing data, starting with minimal imputation and ending with conservative methods to address the plausible sources of bias. For all the described sensitivity analyses, regardless of how they handled missing data, results remained consistent with those from the original primary analyses, thus confirming the conclusions of superiority.

Supportive Endpoints

- The mean diurnal IOP reductions from baseline at Week 2, Week 6, and Month 6 were greater in the Brinzolamide/Brimonidine group than in either the Brinzolamide or Brimonidine groups (p ≤ 0.0001 for each pairwise comparison at every study visit). The
mean differences between the Brinzolamide/Brimonidine group and each of its active components at these study visits ranged from -1.1 to -1.6 mmHg.

- The percentages of patients with an IOP measurement less than 18 mmHg were greater in the Brinzolamide/Brimonidine group than in the Brinzolamide group at eleven of twelve assessments through Month 6 and were greater in the Brinzolamide/Brimonidine group than in the Brimonidine group at all twelve assessments through to Month 6.

For the supportive endpoint of achievement of IOP < 18 mmHg, counting missing data as failures, i.e. IOP ≥ 18 mmHg, had no substantial impact on the overall conclusions.
### Summary of main study

The following table summarises the efficacy results from the main study C-10-040 supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

#### Brinz/Brin MIB vs. Brinz BID

<table>
<thead>
<tr>
<th>Visit Number</th>
<th>Time</th>
<th>Total</th>
<th>Brinz/Brin MIB</th>
<th>Brinz BID</th>
<th>p-vala</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td></td>
</tr>
<tr>
<td>Week 2</td>
<td>9 AM</td>
<td>193</td>
<td>56 29.0</td>
<td>192 42</td>
<td>21.9</td>
</tr>
<tr>
<td></td>
<td>+2 hrs</td>
<td>193</td>
<td>107 55.4</td>
<td>192 70</td>
<td>36.5</td>
</tr>
<tr>
<td></td>
<td>+7 hrs</td>
<td>193</td>
<td>95  49.2</td>
<td>192 70</td>
<td>36.5</td>
</tr>
<tr>
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<td>9 AM</td>
<td>193</td>
<td>56 29.0</td>
<td>192 37</td>
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</tr>
<tr>
<td></td>
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<td>193</td>
<td>119 61.7</td>
<td>192 65</td>
<td>33.9</td>
</tr>
<tr>
<td></td>
<td>+7 hrs</td>
<td>193</td>
<td>101 52.3</td>
<td>192 77</td>
<td>40.1</td>
</tr>
<tr>
<td>Month 3</td>
<td>9 AM</td>
<td>193</td>
<td>53 27.5</td>
<td>192 54</td>
<td>28.1</td>
</tr>
<tr>
<td></td>
<td>+2 hrs</td>
<td>193</td>
<td>119 61.7</td>
<td>192 77</td>
<td>40.1</td>
</tr>
<tr>
<td></td>
<td>+7 hrs</td>
<td>193</td>
<td>105 54.4</td>
<td>192 88</td>
<td>45.8</td>
</tr>
<tr>
<td>Month 6</td>
<td>9 AM</td>
<td>193</td>
<td>48 24.9</td>
<td>192 56</td>
<td>29.2</td>
</tr>
<tr>
<td></td>
<td>+2 hrs</td>
<td>193</td>
<td>104 53.9</td>
<td>192 82</td>
<td>42.7</td>
</tr>
<tr>
<td></td>
<td>+7 hrs</td>
<td>193</td>
<td>88  45.6</td>
<td>192 88</td>
<td>45.8</td>
</tr>
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</table>

#### Brinz BID vs. Brin MIB

<table>
<thead>
<tr>
<th>Visit Number</th>
<th>Time</th>
<th>Total</th>
<th>Brinz BID</th>
<th>Brinz/Brin MIB</th>
<th>p-vala</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td></td>
</tr>
<tr>
<td>Week 2</td>
<td>9 AM</td>
<td>193</td>
<td>27 15.4</td>
<td>175 56 29.0</td>
<td>0.0009</td>
</tr>
<tr>
<td></td>
<td>+2 hrs</td>
<td>193</td>
<td>69 39.4</td>
<td>175 107 55.4</td>
<td>0.0014</td>
</tr>
<tr>
<td></td>
<td>+7 hrs</td>
<td>193</td>
<td>54 30.9</td>
<td>175 95 49.2</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Week 6</td>
<td>9 AM</td>
<td>193</td>
<td>30 17.1</td>
<td>175 56 29.0</td>
<td>0.0055</td>
</tr>
<tr>
<td></td>
<td>+2 hrs</td>
<td>193</td>
<td>73 41.7</td>
<td>175 119 61.7</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td></td>
<td>+7 hrs</td>
<td>193</td>
<td>61 34.9</td>
<td>175 101 52.3</td>
<td>0.0043</td>
</tr>
<tr>
<td>Month 3</td>
<td>9 AM</td>
<td>193</td>
<td>34 19.4</td>
<td>175 53 27.5</td>
<td>0.0976</td>
</tr>
<tr>
<td></td>
<td>+2 hrs</td>
<td>193</td>
<td>70 40.0</td>
<td>175 119 61.7</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td></td>
<td>+7 hrs</td>
<td>193</td>
<td>62 35.4</td>
<td>175 105 54.4</td>
<td>0.0002</td>
</tr>
<tr>
<td>Month 6</td>
<td>9 AM</td>
<td>193</td>
<td>35 20.0</td>
<td>175 48 24.9</td>
<td>0.2085</td>
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<tr>
<td></td>
<td>+2 hrs</td>
<td>193</td>
<td>66 37.7</td>
<td>175 104 53.9</td>
<td>0.0030</td>
</tr>
<tr>
<td></td>
<td>+7 hrs</td>
<td>193</td>
<td>61 34.9</td>
<td>175 88 45.6</td>
<td>0.0076</td>
</tr>
</tbody>
</table>
**Table 3: Summary of efficacy for trial C-10-040**

**Title:** Safety and IOP-Lowering Efficacy of Brinzolamide 10 mg/mL/Brimonidine 2 mg/mL Fixed Combination Eye Drops, Suspension Compared to Brinzolamide 10 mg/mL Eye Drops, Suspension and Brimonidine 2 mg/mL Eye Drops, Solution in Patients with Open-Angle Glaucoma or Ocular Hypertension.

<table>
<thead>
<tr>
<th>Study identifier</th>
<th>C-10-040</th>
</tr>
</thead>
</table>

**Design**

Multicenter, randomized, double-masked, parallel-group, active-controlled study designed to evaluate the safety and efficacy of Brinzolamide/Brimonidine in lowering IOP relative to each of its individual active components in patients with open-angle glaucoma or ocular hypertension.

<table>
<thead>
<tr>
<th>Duration of main phase:</th>
<th>3 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of Run-in phase:</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Duration of Extension phase:</td>
<td>3 months</td>
</tr>
</tbody>
</table>

**Hypothesis**

Superiority of Brinzolamide/brimonidine to each of its individual components with respect to treatment group differences in the mean diurnal IOP change from baseline.

**Treatments groups**

| Brinzolamide/Brimonidine | One drop in each eye BID for 6 months; number randomized =193 |
| Brinzolamide | One drop in each eye BID for 6 months; number randomized =192 |
| Brimonidine | One drop in each eye BID for 6 months; number randomized =175 |

**Endpoints and definitions**

**Primary endpoint**

Mean diurnal IOP change from baseline at month 3 (ie, the patient IOP change from baseline averaged over the 9 AM, +2h and +7 h time points at month 3).

**Supportive endpoints**

Mean diurnal IOP change from baseline at week 2, week 6 and month 6

Mean IOP at week 2, week 6, month 3 and month 6 for each time-point

Mean IOP change from baseline at week 2, week 6, month 3 and month 6 for each time-point

Mean IOP percent change from baseline at week 2, week 6, month 3 and month 6 for each assessment time-point

Percentage of patients with an IOP less than 18 mm Hg at each visit and time-point.
### Results and Analysis

<table>
<thead>
<tr>
<th>Analysis description</th>
<th>Primary Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analysis population and time point description</td>
<td>Applicant defined Intent to treat = Completers Only (therefore not accepted for main assessment of efficacy)</td>
</tr>
<tr>
<td></td>
<td>Assessment carried out in True ITT (with LOCF); Mean change in IOP from baseline at month 3</td>
</tr>
<tr>
<td>Descriptive statistics and estimate variability</td>
<td>Treatment group</td>
</tr>
<tr>
<td>Month 3</td>
<td>N</td>
</tr>
<tr>
<td></td>
<td>Mean change IOP</td>
</tr>
<tr>
<td></td>
<td>SE</td>
</tr>
<tr>
<td>Effect estimate per comparison</td>
<td>Primary endpoint (in true ITT)</td>
</tr>
<tr>
<td></td>
<td>Mean difference between treatments at month 3</td>
</tr>
<tr>
<td></td>
<td>95% CI (-1.9, -0.6)</td>
</tr>
<tr>
<td></td>
<td>p&lt;0.0001</td>
</tr>
</tbody>
</table>
STUDY C-10-041

This study was designed to demonstrate that there was no loss in efficacy with the fixed dose combination as compared to both the components administered concomitantly.

Methods

- **Statistical methods**

Analysis Populations

The intent-to-treat (ITT) analysis set included all patients who received study drug and completed at least one scheduled on-therapy study visit. The per protocol (PP) analysis set included all patients who satisfied pre-randomization inclusion/exclusion criteria, received study drug, and completed at least one scheduled on-therapy study visit. In addition, individual patient visits and data points that did not satisfy the protocol criteria could have been excluded from the PP analysis set. The PP analysis set provided primary inference for the primary and supportive efficacy analyses, while the ITT analysis set was considered supportive. The safety analysis set included all patients who received study drug. Evaluability for inclusion of patients (and where applicable, individual study visits) in the ITT, PP, and safety analysis sets was determined prior to locking the database and breaking the code for masked study drug.

One eye from each patient was chosen as the study eye, as described above for study C-10-040.

Primary Efficacy Endpoint

The primary efficacy endpoint was the mean diurnal IOP change from baseline at Month 3. The mean diurnal IOP change from baseline at Month 3 was calculated as the average of the available IOP changes from baseline across time points (9 AM, + 2 h) at Month 3. For the test of non-inferiority, 95% 2-sided confidence intervals (CIs) were constructed for the differences in the mean diurnal IOP change from baseline between study drug groups at each visit and time point. The non-inferiority of Brinzolamide/Brimonidine relative to Brinzolamide+Brimonidine was assessed through an examination of the CIs for the Month 3 visit; the non-inferiority margin was + 1.5 mmHg.

Treatment group differences in mean diurnal IOP change from baseline were determined using pairwise tests at each on-therapy visit. The pairwise test was based on the least squares means derived from a statistical model that accounted for correlated IOP measurements within patient where investigational centre and actual baseline 9 AM IOP stratum were included in the model.
Supportive Efficacy Endpoints

The supportive efficacy endpoints included:

- The mean diurnal IOP change from baseline (i.e. the patient IOP change from baseline averaged over the 9 AM and + 2 h time points) at Week 2, Week 6, and Month 6
- The mean IOP at Week 2, Week 6, Month 3, and Month 6 for each assessment time point (9 AM and + 2 h)
- The mean IOP change from baseline at Week 2, Week 6, Month 3, and Month 6 for each assessment time point (9 AM and + 2 h)
- The mean IOP percent change from baseline at Week 2, Week 6, Month 3, and Month 6 for each assessment time point (9 AM and + 2 h)
- The percentage of patients with an IOP less than 18 mmHg at each on-therapy visit up to Month 6 for each assessment time point (Week 2, Week 6, Month 3, and Month 6 at 9 AM and + 2 h)

As in study C-10-040, the primary endpoint was analysed on an observed-case basis and a sensitivity analysis was carried out using LOCF.

