13 October 2016
EMA/738656/2016
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Cystadrops

International non-proprietary name: mercaptamine

Procedure No. EMEA/H/C/003769/0000

Note

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

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Administrative information

Name of the medicinal product:	Cystadrops
Applicant:	Orphan Europe S.A.R.L. Immeuble "Le Wilson" 70, avenue du Général de Gaulle FR-92800 Puteaux France
Active substance:	mercaptamine hydrochloride (also known as cysteamine hydrochloride)
International Non-proprietary Name:	mercaptamine
Pharmaco-therapeutic group (ATC Code):	other ophthalmologicals, other ophthalmologicals (S01XA21)
Therapeutic indication(s):	Cystadrops is indicated for the treatment of corneal cystine crystal deposits in adults and children from 2 years of age with cystinosis.
Pharmaceutical form(s):	Eye drops, solution
Strength(s):	3.8 mg/ml
Route(s) of administration:	Ocular use
Packaging:	vial (glass)
Package size(s):	5 ml

Table of contents

List of abbreviations

AEs	adverse events
AGEPS	Agence Générale des Equipements et Produits de Santé
ANCOVA	analysis of covariance
ASMF	active substance master file
BAK	benzalkonium chloride
CCCS	corneal cystine crystal score
CMC	carmellose sodium (carboxymethylcellulose)
CSR	clinical study report
EDTA	ethylenediaminetetraacetic acid
EDS	Ehlers-Danlos syndrome
FAS	full analysis set
GC	gas chromatography
GEE	generalised estimating equation
HDPE	High Density Polyethylene
HPLC	High performance liquid chromatography
HRT	Heidelberg retina tomograph
HRT/RTM	Rostock cornea module of the Heidelberg retina tomograph
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICP-MS	Inductively coupled plasma mass spectrometry
IOP	intraocular pressure
IR	infrared
IVCM	in-vivo confocal microscopy
KF	Karl Fischer titration
LADRs	local adverse drug reactions
LOCF	last observation carried forward
mPas	milliPascal seconds
MS	Mass Spectrometry
NF	new formulation
NMR	Nuclear Magnetic Resonance
NPU	named patient use
OCT	optical coherence tomography
OD	*oculus dexter*, right eye
OS	*oculus sinister*, left eye
PASS	post authorisation safety study
Ph. Eur.	European Pharmacopoeia
PIP	paediatric investigation plan
PPS	per protocol set
RH	Relative Humidity
RCT	randomised controlled trial
SAEs	serious adverse events
SAP	statistical analysis plan
SF	standard formulation
SOC	system organ class
SS	safety set
TEAE	Treatment Emergent Adverse Events
UV	Ultraviolet
VA	visual acuity
VAS	visual analogue scale

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Orphan Europe S.A.R.L. submitted on 30 July 2014 an application for marketing authorisation to the European Medicines Agency (EMA) for Cystadrops, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 25 April 2013.

Cystadrops, was designated as an orphan medicinal product EU/3/08/578 on 7 November 2008. Cystadrops was designated as an orphan medicinal product in the following indication: Treatment of cystinosis.

The applicant applied for the following indication: treatment of corneal cystine crystal deposits in cystinosis patients.

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Cystadrops as an orphan medicinal product in the approved indication. The outcome of the COMP review can be found on the Agency's website: ema.europa.eu/Find medicine/Rare disease designations.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that mercaptamine was considered to be a known active substance.

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

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0322/2013 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

Protocol Assistance

The applicant received Protocol Assistance from the CHMP on 7 November 2012. The Protocol Assistance pertained to quality and clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Kristina Dunder Co-Rapporteur: Greg Markey