Results

- Participant flow

Patient disposition
A total of 890 patients were randomized in the study, including 451 in the Brinzolamide/Brimonidine group and 439 in the Brinzolamide+Brimonidine group. Overall, 83.8% of the patients completed the study; the percentages of patients in each study drug group who completed the study were similar.
The number of discontinuations and the reasons are depicted in the table below:

<table>
<thead>
<tr>
<th>Type of Analysis</th>
<th>Data Set</th>
<th>Exclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized To Treatment (N = 890)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brinz/Brim BID (451)</td>
<td>Brinz+Brim BID (439)</td>
<td></td>
</tr>
<tr>
<td>Safety1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Evaluable For Safety Analysis (N = 888)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brinz/Brim BID (452)</td>
<td>Brinz+Brim BID (436)</td>
<td></td>
</tr>
<tr>
<td>Excluded From Safety Analysis (N = 2)</td>
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<td></td>
</tr>
<tr>
<td>Brinz/Brim BID (1)</td>
<td>Brinz+Brim BID (1)</td>
<td></td>
</tr>
<tr>
<td>Intent-to-Treat2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Evaluable For Intent-to-Treat Analysis (N = 874)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brinz/Brim BID (443)</td>
<td>Brinz+Brim BID (431)</td>
<td></td>
</tr>
<tr>
<td>Excluded From Intent-to-Treat Analysis (N = 16)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brinz/Brim BID (8)</td>
<td>Brinz+Brim BID (8)</td>
<td></td>
</tr>
<tr>
<td>Per Protocol2,3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Evaluable For Per Protocol Analysis (N = 831)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brinz/Brim BID (420)</td>
<td>Brinz+Brim BID (411)</td>
<td></td>
</tr>
<tr>
<td>Excluded From Per Protocol Analysis (N = 59)</td>
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</tr>
<tr>
<td>Brinz/Brim BID (31)</td>
<td>Brinz+Brim BID (28)</td>
<td></td>
</tr>
</tbody>
</table>

Brinz/Brim BID = Brinzolamide/Brimonidine 10 mg/mL + 2 mg/mL Eye Drops, Suspension BID
Brinz+Brim BID = Brinzolamide 10 mg/mL Eye Drops, Suspension BID plus Brimonidine Tartrate 2 mg/mL Eye Drops, Solution BID

1 Patients analyzed according to treatment received. Two patients (5374.8051 and 6200.2801) were randomized to Brinz+Brim but actually received Brinz/Brim.
2 Patients analyzed according to randomized treatment.
3 Primary efficacy is based on an observed case analysis of the PP dataset.
Of the 890 randomized patients, only 874 (98.2%) were included in the ITT analysis set. 831 (93.4%) were included in the PP analysis set, and 888 (99.8%) were included in the safety analysis set.

- **Baseline data**

  Within the PP analysis set, slight majorities of the patients were female (56.1%) and aged 65 years and older (51.1%; overall mean age = 63.3 years). The patients were primarily White (64.6%), had brown eyes (66.1%), and presented with a diagnosis of open-angle glaucoma (75.9%). No clinically meaningful differences were observed between study drug groups in regard to any demographic parameter. The mean diurnal IOP at baseline was similar for Brinzolamide/Brimonidine (26.4 mmHg) and Brinzolamide+Brimonidine (26.5 mmHg) groups. The mean baseline IOP measurements across both time points (9 AM and 11 AM) and study drug groups ranged from 25.8 to 27.0 mmHg. The largest mean IOP measurement was observed in both study drug groups at the 9 AM time point. No important differences were noted in the mean baseline IOP measurements (average of Eligibility Visit 1 and Eligibility Visit 2 for each time point) among the study drug groups at either of the assessment time points.

  The mean corneal thickness at baseline was approximately 0.55 mm in each study drug group. No meaningful differences in baseline corneal thickness measurements were observed between study drug groups.

  The base-line IOP lowering medications prior to study entry were comparable across treatment groups and were consistent with choice of IOP lowering agents in clinical practice.

- **Outcomes and estimation**

  **Primary Endpoint**

  At Month 3, the mean diurnal IOP reduction from baseline was similar for patients in the Brinzolamide/Brimonidine and Brinzolamide+Brimonidine groups (8.5 mmHg and 8.3 mmHg, respectively). The treatment group difference was -0.1 mmHg with an upper bound of the 95% CI equal to 0.2 mmHg, which is below the pre-specified non-inferiority margin of 1.5 mmHg.
PP analysis:

For the primary endpoint, the applicant also submitted 4 types of analyses for handling the missing data, starting with minimal imputation and ending with conservative methods to address the plausible sources of bias. For all the described sensitivity analyses, regardless of how they handled missing data, results remained consistent with those from the original primary analyses, thus confirming the conclusions of non-inferiority.

Supportive Endpoints

- The mean diurnal IOP reductions from baseline at Week 2, Week 6, and Month 6 were similar in the Brinzolamide/Brimonidine and Brinzolamide+Brimonidine groups (Figure 2.5.4–4). The magnitude of the maximum observed mean difference between treatment groups was 0.1 mmHg.
The percentages of patients with an IOP measurement less than 18 mmHg were similar across study visits for the same time point through Month 6 in the Brinzolamide/Brimonidine and Brinzolamide+Brimonidine groups.

For the supportive endpoint of achievement of IOP < 18 mmHg, counting missing data as failures, i.e. IOP ≥ 18 mmHg, had no substantial effect on overall conclusions.

- By definition, numerators remained the same while denominators increased, resulting in reduced percentages of patients having IOP < 18 mmHg at each visit and time point.
- As with the original analysis without imputation, percentages with IOP < 18 mmHg were similar for Brinzolamide/Brimonidine and Brinzolamide+Brimonidine at all visits and time points.
**Summary of main study**

The following table summarises the efficacy results from the main study C-10-041 supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

**Table 4. Summary of efficacy for trial C-10-041**

<table>
<thead>
<tr>
<th>Study identifier</th>
<th>C-10-041</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Design</strong></td>
<td>Multicenter, randomized, double-masked, parallel-group, active-controlled study intended to evaluate the safety and efficacy of the fixed combination product (Brinzolamide/Brimonidine) in lowering IOP relative to each of its individual active constituents instilled concomitantly (Brinzolamide+Brimonidine) in patients with open-angle glaucoma or ocular hypertension.</td>
</tr>
<tr>
<td>Duration of main phase:</td>
<td>3 months</td>
</tr>
<tr>
<td>Duration of Run-in phase:</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Duration of Extension phase:</td>
<td>3 months</td>
</tr>
<tr>
<td><strong>Hypothesis</strong></td>
<td>Non-inferiority of Brinzolamide/brimonidine when compared to concomitant administration of Brinzolamide and Brimonidine</td>
</tr>
<tr>
<td><strong>Treatments groups</strong></td>
<td></td>
</tr>
<tr>
<td>Brinzolamide/Brimonidine</td>
<td>One drop in each eye BID for 6 months; number randomized =451</td>
</tr>
<tr>
<td>Brinzolamide and Brimonidine</td>
<td>One drop of each treatment in each eye BID for 6 months; number randomized =439</td>
</tr>
<tr>
<td><strong>Endpoints and definitions</strong></td>
<td></td>
</tr>
<tr>
<td>Primary endpoint</td>
<td>Mean diurnal IOP change from baseline at month 3 (ie, the patient IOP change from baseline averaged over the 9 AM and +2h time points at month 3)</td>
</tr>
<tr>
<td>Supportive endpoints</td>
<td>Mean diurnal IOP change from baseline at week 2, week 6 and month 6</td>
</tr>
<tr>
<td></td>
<td>Mean IOP at week 2, week 6, month 3 and month 6 for each time-point</td>
</tr>
<tr>
<td></td>
<td>Mean IOP change from baseline at week 2, week 6, month 3 and month 6 for each time-point</td>
</tr>
<tr>
<td></td>
<td>Mean IOP percent change from baseline at week 2, week 6, month 3 and month 6 for each assessment time point</td>
</tr>
<tr>
<td></td>
<td>Percentage of patients with an IOP less than 18 mm Hg at each visit and time-point</td>
</tr>
</tbody>
</table>
### Results and Analysis

<table>
<thead>
<tr>
<th>Analysis description</th>
<th>Primary Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analysis population and time point description</td>
<td>Per protocol and ITT (with LOCF); Mean change in IOP from baseline at month 3</td>
</tr>
<tr>
<td>Descriptive statistics and estimate variability (PP population)</td>
<td>Treatment group</td>
</tr>
<tr>
<td></td>
<td>Month 3</td>
</tr>
<tr>
<td>Effect estimate per comparison</td>
<td>Primary endpoint</td>
</tr>
<tr>
<td></td>
<td>Mean difference between treatments at month 3</td>
</tr>
<tr>
<td></td>
<td>95% CI (-0.5, 0.2)</td>
</tr>
<tr>
<td>Descriptive statistics and estimate variability (ITT population)</td>
<td>Treatment group</td>
</tr>
<tr>
<td></td>
<td>Month 3</td>
</tr>
<tr>
<td>Effect estimate per comparison</td>
<td>Primary endpoint</td>
</tr>
<tr>
<td></td>
<td>Mean difference between treatments at month 3</td>
</tr>
<tr>
<td></td>
<td>95% CI (-0.5, 0.2)</td>
</tr>
</tbody>
</table>

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

No pooled analysis or meta-analysis was submitted.

### Clinical studies in special populations

No specific studies in special populations were conducted.

Special populations (patients with hepatic or renal disease), children, and patients who may become pregnant, or were pregnant or breast-feeding at the beginning of the studies were specifically excluded from enrolment into any of the studies. Descriptive statistical analyses were performed on the data from the clinical studies on the primary efficacy endpoint relative to demographic characteristics, including age, sex, race, iris colour, and diagnosis. Due to variations...
in sample sizes across subgroups, definitive conclusions regarding the impact of the subgroups cannot be made. In general, greater efficacy was observed for Brinzolamide/Brimonidine relative to Brinzolamide and Brimonidine within each subgroup category and the magnitude of the IOP lowering effect of Brinzolamide/Brimonidine relative to Brinzolamide and Brimonidine was generally similar in each subgroup.

In both pivotal studies, randomization was stratified into patients with IOP of 24-27 mm Hg at baseline and patients with IOP of 28-36 mm Hg at baseline. The objective was to balance the distribution of severity of raised in IOP in the treatment arms. The studies were not powered to deduce the comparative efficacy of Brinz/Brim in these two strata, though descriptive statistics have been provided.

From this data, it is seen that the superiority of Brinz/Brim over the monotherapies and the non-inferiority of Brinz/Brim as compared to Brinz+Brim is seen in both strata.

**Supportive studies**

**STUDY C-10-033**

This was a three-month efficacy and safety study of the fixed combination of Brinzolamide/Brimonidine compared to the individual components all dosed three times a day in patients with open-angle glaucoma and ocular hypertension. This study used the TID dosing regimen. This study had a treatment duration of 3 months and was designed to demonstrate the superiority of the combination over the mono-components.

This was a randomized, double-masked, parallel-group, active-controlled study. Adult patients with open-angle glaucoma or hypertension with mean IOP measurements in at least one eye (and the same eye) greater than or equal to 24 mmHg and less than or equal to 36 mmHg at the 8 AM time point in both Eligibility Visits, and greater than or equal to 21 mmHg and less than or equal to 36 mmHg at the 10 AM time point in both eligibility visits were eligible. Eligible patients were randomized to one of three study drug groups.

- Brinzolamide/Brimonidine
- Brinzolamide
- Brimonidine

Patients instilled one drop of their assigned study medications in both eyes three times daily (TID) for 3 months. Evaluations of safety and efficacy were performed variously at fixed times (8 AM, + 2 h, + 7 h, and + 9 h) during the study visits conducted at Week 2, Week 6, and Month 3.

The primary efficacy endpoint was the mean IOP measurement for each assessment time point (8 AM, + 2 h, + 7 h, and + 9 h) at Month 3 and the week 2 and 6 means were the supportive efficacy endpoints.

A total of 750 patients were planned, 660 enrolled and 649 analysed in the ITT analysis set. Overall, at Month 3, the mean IOP measurements were significantly lower in the Brinzolamide/Brimonidine group compared with the Brinzolamide group or Brimonidine group at all time-points as shown in the table below.
### Comparison of Mean IOP (mmHg) at Week 2, Week 6, and Month 3 (Intent-to-Treat Data)

<table>
<thead>
<tr>
<th>VISIT TIME point</th>
<th>BRINZ/BRIM Mean (SE)</th>
<th>BRINZ TID Mean (SE)</th>
<th>BRIM TID Mean (SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean difference*&lt;br&gt;p value</td>
<td>N</td>
</tr>
<tr>
<td>Week 2 8 AM</td>
<td>209 20.4 (0.29)</td>
<td>-1.6 &lt;.0001</td>
<td>216 22.0 (0.28)</td>
</tr>
<tr>
<td>+ 2 h</td>
<td>205 17.1 (0.29)</td>
<td>-3.4 &lt;.0001</td>
<td>212 19.3 (0.28)</td>
</tr>
<tr>
<td>+ 7 h</td>
<td>205 18.4 (0.29)</td>
<td>-1.9 &lt;.0001</td>
<td>212 20.6 (0.28)</td>
</tr>
<tr>
<td>+ 9 h</td>
<td>204 16.6 (0.29)</td>
<td>-3.2 &lt;.0001</td>
<td>212 18.4 (0.28)</td>
</tr>
<tr>
<td>Week 6 8 AM</td>
<td>198 20.4 (0.29)</td>
<td>-1.5 &lt;.0001</td>
<td>203 22.0 (0.28)</td>
</tr>
<tr>
<td>+ 2 h</td>
<td>197 17.5 (0.29)</td>
<td>-2.7 &lt;.0001</td>
<td>201 19.5 (0.28)</td>
</tr>
<tr>
<td>+ 7 h</td>
<td>196 18.9 (0.29)</td>
<td>-1.2 &lt;.0001</td>
<td>200 21.1 (0.28)</td>
</tr>
<tr>
<td>+ 9 h</td>
<td>196 17.0 (0.29)</td>
<td>-2.6 0.0007</td>
<td>199 18.6 (0.28)</td>
</tr>
<tr>
<td>Month 3 8 AM</td>
<td>189 20.5 (0.29)</td>
<td>-1.1 0.0016</td>
<td>192 23.2 (0.29)</td>
</tr>
<tr>
<td>+ 2 h</td>
<td>189 17.2 (0.29)</td>
<td>-3.2 &lt;.0001</td>
<td>192 19.7 (0.29)</td>
</tr>
<tr>
<td>+ 7 h</td>
<td>189 18.7 (0.29)</td>
<td>-1.8 &lt;.0001</td>
<td>192 21.3 (0.29)</td>
</tr>
<tr>
<td>+ 9 h</td>
<td>189 20.0 (0.29)</td>
<td>-3.0 &lt;.0001</td>
<td>190 18.8 (0.29)</td>
</tr>
</tbody>
</table>

Brinz/Brim TID = brinzolamide 1% / brimonidine tartrate 0.2% ophthalmic suspension TID; Brinz TID = brinzolamide ophthalmic suspension, 1% TID; Brim TID = brimonidine tartrate ophthalmic solution, 0.2% TID. SE = Standard Error; (a) Estimates based on the least squares means derived from a statistical model that accounts for correlated IOP measurements within patient.

### STUDY C-10-039

This was a randomized, double-masked, parallel-group, active controlled study. Eligible subjects were adult patients aged 18 years and above with a diagnosis of open-angle glaucoma or ocular hypertension, with mean IOP measurements in at least one eye (and the same eye[s]) greater than or equal to 24 mmHg and less than or equal to 36 mmHg at the 8 AM time point in both eligibility visits, and greater than or equal to 21 mmHg and less than or equal to 36 mmHg at the 10 AM time point in both eligibility visits. The eligible subjects were randomized to either

- Brinzolamide/Brimonidine
- Brinzolamide
- Brimonidine

Patients instilled one drop of their assigned study medications in both eyes three times daily (TID) for 6 months. Evaluations of safety and efficacy were performed variously at fixed times (8 AM, + 2 h, + 7 h, and + 9 h) during the study visits conducted at Week 2, Week 6, Month 3 and Month 6. The efficacy endpoints included data collected through Month 3, while the safety endpoints included data collected through Month 6.

The primary efficacy endpoint was the mean IOP measurement for each assessment time point (8 AM, + 2 h, + 7 h, and + 9 h) at Month 3 and the week 2 & 6 means were the supportive efficacy endpoints.
A total of 750 patients were planned, 690 enrolled and 679 analysed in the ITT analysis set.

Of the 690 patients enrolled in the study, 221 were randomized to the Brinzolamide/Brimonidine group, 233 to the Brinzolamide group, and 236 to the Brimonidine group. Overall, at Month 3, the mean IOP measurements were significantly lower in the Brinzolamide/Brimonidine group compared with the Brinzolamide group or Brimonidine group at all time-points as shown in the table below.

![Table showing comparison of mean IOP (mmHg) at Week 2, Week 6, and Month 3 (Intent-to-Treat Data)](image)

Brinz/Brim TID = brinzolamide 1% / brimonidine tartrate 0.2% ophthalmic suspension TID; Brinz TID = brinzolamide ophthalmic suspension, 1% TID; Brim TID = brimonidine tartrate ophthalmic solution, 0.2% TID; SE = Standard Error; (a)Estimates based on the least squares means derived from a statistical model that accounts for correlated IOP measurements within patient.

While not planned as part of the formal efficacy analysis, IOP efficacy data through Month 6 (i.e. the completion of the study) were collected and evaluated descriptively. The results of the analysis were consistent with the results of the planned analyses through to Month 3.

### 2.5.3. Discussion on clinical efficacy

**Design and conduct of clinical studies**

The applicant submitted two pivotal efficacy studies in support of the efficacy of the fixed dose combination of Brinz/Brim in open-angle glaucoma/ocular hypertension. As both Brinz and Brim are established in the treatment of OAG/OHT, the approach taken by the applicant was to show that the efficacy of Brinz/Brim was superior to Brinz alone and Brim alone (study C-10-040) as well as to show that Brinz/Brim is non-inferior to Brinz + Brim (study C-10-041) administered concomitantly 10 minutes apart.
Both studies were randomized, double-masked, multi-centre, active controlled studies. The active control (Brinz alone, Brim alone and Brinz +Brim administered concomitantly 10 minutes apart) are authorised in the treatment of OAG/OHT and the efficacy sizes of these medicines are well established. The study designs are appropriate for the study objectives.

The dose-strength in the Brinz/Brim combination was the same as the approved dose-strengths of Brinz alone and Brim alone, respectively. This approach was supported by the results of the PK study and is a direct reflection of the way the two active ingredients are used concomitantly in clinical practice.

Both studies were conducted in patients with OAG/OHT who were inadequately controlled on mono-therapy or who were already on two or more medications for their glaucoma. The study population is appropriate.

Both studies were of 6-month treatment duration and investigated the BID dosing regimen (the posology approved for Brinz alone and Brim alone in the EU). The primary endpoint was the difference in mean diurnal change in IOP from baseline between the treatment arms at month 3 assessment. The applicant had sought CHMP Scientific Advice and had based the primary endpoint on the advice given. The secondary endpoints were appropriate.

The efficacy assessments were planned at pre-dose (9AM), +2 hrs, +7hrs in study C-10-040 and at 9AM and +2hrs in study C-10-041. These time-points adequately cover the anticipated trough effect and peak effect of treatment on IOP.

Both studies were multi-centre studies including study centres in Europe. The applicant stated that both the studies have been conducted in accordance to ICH-GCP standards and was compliant to all relevant regulations. The amendments and protocol deviations were small in number and were not considered to be major to significantly impact on the conclusions of the studies.

The intent-to-treat (ITT) analysis set included all patients who received study drug and completed at least one scheduled on-therapy study visit. The per protocol (PP) analysis set included all patients who satisfied pre-randomization inclusion/exclusion criteria, received study drug, and completed at least one scheduled on-therapy study visit. The PP analysis set provided primary inference for the primary and supportive efficacy analyses, while the ITT analysis set was considered supportive.

**Efficacy data and additional analyses**

- Study C-10-040 was designed to demonstrate that the IOP lowering efficacy of Brinz/Brim was superior to both Brinz alone and Brim alone. In this study the primary endpoint was assessed after treatment duration of 3 months with Brinz/Brim (n=176), Brinz alone (n=182) or Brim alone (n=161) in parallel groups. At the end of 3 months treatment, the mean diurnal IOP reduction from baseline in the Brinz/Brim, Brinz alone or Brim alone groups were 7.9mm Hg, 6.5mm Hg and 6.4 mm Hg respectively. The difference between Brinz/Brim and Brinz alone was -1.4 mm Hg and the difference between Brinz/Brim and Brim alone was -1.5mm Hg. These differences were statistically significant (p<0.00001 for both comparisons). For all the described sensitivity analyses, regardless of how they handled missing data, results remained consistent with those from the original primary analyses, thus confirming the conclusions of superiority.
The secondary endpoint of mean diurnal IOP reduction from baseline at other visits (week 2, 6 and month 6) were greater (statistically significant) in the Brinz/Brim group as compared to either Brinz alone or Brim alone for each pair wise comparison. The mean differences for these comparisons ranged from -1.1 to -1.6.

The other secondary endpoints of mean IOP change from baseline and mean percent IOP change from baseline at each time-point and study visit were greater (statistically significant) in the Brinz/Brim group as compared to Brinz alone and Brim alone for each pair-wise comparison.

The percentages of patients with an IOP measurement less than 18 mmHg were greater in the Brinzolamide/Brimonidine group than in the Brinzolamide group at 11 of 12 assessments through Month 6. The percentages of patients with an IOP measurement less than 18 mmHg were greater in the Brinzolamide/Brimonidine group than in the Brimonidine alone group at all 12 assessments through to Month 6. The study was not, however, powered to demonstrate superiority for this endpoint.

The percentages of patients with an IOP measurement less than 18 mmHg per were greater in the Brinzolamide/Brimonidine group than in the Brimonidine alone group at all 12 assessments through to Month 6.

- Study C-10-041 was designed to demonstrate that the fixed dose combination of Brinz/Brim was not inferior to Brinz+Brim added concomitantly 10 minutes apart. In this study, the primary endpoint was assessed after treatment duration of 3 months with Brinz/Brim (n=384) and Brinz+Brin (n=373) in parallel groups. At the end of the 3 months, the mean diurnal IOP reduction from baseline in the Brinz/Brim and Brinz+Brim arms were -8.5 and -8.3 respectively. The mean difference between treatment groups was -0.1 and the 95% C.I was (-0.5, 0.2). These results were from the per-protocol population. For all the described sensitivity analyses, regardless of how they handled missing data, results remained consistent with those from the original primary analyses, thus confirming the conclusions of non-inferiority. The secondary endpoints of mean diurnal IOP reduction from other visits (week 2, 6 and month 6) were similar in both the Brinz/Brim and the Brinz+Brim groups. The maximum difference was ±0.1 between both groups.

The other secondary endpoints of mean IOP measurements at each time point (9AM and 9AM+2 hrs) at each study visit were similar in both treatment groups (max mean difference was 0.2 mm Hg) as were the percentage of patients with an IOP measurement less than 18 mm Hg.

The results of the primary and secondary endpoints from this study support the conclusion that Brinz/Brim is not inferior in the IOP-lowering efficacy as compared to Brinz+Brim administered concomitantly 10 minutes apart.

In both studies, consistency of IOP-lowering efficacy by Brinzolamide/Brimonidine was evident beginning at Week 2 (the first on-therapy visit) and appeared to be generally maintained throughout the 6-month study duration.

From the discussion presented by the applicant, it is seen that the IOP lowering efficacy reported for prostaglandin analogues and beta blockers are approximately 6 to 10 mm Hg and mean percent IOP reduction between 23 to 37%. Across both studies, the mean IOP reduction for Brinz/Brim was shown to be in a similar range with mean values of 8 mm Hg and mean percent IOP reduction is between 23 to 37%.
- In addition to the above two main studies, there is efficacy data from the proof-of-concept study which evaluated the TID dosing regimen but nevertheless the results were along the same lines and hence supportive.

- Furthermore, supportive evidence is provided by two larger studies (used as pivotal for US registration) which evaluated, however, the TID dosing regimen. Both these studies compared Brinz/Brim over Brinz alone and Brim alone. The endpoint for these studies was the mean IOP at the end of three months of treatment in each of the treatment arms. These studies also concluded that Brinz/brim was superior to Brinz alone and Brim alone.

Overall, the results from the supportive studies do not raise any concern/queries regarding the conclusions drawn from the pivotal efficacy studies for this MAA.

2.5.4. Conclusions on the clinical efficacy

The superior IOP reducing efficacy of the combination of Brinz/Brim over Brim alone and Brinz alone was conclusively demonstrated. The non-inferiority in the IOP reducing efficacy of the fixed dose combination Brinz/Brim as compared to the concomitant administration of Brinz +Brim, each administered 10 minutes apart was conclusively demonstrated. The conclusions drawn from the primary endpoint are fully supported by the results of the secondary endpoints in both pivotal studies. Other clinical studies (with the TID dosing regimen) also provide supportive evidence of efficacy. Therefore, it was accepted that adequate evidence of efficacy was provided in support of the fixed dose combination of Brinzolamide/Brimonidine administered BID.

2.6. Clinical safety

The summary of clinical safety reported below includes data from four phase 3 studies, which constitute the instrumental contribution to the safety database in defining the safety profile of the combination of Brinzolamide/Brimonidine:

- two studies (C-10-040 and C-10-041) of 6 months duration that evaluated the BID dose and exposed 645 patients;
- two studies (C-10-033 and C-10-039), one of 3 month duration and the other of 6 month duration both evaluating the TID dose regimen and exposed 435 patients.

The methods and design of these studies have been described in section 2.5.2.

In addition, there was a specific descriptive comfort study in 101 patients with treatment duration of 1 week that provides information on the safety of the combination (study C-11-002). This study and its results are discussed below.

It is pertinent to point out that the individual active components of the fixed combination at the same concentration as in Simbrinza were marketed at the time of this MAA. This provides supportive safety information and the applicant presented the adverse event listing of both Brimonidine alone and Brinzolamide alone in clinical trials and post-marketing surveillance.
Patient exposure

The phase 3 development of Brinzolamide/Brimonidine (BID and TID) included 1080 patients exposed to Brinzolamide/Brimonidine (BID or TID) during its development.

On the whole, 1080 patients (645 in BID studies and 435 in TID studies) were exposed to the fixed dose combination Brinzolamide/Brimonidine BID and TID. The majority of patients (about 80%) were exposed to Brinz/Brim BID at least 173 days, thus making the data supportive from a safety point of view.

Patients in the safety and efficacy clinical trials C-10-040 and C-10-041 received one drop of Brinzolamide/Brimonidine, Brinzolamide + Brimonidine, Brinzolamide, or Brimonidine BID in both eyes for up to 6 months. Table 2.7.4.1–4 summarizes pooled exposure data for clinical trials C-10-040 and C-10-041.

<table>
<thead>
<tr>
<th>Duration of Exposure to Study Drug – C-10-040/C-10-041</th>
<th>Brinz/Brim BID</th>
<th>Brinz+Brim BID</th>
<th>Brinz BID</th>
<th>Brim BID</th>
</tr>
</thead>
<tbody>
<tr>
<td>(N=645)</td>
<td>(N=436)</td>
<td>(N=192)</td>
<td>(N=175)</td>
<td></td>
</tr>
<tr>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td></td>
</tr>
<tr>
<td>1-17 Days</td>
<td>24 (3.7)</td>
<td>12 (2.8)</td>
<td>2 (1.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>18-45 Days</td>
<td>14 (2.2)</td>
<td>20 (4.6)</td>
<td>5 (2.6)</td>
<td>7 (4.0)</td>
</tr>
<tr>
<td>46-97 Days</td>
<td>28 (4.3)</td>
<td>17 (3.9)</td>
<td>6 (3.1)</td>
<td>11 (6.3)</td>
</tr>
<tr>
<td>98-187 Days</td>
<td>535 (82.9)</td>
<td>343 (78.7)</td>
<td>163 (84.9)</td>
<td>146 (83.4)</td>
</tr>
<tr>
<td>&gt;187 Days</td>
<td>44 (6.8)</td>
<td>44 (10.1)</td>
<td>16 (8.3)</td>
<td>11 (6.3)</td>
</tr>
</tbody>
</table>

In general, patients included in the study were representative of the population that would be expected to receive Brinzolamide/Brimonidine BID. In addition, treatment groups were well balanced with respect to demographic characteristics.

Adverse events

The majority of adverse drug reactions (ADRs) reported during the studies were related to local ocular side effects (i.e. ADRs coding to the System Organ Classification [SOC] of Eye Disorders) with a known causal association with one or more of the individual components.

The most common ocular ADRs reported during the studies were for hyperaemia of the eye (reported as ocular or conjunctival hyperaemia), ocular allergic type reactions, visual disturbances (i.e. blurred vision, visual acuity reduced, visual impairment, and hypermetropia), and ocular discomfort (i.e. eye irritation, eye pain, eye pruritus, foreign body sensation in eyes, ocular discomfort, and conjunctival irritation). Common systemic ADRs reported included dysgeusia, oral dryness (i.e. dry mouth, dry throat, mucosal dryness, and nasal dryness) and fatigue/drowsiness (i.e. asthenia, fatigue, hypotonia, sedation, hypersomnia, and somnolence).
Hyperaemia of the eye (ocular hyperaemia and conjunctival hyperaemia) was reported at a higher incidence in the Brinzolamide + Brimonidine BID and Brimonidine BID groups relative to the Brinzolamide/Brimonidine BID and Brinzolamide BID (lowest incidence) groups.

Adverse drug reactions for visual disturbances (vision blurred, visual acuity reduced, hypermetropia and visual impairment) were reported at a numerically slightly higher incidence in the Brinzolamide + Brimonidine BID group relative to the Brinzolamide/Brimonidine BID group. Visual disturbances were reported at a higher incidence in the Brinzolamide/Brimonidine BID and Brinzolamide + Brimonidine groups relative to BID dosing with either of the individual components.

Adverse drug reactions for visual acuity reduced and visual impairment were only reported in the Brinzolamide + Brimonidine BID group.

Hypermetropia was reported in a single patient dosed with Brinzolamide/Brimonidine BID. The applicant argued that the likelihood that the occurrence of hypermetropia is associated with the
use of Brinzolamide/Brimonidine BID is remote, as no signal supporting a causal association the development of hypermetropia has been identified from clinical trials, post-marketing surveillance, or peer-reviewed literature articles with Brinz alone or Brim alone.

Ocular discomfort (Eye pain, Eye pruritus, Eye irritation, Foreign body sensation in eyes, ocular discomfort and conjunctival irritation) was reported at a higher incidence in the Brinzolamide/Brimonidine BID and Brinzolamide + Brimonidine BID groups relative to the individual components. Between the fixed combination and concomitant dosing more ocular discomfort was reported in the Brinzolamide/Brimonidine BID group

**Ocular allergic reactions**

Table 2.7.4.2–9 presents the frequency and incidence of these events reported in clinical trials C-10-041 and C-10-040. A review of these data revealed no clinically relevant difference between the Brinzolamide/Brimonidine BID and Brinzolamide + Brimonidine BID treatment groups in the number of patients who experienced an ocular allergic reaction over a 6 month period. When compared to the individual components for the same time period, the incidence of patients with ocular allergic reactions was slightly higher in the Brinzolamide/Brimonidine BID group versus the Brimonidine BID group. No ocular allergic reactions were reported in the Brinzolamide BID group. The rate of discontinuations due to an ocular allergic reaction was similar among the brimonidine containing study medications.

<table>
<thead>
<tr>
<th>Coded Adverse Event (LLT)</th>
<th>Brinz/Brim BID (N=645)</th>
<th>Brinz+Brim BID (N=436)</th>
<th>Brinz BID (N=192)</th>
<th>Brim BID (N=175)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eye disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allergic conjunctivitis</td>
<td>17 (2.6%)</td>
<td>9 (2.1%)</td>
<td>-</td>
<td>2 (1.1%)</td>
</tr>
<tr>
<td>Eye allergy</td>
<td>8 (1.2%)</td>
<td>6 (1.4%)</td>
<td>-</td>
<td>2 (1.1%)</td>
</tr>
<tr>
<td>Follicular conjunctivitis</td>
<td>7 (1.1%)</td>
<td>5 (1.1%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>2 (0.3%)</td>
<td>-</td>
<td>-</td>
<td>1 (0.6%)</td>
</tr>
<tr>
<td>Acute conjunctivitis</td>
<td>2 (0.3%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Chronic conjunctivitis</td>
<td>1 (0.2%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Conjunctival follicles</td>
<td>3 (0.5%)</td>
<td>3 (0.7%)</td>
<td>-</td>
<td>1 (0.6%)</td>
</tr>
<tr>
<td>Allergic blepharitis</td>
<td>1 (0.2%)</td>
<td>1 (0.2%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Allergic blepharoconjunctivitis</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1 (0.6%)</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Drug intolerance</td>
<td>-</td>
<td>-</td>
<td>1 (0.2%)</td>
<td>-</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Drug allergy</td>
<td>1 (0.2%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Allergic dermatitis</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1 (0.6%)</td>
</tr>
</tbody>
</table>

Total Number of Patients with an ADR for an Ocular Allergy:

- Brinz/Brim BID (N=645): 41 (6.4%)
- Brinz+Brim BID (N=436): 24* (5.5%)
- Brinz BID (N=192): 0 (0.0%)
- Brim BID (N=175): 8 (4.6%)

Total Number of Patients who Discontinued due to an ADR for an Ocular Allergy:

- Brinz/Brim BID (N=645): 25 (3.9%)
- Brinz+Brim BID (N=436): 15 (3.4%)
- Brinz BID (N=192): 0 (0.0%)
- Brim BID (N=175): 6 (3.4%)

*Patient C10941_62233803 experienced both allergic conjunctivitis and eye allergy

**Reactions of the corneal surface**

Regarding adverse drug reactions of the corneal surface, the incidence of punctate keratitis and keratitis was slightly higher in the Brinzolamide + Brimonidine BID group relative to the other 3
treatment groups and similar between the Brinzolamide/Brimonidine BID and Brimonidine BID groups. The lowest incidence was reported in the Brinzolamide BID group.

### Systemic adverse reactions

Dysgeusia was reported at a similar incidence between the Brinzolamide/Brimonidine BID and Brinzolamide + Brimonidine BID groups. A lower incidence of dysgeusia was reported in the individual components relative to the fixed combination or the individual components dosed concomitantly BID.

A higher incidence of oral dryness was reported in the Brimonidine BID group relative to either the Brinzolamide/Brimonidine BID or Brinzolamide + Brimonidine BID groups. Between the Brinzolamide/Brimonidine BID and Brinzolamide + Brimonidine BID groups the incidence of oral dryness was similar. The lowest incidence of oral dryness was reported in the Brinzolamide BID group (Table 2.7.4.2–5).

#### Table 2.7.4.2–4 Adverse Drug Reactions – Corneal Surface – C-10-040/C-10-041

<table>
<thead>
<tr>
<th>Coded Adverse Event</th>
<th>Brinz/Brim BID N=645</th>
<th>Brinz/Brim+Brim BID N=436</th>
<th>Brinz BID N=192</th>
<th>Brim BID N=175</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Eye disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Punctate keratitis</td>
<td>4 (0.6%)</td>
<td>6 (1.4%)</td>
<td>1 (0.5%)</td>
<td>2 (1.1%)</td>
</tr>
<tr>
<td>Keratitis</td>
<td>3 (0.5%)</td>
<td>3 (0.7%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corneal erosion</td>
<td>2 (0.3%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corneal deposits</td>
<td>1 (0.2%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Investigations</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corneal staining</td>
<td>1 (0.6%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Coded adverse event = MedDRA Preferred Term (version 13.0) presented by System Organ Class. Data in table are a subset of Table 5.3.5.3.2.3

#### Table 2.7.4.2–5 Adverse Drug Reactions – Oral Dryness – C-10-040/C-10-041

<table>
<thead>
<tr>
<th>Coded Adverse Event</th>
<th>Brinz/Brim BID N=645</th>
<th>Brinz/Brim+Brim BID N=436</th>
<th>Brinz BID N=192</th>
<th>Brim BID N=175</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dry mouth</td>
<td>18 (2.8%)</td>
<td>14 (3.2%)</td>
<td>2 (1.0%)</td>
<td>9 (5.1%)</td>
</tr>
<tr>
<td><strong>General disorders and administration site conditions</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mucosal dryness</td>
<td>1 (0.5%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Respiratory, thoracic and mediastinal disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dry throat</td>
<td>1 (0.2%)</td>
<td>1 (0.2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasal dryness</td>
<td>2 (0.3%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Coded adverse event = MedDRA Preferred Term (version 13.0) presented by System Organ Class. Data in table are a subset of Table 5.3.5.3.2.3
Patients who dosed with Brinzolamide + Brimonidine BID experienced a higher incidence of fatigue/drowsiness relative to the other 3 treatment groups. The incidence of fatigue/drowsiness was similar between the Brinzolamide/Brimonidine BID and Brimonidine BID groups. The lowest incidence of fatigue/drowsiness was reported in the Brinzolamide BID group (Table 2.7.4.2–6).

### Table 2.7.4.2–6

<table>
<thead>
<tr>
<th>Coded Adverse Event</th>
<th>Brinz/Brim</th>
<th>Brinz+Brim</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=645</td>
<td>N=436</td>
</tr>
<tr>
<td><strong>General disorders and administration site conditions</strong></td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Asthma</td>
<td>2</td>
<td>0.3</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1</td>
<td>0.2</td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td>4</td>
<td>2.3</td>
</tr>
<tr>
<td>Somnolence</td>
<td>14</td>
<td>2.2</td>
</tr>
<tr>
<td>Hypersomnia</td>
<td>1</td>
<td>0.2</td>
</tr>
<tr>
<td>Hypotonia</td>
<td>1</td>
<td>0.2</td>
</tr>
<tr>
<td>Sedation</td>
<td>1</td>
<td>0.2</td>
</tr>
</tbody>
</table>

*Decreased blood pressure (i.e. hypotension and blood pressure decreased) was reported at a higher incidence in the Brimonidine BID group relative to the other 3 treatment groups. Between the Brinzolamide/Brimonidine BID and Brinzolamide + Brimonidine BID groups the incidence of decreased blood pressure was slightly higher in the fixed combination. No patient treated with Brinzolamide BID reported an ADR for a decrease in blood pressure.*

### Table 2.7.4.2–7

<table>
<thead>
<tr>
<th>Coded Adverse Event</th>
<th>Brinz/Brim</th>
<th>Brinz+Brim</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=645</td>
<td>N=436</td>
</tr>
<tr>
<td><strong>Investigations</strong></td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Blood pressure decreased</td>
<td>2</td>
<td>0.3</td>
</tr>
<tr>
<td>Hypotension</td>
<td>2</td>
<td>0.3</td>
</tr>
</tbody>
</table>

*The applicant stated that the pooled safety data for Brinz/Brim from the two pivotal study were consistent with those reported with use of Brinz alone and Brim alone BID.*
Safety data from TID dosing C-10-033 and C-10-039

A review ADRs through 3 months of dosing revealed that the majority were for local ocular side effects (e.g. blurred vision, ocular allergic reactions, ocular inflammation, and ocular discomfort) with a known causal association with the individual components. The most prevalent preferred term (PT) reported during the studies was blurred vision. Other common ocular ADRs reported at an incidence of ≥ 1% were for the development of ocular allergies, ocular inflammation, and ocular discomfort. Common systemic ADRs reported included dysgeusia, dry mouth, and fatigue/drowsiness (including the PT terms of asthenia, fatigue, lethargy and somnolence).

A review of ADRs reported at an incidence of ≥ 1% through the Month 6 time point revealed that the common adverse events were similar to the month 3 time point. No increase in the incidence of ADRs reported for blurred vision was observed between the Month 3 and Month 6 time points.

Small incremental increases in ADRs reported for ocular inflammation and ocular discomfort were observed between the Month 3 and Month 6 time points in the treatment groups. In addition, an incremental increase in the number of ADRs reported for an ocular allergic reaction was observed between the Month 3 and Month 6 time points.

The incidence of dry mouth and fatigue/drowsiness was similar, with no meaningful difference between the 2 groups in the incidence at the Month 3 and Month 6 time points.

The treatment-emergent adverse events after TID administration of Brim/Brinz was compared against that of Brim alone and Brinz alone. A review of these data revealed that the majority of treatment-emergent AEs reported during the study (up to Month 3 and up to Month 6) were for local ocular side effects or systemic effects associated with the formulations and/or the pharmaceutical class of the study medications. No increased ocular or systemic risk with the use of Brinzolamide/Brimonidine TID relative to the individual components dosed TID was identified at the Month 3 interim time point or with an additional 3 months of dosing based upon a review of treatment emergent adverse events.

The applicant presented and discussed the comparison of the safety profiles between the BID and TID dosing as well as the comparison of the safety profiles between the first three months and the last three months of the 6 month dosing studies.

It was observed that the overall incidence of adverse events is higher with TID dosing as compared to the BID dosing when the 6 month treatment duration studies are compared. This was expected, based on the higher daily dose administered in these studies. This higher incidence with TID dosing is also observed with the specific adverse events of vision blurred and eye allergies.

Regarding ocular allergy reactions, these events are already known ADR due to Brimonidine. According to the literature provided by the Company in relation to ocular allergy reactions induced by brimonidine, it seems that these reactions do not decrease over time with the administration of brimonidine.

Comparison of the ADRs between the first 3 months and the last 3 months showed that local ADRs of ocular discomfort were higher in the first three months. However, the incidence of
allergic reactions was similar in both periods, which showed that the risk of developing ocular allergic reaction does not decrease over time.

Given that open-angle glaucoma is a chronic condition, ocular allergy reactions cannot be ruled out during Brinz/Brim BID treatment. These reactions are already considered in the RMP as important identified risks. Taking into account the chronic nature of the disease, an appropriate monitoring of this risk is relevant in order to characterise this occurrence during long-term use.

Additionally, a warning regarding the discontinuation of treatment if ocular allergic reactions occur is reflected under section 4.4 of SmPC, which was acceptable to the CHMP.

**Onset of adverse events across studies**

A review of adverse events by onset day revealed that the majority of local-ocular side effects reported for blurred vision and ocular discomfort occurred within the first 2 weeks of use with study medication. The majority of ocular allergic type reactions occurred after 30 days or more of dosing, specifically within patients exposed to the brimonidine containing study medications. Common systemic side-effects (e.g. dry mouth, fatigue/drowsiness) were generally reported within the first 30 days of dosing while dysgeusia was generally reported within the first 2 weeks of dosing.

Overall, no clinically relevant treatment group differences were identified for the onset of adverse events.

**Serious adverse event/deaths/other significant events**

No treatment-related fatal AEs were reported during the clinical development of Brinzolamide/Brimonidine (BID or TID). One patient who dosed with Brinzolamide + Brimonidine BID suffered a fatal myocardial infarction during clinical trial C-10-041. The event was assessed as unrelated to the use of Brinzolamide + Brimonidine BID.

Table 2.7.4.2–28 presents the frequency and incidence of patients with SAEs reported in clinical trials C-10-040 and C-10-041.

<table>
<thead>
<tr>
<th>Patients with Adverse Events</th>
<th>Brinz/Brim BID N=645</th>
<th>Brinz/Brim BID N=436</th>
<th>Brinz BID N=192</th>
<th>Brim BID N=175</th>
</tr>
</thead>
<tbody>
<tr>
<td>Related</td>
<td>2</td>
<td>0.3</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>Not Related</td>
<td>14</td>
<td>2.2</td>
<td>8</td>
<td>1.8</td>
</tr>
<tr>
<td>Overall</td>
<td>16</td>
<td>2.5</td>
<td>8</td>
<td>1.8</td>
</tr>
</tbody>
</table>

Related (R) = Event was assessed as related to the use of test article
Not Related (NR) = Event was assessed as unrelated to the use of test article
The two cases of related serious adverse reactions were the report of development of corneal erosion under the category of an ‘other important medical event’ in 2 patients dosed with the combination in the C-10-041 trial. In both cases, corneal erosion was reported as a finding and treatment was continued, however at a later visit there was a upgrading in the severity of the corneal erosion resulting in them being classified as serious adverse reactions. Both cases, the corneal erosion resolved with the use of concomitant medications upon exiting from the study. The event of corneal erosion is listed in the labelling of both the individual components and analysis and comparison of results across the TID studies did not show an increased incidence of these events with the combination.

All other serious adverse events were considered unrelated to the study drug.

While a higher number of patients in the Brinzolamide/Brimonidine BID group reported an SAE relative to either BID dosing of the individual components as monotherapy or concomitantly, no patterns emerged that would suggest an issue concerning patient safety when dosing with the fixed combination of Brinzolamide/Brimonidine BID based on a thorough review of the types and characteristics of SAEs reported, coupled with an evaluation of overall patient characteristics.

Table 2.7.4.2–30 presents the frequency and incidence of patients with SAEs reported in the studies C-10-033 and C-10-039

<table>
<thead>
<tr>
<th>Patients with Adverse Events</th>
<th>Brinz/Brim TID N=435</th>
<th>Brinz TID N=460</th>
<th>Brim TID N=455</th>
</tr>
</thead>
<tbody>
<tr>
<td>Related</td>
<td>1 0.2</td>
<td>12 2.6</td>
<td>9 2.0</td>
</tr>
<tr>
<td>Not Related</td>
<td>9 2.1</td>
<td>13 2.8</td>
<td>9 2.0</td>
</tr>
<tr>
<td>Overall</td>
<td>9 2.1</td>
<td>13 2.8</td>
<td>9 2.0</td>
</tr>
</tbody>
</table>

Related (R) = Event was assessed as related to the use of test article
Not Related (NR) = Event was assessed as unrelated to the use of test article

One serious adverse drug reaction (SAR) was reported for chest pain in a patient who dosed with Brinzolamide TID in clinical trial C-10-033. The patient discontinued participation in the study due to the chest pain. All other SAEs reported in the clinical studies were assessed as unrelated to the use of study medication by the study Investigator.

No patterns emerged that would suggest an issue concerning patient safety when dosing with Brinzolamide/Brimonidine TID or either of the individual components dosed TID based on a thorough review of the types and characteristics of SAEs reported, coupled with an evaluation of overall patient characteristics.

**Laboratory findings**

No clinical laboratory evaluations were performed in the phase 3 clinical trials for Brinzolamide/Brimonidine BID or TID (C-10-041, C-10-040, C-10-039 or C-10-033).
**Physical and ocular examination findings**

Based on a review of changes from baseline in safety assessments of vital signs and physical findings no additional safety concerns were identified for the use of the fixed combination Brinzolamide/Brimonidine (dosed BID or TID) relative to the known risks of the individual components (dosed BID or TID) or in comparison to the concomitant use of the individual components (dosed BID or TID). A summary of findings on the physical findings are as below:

- **No clinically meaningful decrease in pulse rate or blood pressure (systolic and diastolic) was observed with the use of Brinzolamide/Brimonidine (BID or TID).**
  - A trend towards a slight decrease in pulse rate was observed during the course of the study in patients who dosed with Brinzolamide/Brimonidine (BID or TID). The magnitude of the decrease in pulse rate was similar between the treatment groups containing an α2-adrenergic agonist (Brinzolamide/Brimonidine, Brinzolamide + Brimonidine, and Brimonidine).
  - A trend towards a slight decrease in blood pressure was observed during the course of these studies in patients who dosed with Brinzolamide/Brimonidine (BID or TID). The magnitude of the decrease in blood pressure was similar between the treatment groups containing an α2-adrenergic agonist (Brinzolamide/Brimonidine, Brinzolamide + Brimonidine, and Brimonidine).
  - It was noted that several patients in Brinz/Brim BID group versus unfixed combination, brinzolamide and brimonidine groups experienced a shift from normal to high diastolic blood pressure (8.5% versus 6.5%, 4.1% and 6.9%, respectively. Section 4.8 of SmPC includes 'hypertension' as a very rare adverse event induced by brimonidine. This was thought sufficient to adequately inform health professionals and patients on the possible occurrence of this adverse event.

- **No trend toward a decrease in visual acuity was observed over the course of the studies in any treatment group.**

- **The most common slit-lamp exam finding was a change from baseline in the assessment of eyelids/conjunctiva.**
  - The majority of these changes were associated with known local ocular effects (e.g. ocular hyperaemia and ocular allergic type reactions) of the individual components, particularly brimonidine, and do not represent a previously unknown risk or an exacerbation of the known risks relative to the individual components.
  - A higher incidence of changes from baseline in eyelids/conjunctiva was observed in patients who dosed with study medications containing brimonidine relative to patients who received Brinzolamide only. The incidence was higher in patients dosing TID with brimonidine containing study medications relative to those patients who dosed BID with brimonidine containing study medications for up to 6 months.

- **No clinically relevant treatment group differences were observed for changes in iris/anterior chamber.**
Ocular signs

Patients who dosed with Brinzolamide+Brimonidine BID (C-10-041) and Brimonidine/Brinzolamide TID (C-10-039) for up to 6 months experienced the highest incidence of changes from baseline in cornea (5.1% and 6.8%, respectively) among the 4 treatment groups.

- A review of the changes in cornea in the Brinzolamide/Brimonidine TID group revealed that the majority of changes (9 of the 15 changes) were either not considered adverse events or assessed as not related to the use of Brinzolamide/Brimonidine TID (e.g. corneal abrasion, ocular foreign body) by the study Investigator. Similar to the Brinzolamide/Brimonidine TID group the majority of changes in cornea (5 of the 9 changes) reported in the Brinzolamide TID group were either not considered adverse events or assessed as not related to the use of Brinzolamide TID (e.g. corneal abrasion) by the study Investigator. In contrast, all 6 changes in cornea reported in the Brimonidine TID group were assessed as related to the use of the study medication.

### Table 2.7.4.4–46
<table>
<thead>
<tr>
<th>Ocular Signs</th>
<th>Brinz/Brim BID</th>
<th>Brinz+Brim BID</th>
<th>Brinz BID</th>
<th>Brim BID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cornea</td>
<td>N 642</td>
<td>n 22 (3.4%)</td>
<td>N 192</td>
<td>n 4 (2.1%)</td>
</tr>
<tr>
<td>Iris/Anterior Chamber</td>
<td>N 642</td>
<td>n 2 (0.3%)</td>
<td>N 192</td>
<td>n 0 (0.0%)</td>
</tr>
<tr>
<td>Lens</td>
<td>N 642</td>
<td>n 14 (2.2%)</td>
<td>N 192</td>
<td>n 3 (1.6%)</td>
</tr>
<tr>
<td>Eyelids/Conjunctiva</td>
<td>N 642</td>
<td>n 103 (16.0%)</td>
<td>N 192</td>
<td>n 13 (6.8%)</td>
</tr>
</tbody>
</table>

Brinz/Brim BID = Brinzolamide/Brimonidine 10 mg/mL + 2 mg/mL Eye Drops, Suspension BID
Brinz+Brim BID = Brinzolamide 10 mg/mL Eye Drops, Suspension BID plus Brimonidine Tartrate 2 mg/mL Eye Drops, Solution BID
Brinz BID = Brinzolamide 10 mg/mL Eye Drops, Suspension BID
Brim BID = Brimonidine Tartrate 2 mg/mL Eye Drops, Solution BID
Baseline = Eligibility 2 (9 AM) Visit
Change in ocular signs is defined as a one unit or more increase from baseline to any visit for either study eye compared to the same eye at baseline.

### Table 2.7.4.4–48
<table>
<thead>
<tr>
<th>Ocular Signs</th>
<th>Brinz/Brim TID</th>
<th>Brinz TID</th>
<th>Brim TID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cornea</td>
<td>N 221</td>
<td>n 15 (6.8%)</td>
<td>N 232</td>
</tr>
<tr>
<td>Iris/Anterior Chamber</td>
<td>N 221</td>
<td>n 2 (0.9%)</td>
<td>N 232</td>
</tr>
<tr>
<td>Lens</td>
<td>N 221</td>
<td>n 8 (3.6%)</td>
<td>N 232</td>
</tr>
<tr>
<td>Eyelids/Conjunctiva</td>
<td>N 221</td>
<td>n 59 (26.7%)</td>
<td>N 232</td>
</tr>
</tbody>
</table>

Brinz/Brim TID = brinzolamide 1% / brimonidine tartrate 0.2% ophthalmic suspension TID
Brinz TID = brinzolamide ophthalmic suspension, 1% TID
Brim TID = brimonidine tartrate ophthalmic solution, 0.2% TID
Baseline = Eligibility 2 (8 AM) Visit
Change in ocular signs is defined as a one unit or more increase from baseline to any visit for either study eye compared to the same eye at baseline.
Any visit includes any on therapy visit up to and including Month 6 for each patient.
Corneal erosion is a known adverse event of the individual components and the administration of the fixed combination does not seem to increase the incidence of this event. In addition, this event is already included in the RMP as an important potential risk. Concerning data provided related to corneal deposits, no firm conclusions can be drawn. According to RMP requirements, post marketing surveillance will help to clarify the nature of these corneal deposits, the causality with the fixed combination and the potential incidence with long-term use.

Overall, a review of corneal changes over the course of the study did not reveal any meaningful differences between the treatment groups that would indicate a previously unknown risk.

- Patients who dosed with Brinzolamide+Brimonidine BID (C-10-041) and Brinzolamide/Brimonidine TID (C-10-039) for up to 6 months experienced the highest incidence of lenticular changes from baseline (3.2% and 3.6%, respectively) among the four treatment groups.

  - A review of lenticular changes from baseline in the Brinzolamide/Brimonidine TID group revealed that the majority of these changes were not considered AEs by the study Investigator (6 of the 8 changes). In one of the changes reported as an AE it was documented by the study Investigator as an expected occurrence following 3 retinal surgeries. Overall, the development of or worsening of a lenticular opacity has not been associated with the use of either of the individual components.

- No clinically meaningful treatment group differences were observed for changes from baseline in fundus parameters vitreous and retina/macula/choroids.

  - Individual changes in vitreous and retina/macula/choroids were either not considered untoward by the study Investigator and/or assessed as unrelated to the use of study medication.

- Patients who dosed with Brimonidine BID (C-10-040) and Brinzolamide TID (C-10-039) for up to 6 months experienced the highest incidence of optic nerve changes from baseline (3.1% and 3.1%, respectively) among the four treatment groups.

- No trend was observed for an increase in cup/disc ratio over the course of the study in any treatment group.

- No trend was observed toward an increase in corneal thickness over the course of the study in any treatment group.

- No trend toward a decrease in retinal ganglion sensitivity or loss was observed during the course of the studies in any treatment group.

**Safety in special populations**

There are no specific studies in special populations.

Based on a review of adverse events by intrinsic factors no additional risks in any of the intrinsic subpopulations were identified for the fixed combination of Brinzolamide/Brimonidine relative to dosing with the individual components as monotherapy or concomitantly. The intrinsic factors
reviewed include age, gender, race, concomitant disease, concomitant medications, iris colour and time of onset.

**Safety related to drug-drug interactions and other interactions**

No specific drug-drug interaction studies were conducted. No drug interactions were reported in any of the clinical trials involving Brinzolamide/Brimonidine (BID or TID).

Data from clinical trial C-10-010 did not indicate a drug-drug interaction between the individual active components in Brinzolamide/ Brimonidine (BID or TID).

In the main efficacy studies, patients were allowed the use of concomitant medications not specifically prohibited by the protocols over the course of the clinical studies. Exposure to concomitant medications could be present at baseline and continuing after exposure to study medication or the concomitant medication may have been initiated during trial participation. The overall frequency and incidence of adverse events for patients on concomitant medication categories were reviewed based on the concomitant medication.

The primary focus of the review by concomitant medication categories was to assess whether the adverse event profile was altered in those patients with a specific concomitant medication category when compared to the other treatment groups within the subpopulation. This review would also determine if the specific subpopulation behaved differently than the overall population of patients participating in clinical studies C-10-040 and C-10-041.

A review of adverse events in patients with exposure to Brinzolamide/Brimonidine BID revealed no additional risks in each of the subpopulations categorized by concomitant medication relative to the individual components.

The applicant discussed the potential for drug interactions with Brinz/Brim with some classes of drugs which include oral carbonic anhydrase inhibitors (potential additive effect), high-dose salicylate therapy (rare case of acid-base alterations reported with other carbonic anhydrase inhibitors but not Brinz), CNS depressants (potential additive/potentiating effect with Brim), antihypertensives (potential adrenergic interactions), tricyclic antidepressants (potentially may blunt the effect of adrenergic agonists) and MAO- inhibitors (theoretical interference with metabolism of brimonidine).

Appropriate warnings and contra-indications are included in the SmPC to inform about the consequences of these interactions.

**Discontinuation due to adverse events**

Table 2.7.4.2–32 presents the frequency and incidence of patients who discontinued participation in clinical studies C-10-040 and C-10-041 due to an AE.
Brinzolamide/Brimonidine BID group discontinued study participation due to an AE relative to the individual components. The majority of AEs leading to patient discontinuation from study participation were for the types of local ocular events that have been associated with the use of the individual components (e.g. ocular discomfort, ocular hyperaemia, and ocular allergies). The incidence of patients discontinuing due to these events was similar between the fixed combination of Brinzolamide/Brimonidine BID and concomitant dosing with Brinzolamide + Brimonidine BID with the exception of ocular hyperaemia where a higher incidence of discontinuations were observed in the Brinzolamide + Brimonidine BID group relative to the Brinzolamide/Brimonidine BID group.

The incidence of patients discontinuing due to an ocular allergic type reaction was similar among the 3 treatment groups containing brimonidine (Table 2.5.5–6). One patient treated with Brinzolamide/Brimonidine BID discontinued study participation due to a SAR.

Table 2.5.5–6  Number of Patients who Discontinued due to an Ocular Allergic Reaction – C-10-040/C-10-041

<table>
<thead>
<tr>
<th></th>
<th>Brinz/Brimonidine BID (N=645)</th>
<th>Brinz+Brimonidine BID (N=436)</th>
<th>Brinz BID (N=192)</th>
<th>Brim BID (N=175)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Number of Patients who Discontinued due to an ADR for an Ocular Allergy</td>
<td>25 (3.9%)</td>
<td>15 (3.4%)</td>
<td>0 (0.0%)</td>
<td>6 (3.4%)</td>
</tr>
</tbody>
</table>

Data in table are a subset of Table 5.3.3.2-54.

Table 2.7.4.2–34 presents the frequency and incidence of patients who discontinued participation in clinical studies C-10-033 and C-10-039 due to an AE.
More patients in the brimonidine containing groups discontinued participation in the clinical study due to an adverse event relative to the Brinzolamide TID group. Between the brimonidine containing groups a greater number of patients in the Brinzolamide/Brimonidine TID group discontinued study participation due to an AE versus the Brimonidine TID group. More patients in the Brinzolamide/Brimonidine TID group discontinued study participation due to an AE associated with an ocular allergic reaction versus the Brimonidine TID group. The individual characteristics of the ocular allergic reactions did not reveal an untoward difference between the Brinzolamide/Brimonidine TID and Brimonidine TID groups that would pose a greater risk to patients using the fixed combination.

Table 2.7.4.2–35 presents the frequency and incidence of patients who discontinued participation in clinical study C-10-039 due to an AE through the Month 6 time point.

The majority of AEs leading to patient discontinuation were for the types of events that have been associated with the use of the individual components of Brinzolamide/Brimonidine TID. A comparison between the fixed combination and Brimonidine TID group (the groups with the highest incidence of patients who discontinued due to an adverse event) did not reveal an appreciable difference between the groups in relation to the types of AEs leading to patient discontinuation with the exception of ocular allergic reactions.
During the first 3 months of the study a greater number of patients in the fixed combination group discontinued study participation due to an ocular allergic reaction compared to the Brimonidine TID group. However, during the additional 3 months of dosing the incidence of patients discontinuing study participation due to an ocular allergic reaction was similar between the Brinzolamide/Brimonidine TID and Brimonidine TID treatment groups. During the first 3 months of the study a greater number of patients in the fixed combination group discontinued study participation due to an ocular allergic reaction compared to the Brimonidine TID group. However, during the additional 3 months of dosing the incidence of patients discontinuing study participation due to an ocular allergic reaction was similar between the Brinzolamide/Brimonidine TID and Brimonidine TID treatment groups.

The applicant presented a comparison of the withdrawal rates due to ocular allergies with both the BID and TID dosing. It is observed that there is a much higher incidence of withdrawal due to ocular allergies with the TID regimens for both Brim alone and Brinz/Brim as compared to the BID regimen. This is consistent with the expectation of higher incidence due to larger daily dose and is consistent with the observation from other ADRs.

**Post-marketing experience**

The fixed combination product Brinzolamide 10 mg/ml / Brimonidine 2 mg/ml Ophthalmic Suspension received approval in the US on 19 April 2013. No post-marketing data is currently available. However, the individual components are currently marketed and data from post-marketing experience involving each of these products will be briefly described below.

Brinzolamide 10mg/ml was first authorised in 1998.

Brimonidine 2mg/ml was first authorised in 2002.

The safety data emerging from the clinical trials submitted in support of this MAA for the two above products is in concordance with the previous post-marketing cumulative experience. The Applicant submitted the last 3 PSURs for both products at the time of the application. The risk-benefit profile of both these products continue to be considered positive as per the conclusions of the PSURs.

**STUDY C-11-002**

This was a randomized, double-masked, parallel-group, active controlled descriptive study. Adult subjects 18 years of age with open-angle glaucoma or ocular hypertension were eligible.

The primary comfort endpoint was the mean ocular discomfort score on a 5-point ocular discomfort scale evaluated immediately after instillation of Brinzolamide/Brimonidine, Brinzolamide, or Brimonidine at Week 1 (Visit 2). The ocular discomfort scale consisted of the following ratings: 0 (none), 1 (mild), 2 (moderate), 3 (severe), and 4 (very severe). The supportive comfort endpoint was the percentage of patients in each ocular discomfort score category.

Overall 101 patients were enrolled and formed the ITT population. The mean ocular discomfort immediately after instillation of Brinzolamide/Brimonidine (0.8) was higher than the mean ocular discomfort of its components, Brinzolamide (0.4) and Brimonidine (0.3).
The percentage of patients who experienced no or mild ocular discomfort immediately after instillation was lower in the Brinzolamide/Brimonidine treatment group (78.8%) compared to the Brinzolamide (94.1%) and Brimonidine (97%) treatment groups.

To put the results in context, the applicant described two other ocular comfort studies in patients with OAG and OHT, comparing 2 timolol-containing combination products, Brinzolamide 1%/Timolol 0.5% Ophthalmic Suspension (Azarga) and Dorzolamide 2%/Timolol 0.5% Ophthalmic Solution. The mean discomfort score at Week 1 for patients dosed with Azarga was 0.77 and for patients dosed with Dorzolamide 2%/Timolol 0.5% Ophthalmic Solution was 1.53. This discomfort scale was the same as the one used in the current study. Both Azarga and Dorzolamide 2%/Timolol 0.5% Ophthalmic Solution, are found in ophthalmic practice to be well tolerated by glaucoma patients. Therefore, a score of 0.8 for Brinzolamide/Brimonidine in the present study demonstrates an acceptable comfort level by comparison.

2.6.1. Discussion on clinical safety

The safety analysis of Brinzolamide/Brimonidine BID is mainly focused on the safety data obtained from the pivotal clinical studies (C-10-040 and C-10-041, BID dosing) and USA phase 3 clinical studies (C-10-033 and C-10-039, TID dosing). In addition, an ocular comfort study performed in the USA, and the SmPCs of individual components were also evaluated. This approach for the safety assessment was acceptable.

Both the mono-components of Brinz/Brim were authorised at the time of this report and have been in clinical use for a considerable period of time. Consequently their safety profiles are well-established. Both Brinz and Brim are used concomitantly in clinical practice and this provides additional reassurance, although no robust literature reporting on the use of the specific combination was available at the time of this report.

In this context, the overall patient exposure of 1080 patients in the pivotal efficacy studies from both the BID and TID studies was considered an adequate safety database in support of this application. A total of 535 patients (82.9%) were exposed to Brinz/Brim BID beyond 3 months, and the majority of them (about 80%) were exposed to Brinz/Brim for at least 173 days.

Given the set of exclusion criteria described above for the phase III clinical trials, the safety data from the excluded groups are not available. However, this was considered acceptable, as the SmPC for Sibmrinza lists the pre-cautions and warnings at the time of this report that are present in both the mono-therapies.

In the BID studies, the most common adverse reactions were generally ocular (topical) reactions including ocular hyperaemia, ocular discomfort, visual disturbances and ocular allergy. The topical adverse reaction profiles were comparable across the combination treatments and mono-therapies, except that Brinzolamide showed generally fewer topical adverse reactions as compared to the Brimonidine containing treatments. There was an increased incidence of topical reactions of ocular discomfort, visual disturbances and ocular allergies in the fixed dose combination Brinz/Brim as compared to the mono-therapies, while the incidence seemed comparable to the Brinz+Brim treatment arm. Overall, incidences of hyperaemia of the eye,
visual disturbances, punctate keratitis, keratitis ocular discomfort, dysgeusia, oral dryness, fatigue/drowsiness were reported in a numerically slightly higher incidence in the Brinz+Brim arm. Adverse reactions of corneal erosion, corneal deposit, hypermetropia and drug allergy were reported in very small numbers in the Brinzolamide/ Brimonidine BID group but not in the Brinz+Brim group. Corneal erosion is a known risk of the mono-components and the reported incidences for Brinz/Brim in these studies are consistent with the established risk for the mono-components.

Of the topical events, ocular allergies appear to have resulted in a substantial number of treatment discontinuations and hence this was considered a significant safety event. The withdrawals due to Brinz/Brim (3.9%) and Brim alone (3.4%) due to allergies appeared to be comparable

Dysgeusia, dry mouth and fatigue/drowsiness were the most common systemic events reported in these studies and the incidence of dry mouth and fatigue were more common with the Brimonidine containing treatment arms.

The safety profile in the TID studies was qualitatively similar to the one derived from the BID studies. However, there appeared to be differences in the incidence rates of certain events between the BID and TID studies. It was generally seen that the incidences of ADRs were higher in the TDI dosing regimen as compared to the BID dosing regimen. This was consistent with the higher daily dose administered in this group. The withdrawal rates due to ocular allergies also showed a similar higher incidence in the TID dosing regimen. The risk of occurrence of ocular allergies did not decrease over time as seen by similar rates of occurrence in the first and second three-month period. There was an increase in incidence of allergies for the combination with increased treatment duration as seen from the 3 months vs 6 months comparison in the TID studies. This was also seen for Brimonidine alone.

The results of physical examination data did not generally give cause for concern. Regarding vital signs, the fixed dose combination did not seem to increase the incidence of pulse rate or blood pressure decreased in comparison to the other treatment groups. However, several patients in Brinz/Brim BID group versus unfixed combination, brinzolamide and brimonidine groups experienced a shift from normal to high diastolic blood pressure (8.5% versus 6.5%, 4.1% and 6.9%, respectively). The SmPC includes hypertension as a very rare adverse event of brimonidine. This was considered adequate to mitigate the potential small risk of increasing blood pressure. A warning on hypotension is also included in the SmPC.

The overall discontinuation rate in the BID studies for Brinz/Brim, Brinz+Brim and Brim alone were 11%, 13.3% and 8.6%, respectively. The majority of these were due to ADRs (e.g. ocular discomfort, ocular hyperaemia, and ocular allergies). Brinz alone had very low discontinuation rates. In the TID studies, the overall discontinuation rates for Brinz/Brim and Brim alone were 14.4% and 11.9% (at 3 month interval) and 19% and 16.2% respectively at 6 months.

Data either from clinical studies or published data on concomitant clinical use was not available. However, it was agreed that this can be addressed in the post-marketing phase. The proposal of the applicant to include long-term safety as missing information in the RMP and to monitor for this risk by routine pharmacovigilance measures was considered acceptable by the PRAC, as the long-term safety of the mono-components is well-established.
There is potential for drug interactions with Brinz/Brim with some classes of drugs, including oral carbonic anhydrase inhibitors (potential additive effect), high-dose salicylate therapy (rare case of acid-base alterations reported with other carbonic anhydrase inhibitors but not Brinz), CNS depressants (potential additive/potentiating effect with Brim), antihypertensives (potential adrenergic interactions), tricyclic antidepressants (potentially may blunt the effect of adrenergic agonists) and MAO- inhibitors (theoretical interference with metabolism of brimonidine). Appropriate warnings and contra-indications are included in the SmPC to inform about the consequences of these interactions.

Overall, the safety profile of Brinz/Brim was adequately characterised in the pivotal studies. As expected, for a topical treatment, most of the adverse events are local reactions. The types of adverse events reported are in line with the known safety profiles of the mono-therapies. The incidence of adverse events appeared to be higher with Brinz/Brim as compared to mono-therapies, which was not unexpected.

From the safety database all the adverse reactions reported in clinical trials and post-marketing for the individual active components have been included in the Summary of Product Characteristics.

**Comparative safety profile between Brinz/Brim and Brinz+Brim**

The applicant discussed the safety data of C-10-041 alone to provide a direct comparison of Brinz/brim with concomitant dosing of Brinz+Brim as used in clinical practice. The adverse reaction profile in the two groups was broadly comparable. Some reported differences are:

Adverse drug reactions for Hyperaemia of the eye, visual disturbances, punctuate keratitis, keratitis ocular discomfort, dysgeusia, oral dryness, fatigue/drowsiess were reported at a slightly higher incidence in the Brinzolamide + Brimonidine BID relative to the Brinzolamide/Brimonidine BID group.

Adverse drug reactions for corneal erosion, corneal deposit, hypermetropia and drug allergy were reported in very small numbers the Brinzolamide/Brimonidine BID group but not in the Brinz+Brim group.

Adverse drug reactions of eye irritation and allergic conjunctivitis were slightly higher in the Brinz/Brim group as compared to the Brinz+Brim group.

**2.6.2. Conclusions on the clinical safety**

The safety profile of Brinz/Brim in terms of the types of adverse events is broadly comparable to the safety profiles of the mono-therapies and concomitant administration of Brinz+Brim. As expected, most of the observed adverse events were topical ocular events, of which common events included hyperaemia, visual disturbances, allergic reactions and ocular discomfort.

The data from the clinical studies suggest that the overall safety profile in terms of the incidence of reported events is better for the mono-therapies as compared to Brinz/Brim, which in turn is comparable with a trend to be marginally better than Brinz+Brim concomitant administration.
There is no long-term safety data for the combination, although it was acknowledged that there was long-term safety data for the mono-therapies. Therefore, the long-term safety for Brinz/brim can be addressed in the post-marketing phase.

Overall, it was accepted that the safety profile of Brinz/Brim had been adequately characterised and did not raise any significant concerns as compared to Brinz alone and Brim alone, which are both currently used in clinical practice.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

2.8. Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

PRAC Advice

The RMP (version 2.0 dated 11 Feb 2014) is considered acceptable.

This advice is based on the following content of the Risk Management Plan:

- **Safety concerns**
  - Important identified risks
    - Hypersensitivity / ocular allergy/ anaphylaxis/severe cutaneous reactions
    - CNS depression in paediatrics
    - Cardiac and vascular disorders
    - Corneal Oedema and/or corneal decompensation
    - Metabolic Acidosis and/or renal impairment
  - Important potential risks
    - Corneal epithelium damage due to use of preserved eye drops
    - Accidental overdose/ingestion in children
  - Missing information
    - Pregnancy
    - Breastfeeding
    - Long term safety
• **Pharmacovigilance plans**

There are no additional studies/activities in the Pharmacovigilance Plan.

• **Risk minimisation measures**

<table>
<thead>
<tr>
<th>Safety concern</th>
<th>Routine risk minimisation measures</th>
<th>Additional risk minimisation measures</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Important identified risks</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypersensitivity / ocular allergy/ anaphylaxis/ severe cutaneous reactions</td>
<td>Appropriate identification in the medicinal product labeling.</td>
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</tr>
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</tr>
</tbody>
</table>

The CHMP endorsed this advice without changes.

**2.9. 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*.  

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3. Benefit-Risk Balance

Simbrinza is a fixed dose combination of Brinzolamide/Brimonidine (Brinz/Brim) developed to decrease elevated intra-ocular pressure (IOP) in adult patients with open-angle glaucoma or ocular hypertension. Both Brinzolamide (Brinz) and Brimonidine (Brim) are authorised for the same indication and their efficacy and safety profiles are well-established.

Benefits

Beneficial effects
The combination of Brinz/Brim showed superior IOP lowering efficacy (statistically significant and clinically relevant) as compared to Brinz alone and Brim alone (study C-10-040). This was demonstrated in one pivotal study with BID dosing as measured by the mean diurnal IOP reduction from baseline after 3 months of treatment. The reduction values were 7.9 mm Hg, 6.5 mm Hg and 6.4 mm Hg in Brinz/Brim, Brinz and Brim alone arms, respectively. Superiority of the combination was also generally seen for other secondary endpoints (mean IOP & mean change in IOP from baseline at all assessed time-points and visits). In terms of responders, at time of morning efficacy peak (+ 2h time point) through to month 6, up to 68% of patients on Brinzolamide/Brimonidine, 46% on Brinzolamide and 45% patients on Brimonidine achieved IOP < 18 mmHg. The difference between the study arms was statistically significant in favour of the combination.

The efficacy of the fixed dose combination Brinz/Brim is not inferior to the efficacy of concomitant administration of Brinz+Brim as measured by the mean diurnal IOP reduction from baseline after 3 months of treatment (study C-10-041). The treatment group difference was -0.1 mmHg with an upper bound of the 95% CI equal to 0.2 mmHg, which is below the pre-specified non-inferiority margin of 1.5 mmHg. All of the supportive endpoints in this study were also supportive of the conclusion drawn from the primary endpoint.

The overall IOP lowering efficacy of Brinz/Brim was shown to have mean values of approximately 8 mm Hg, which constitutes a mean IOP reduction of 23 to 37% and is considered clinically relevant. This is similar to the effect sizes for prostaglandin analogues (which are generally the preferred first-choice treatment) and beta-blockers.

Simbrinza contains a lower amount of the preservative BAK than the concomitant administration of the two active components. In principle, a better safety profile would be expected from a reduced daily exposure to BAK.

Uncertainty in the knowledge about the beneficial effects
No direct comparison between BID and TID dosages has been performed for the combination. From an indirect comparison no major differences were observed in terms of IOP levels reached when Brinzolamide/Brimonidine was dosed twice or three times daily. Whilst the magnitude of the effect (mean differences) with respect to each monotherapy could be slightly greater under TID regimen, results do not appear to be sufficiently meaningful to recommend a change in the posology.

Long-term efficacy data for Brinzolamide/Brimonidine is available only up to 6 months. As Brinz alone and Brim alone do not have any known waning of effects with long-term treatment, it is
reasonable to expect a similar maintenance of effect with long-term treatment with Brinzolamide/Brimonidine. However, direct evidence is not available.

It was furthermore observed that the difference in the IOP lowering effect between Brinzolamide/Brimonidine and Brinz alone increases with time especially at the trough IOP point (pre-dose). The clinical relevance of this observation with regard to the choice of using monotherapy vs. combination therapy is not known and cannot be determined based on the available data. However, based on the knowledge of maintenance of effects of Brinz alone and Brim alone and the observation of results of use of Brinzolamide/Brimonidine for 6 months, it is reasonable to expect that there will not be significant loss of efficacy when Brinzolamide/Brimonidine is used continuously for longer than 6 months.

**Risks**

**Unfavourable effects**

As expected, the most common adverse reactions reported in the pivotal studies of Brinzolamide/Brimonidine were ocular reactions. They were ocular hyperaemia, ocular discomfort, visual disturbances and ocular allergy. The incidence of ocular discomfort, visual disturbances and ocular allergies is higher in the fixed dose combination Brinzolamide/Brimonidine as compared to the monotherapies and generally slightly lower than the concomitant administration of Brinz+Brim. Brinzolamide had the lowest incidence for many of the adverse reactions.

Other topical events included adverse reaction of the corneal surface like punctuate keratitis, keratitis, corneal erosions, corneal deposits, which, however, generally have a low incidence. Two events of corneal erosions were classified as serious in the Brinzolamide/Brimonidine, both of which healed after appropriate treatment including discontinuation of Brinzolamide/Brimonidine.

Dysgeusia, dry mouth and fatigue/drowsiness were the common systemic events reported in these studies and the incidence of dry mouth and fatigue were more common with the Brimonidine containing treatment arms.

The safety profile in the TID studies included the same type of adverse reactions as reported in the BID studies, although there were differences in the incidence of these events between the two sets of studies. The incidences of ADRs were generally higher in the TDI group, which is consistent with the higher daily dose administered in this regimen. The natures of the reactions reported are comparable with the reactions reported for the mono-therapies and the concomitant administration of Brinz+Brim and no new adverse reactions have been identified with the use of Brinzolamide/Brimonidine in these studies.

Other less common but significant risks include decreased blood pressure and pulse rate, an effect known with use of an alpha-2 adrenergic agonist. Topical carbonic anhydrase inhibitors can cause increased potential for developing corneal oedema, although none have been reported in the clinical studies.
Several events of diastolic blood pressure increased (8.5% in Brinzolamide/Brimonidine versus 6.5% in Brinz+Brim, 4.1% in Brinz and 6.9% in Brim, respectively) were reported. Whilst the applicant did not provide explanations for these observations, it was agreed that the communication of this risk in the SmPC could be considered adequate as risk-mitigation measure.

Potential significant interactions include acid-base and electrolyte alterations with carbonic anhydrase inhibitors, rare fatalities due to systemic reactions to sulphonamide use (brinzolamide is a sulphonamide). Another potential risk is toxic ulcerative keratopathy due to the preservative benzalkonium chloride. Whilst none of these were reported in the clinical studies with Brinz/Brim, they are potential risks based on knowledge of the mechanism of action of the individual components.

**Uncertainty in the knowledge about the unfavourable effects**

Corneal erosion (reported as serious adverse event) and corneal deposits were only observed in Brinzolamide/Brimonidine BID group as compared to the other treatment groups in the clinical studies. However, this is a known adverse event with the mono-therapies, although no event was reported in the monotherapy arms in these studies. The number of events of such occurrence was very small and so it cannot be said with certainty if there is an increased incidence with the combination. However, it was agreed that based on the low numbers reported in the clinical studies, the risk of these events can be considered to be consistent with the known risk profiles of the mono-therapies.

Direct safety data on long-term use of Brinzolamide/Brimonidine is not available and bibliographic data from its concomitant clinical use was also not discussed. It was acknowledged that there is long term safety for the two components that constitute the fixed dose combination. This will be addressed in the post-marketing phase.

**Benefit-risk balance**

**Importance of favourable and unfavourable effects**

Brinzolamide/Brimonidine showed superiority over the mono-components with regards to IOP lowering efficacy and the magnitude of this increased efficacy is clinically relevant. Therefore, patients who are inadequately controlled with either of the mono-components are likely to experience a greater benefit with this combination. All fixed dose combinations currently available include a beta-blocker as a component. Therefore, a fixed dose combination which does not include a beta-blocker would be an important alternative for patients. Combining of two active substances in one preparation is convenient for patients and is likely to have a positive impact on compliance.

The topical ocular adverse reactions reported for Brinzolamide/Brimonidine are similar to the reactions reported for the mono-therapies. However, as they are chronic treatments, some of the reactions in the long-term may potentially be different for Brinzolamide/Brimonidine as compared to the mono-therapies. This needs to be monitored in the post-marketing phase. The number of withdrawals due to adverse reactions is more than 10% for Brinzolamide/Brimonidine in the
studies, which is a significant figure. This is generally comparable to the discontinuation rates with Brim alone, hence acceptable.

**Benefit-risk balance**
The fixed dose combination Brinzolamide/Brimonidine is superior to Brinz alone and Brim alone and non-inferior to concomitant administration of Brinz+Brim in patients with open-angle glaucoma or ocular hypertension inadequately controlled on monotherapy.

Brinzolamide/Brimonidine appears to have a similar safety profile as that of Brinz and Brim in combined terms of the nature of adverse reactions. The incidence of adverse reactions appears to be marginally higher with Brinzolamide/Brimonidine as compared to mono-therapies. However, the incidence of adverse reactions with Brinzolamide/Brimonidine is comparable to that of Brinz+Brim concomitant administration. This concomitant administration is used in clinical practice for patients who do not respond adequately to one treatment alone.

On balance, the benefits outweigh the risks for the use in patients whose IOP are inadequately controlled with a monotherapy. The benefit-risk balance for Brinzolamide/Brimonidine is considered positive for the approved indication.

**Discussion on the benefit-risk balance**
The benefits of Brinzolamide/Brimonidine over the mono-components in the treatment of open-angle glaucoma or ocular hypertension have been demonstrated. The mono-components are currently used in the treatment of the claimed indication. The efficacy of Brinzolamide/Brimonidine is non-inferior to the efficacy of concomitant administration of Brinz+Brim. These conclusions support the use of Brinzolamide/Brimonidine only in patients who are not adequately controlled with mono-therapies alone. The safety profile of Brinzolamide/Brimonidine in terms of the nature of adverse reactions is similar to the mono-components in that there are no new adverse reactions of significance or adverse events with greater severity that seems to be reported with Brinzolamide/Brimonidine in these studies. Safety data are available only for 6 months and direct data on longer-term is not available. However, taking in to consideration that there is long-term safety data available with Brinz alone and Brim alone, it was accepted that data on long-term safety of Brinzolamide/Brimonidine can be collected in the post-marketing setting.

Overall, the CHMP considered that with Simbrinza patients and doctors will benefit from the availability of a fixed dose combination that does not contain a beta-blocker (timolol). This would mean that patients who need more than one treatment to control their IOP and have a contra-indication to timolol will have another option. Moreover, the fixed dose combination will be convenient for patients who would otherwise need to use two different drops and this convenience is also likely to translate into better compliance and consequently better efficacy.
4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus decision that the risk-benefit balance of Simbrinza for the decrease of elevated intraocular pressure (IOP) in adult patients with open-angle glaucoma or ocular hypertension for whom monotherapy provides insufficient IOP reduction is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Conditions and requirements of the Marketing Authorisation

• Periodic Safety Update Reports

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

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.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.