- The application was received by the EMA on 30 July 2014.
- The procedure started on 24 September 2014.
- The CHMP adopted a report on similarity of Cystadrops with Cystagon and Procysbi on 18 December 2014.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 12 December 2014. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 12 December 2014. The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 19 December 2014.
- During the meeting on 8 January 2015, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP. The PRAC Assessment Overview and Advice was sent to the applicant on 12 January 2015.
- During the meeting on 22 January 2015, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 26 January 2015.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 20 April 2015.
- The following GMP inspection was requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:
  - A GMP inspection at one finished product manufacturing site in the United Kingdom was conducted on 22 July 2015. The outcome of the inspection carried out was issued on 27 July 2015.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Questions to all CHMP members on 2 June 2015.
- During the PRAC meeting on 11 June 2015, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP. The PRAC Assessment Overview and Advice was sent to the applicant on 12 June 2015.
- During the CHMP meeting on 25 June 2015, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 5 August 2015.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of outstanding issues to all CHMP members on 3 September 2015.
- During the PRAC meeting on 10 September 2015, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP. The PRAC Assessment Overview and Advice was sent to the applicant on 11 September 2015.
- During the CHMP meeting on 22 October 2015, second the CHMP agreed on a list of outstanding issues to be addressed in an oral explanation by the applicant.
- The applicant submitted the responses to the second CHMP List of Outstanding Issues on 29 October 2015.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of outstanding issues to all CHMP members on 6 November 2015.
- During the PRAC meeting on 6 November 2015, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP. The PRAC Assessment Overview and Advice was sent to the applicant on 9

November 2015.

- During the CHMP meeting on 19 November 2015, the CHMP agreed on a third list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the third CHMP List of Outstanding Issues on 9 September 2016.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the third List of outstanding issues to all CHMP members on 26 September 2016.
- During the meeting on 13 October 2016, 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 Cystadrops on 13 October 2016.

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Cystinosis is a rare genetic autosomal recessive disease. It is caused by a lysosomal transport defect resulting in the intracellular accumulation of cystine.

2.1.2. Epidemiology

Cystinosis affects approximately 0.15 in 10,000 people in the European Union (EU). This is equivalent to a total of around 7,600 people, and is below the ceiling for orphan designation, which is 5 people in 10,000.

2.1.3. Aetiology and pathogenesis

Cystine accumulates within lysosomes, forming crystal deposits in many tissues, including the kidneys and the eyes, but also in bone marrow, lymph nodes, intestine, spleen, liver, pancreas, gonads, thyroid, muscles, and in the central nervous system. In the CTNS gene responsible for coding cystinosin that transports cystine out of the lysosomes, more than 90 mutations and slice regions have been reported.

2.1.4. Clinical presentation

Different CTNS gene mutations produce different phenotypes that vary based upon the amount of residual cystinosin. Usually, three phenotypes, based on the age of onset and severity of symptoms, are described. Nephropathic infantile cystinosis is the most common (95% of patients) and the most severe form of cystinosis with an onset around 6 to 12 months of age. It starts with the renal tubular Fanconi syndrome which leads to malnutrition and nutrient imbalance with growth impairment including soft, bowed bones, increased urination, thirst, dehydration and acidosis. If untreated, it progresses to end-stage renal failure at approximately 10 years of age. The intermediate form of nephropathic cystinosis has most of the clinical symptoms of infantile cystinosis, but appears in children aged 12-15 years. Adult type non-nephropathic, or ocular, cystinosis is characterised only by cystine crystal deposits in the cornea and conjunctiva without any apparent systemic manifestations.

Corneal cystine crystals that can be seen in the corneal epithelium and the stroma are specific characteristics of all three phenotypes of cystinosis. They appear as a myriad of needle-shaped highly

reflective opacities. By 1 year of age, cystine crystals can be evidenced in the cornea by slit lamp. By approximately 7 years of age, the entire peripheral stroma accumulates crystals, and by approximately 20 years of age, crystals can be seen in the entire corneal stroma.

The crystals are initially asymptomatic but photophobia, resulting from the diffraction of light by the cystine crystals, is common and develops within the first few years of life. Many patients begin wearing sunglasses in early childhood. Superficial punctate keratopathy and pain are occasionally observed, mostly in patients older than 10 years of age. Other more severe complications of crystal deposits are corneal erosions, loss of visual contrast sensitivity, increased glare disability, decreased corneal sensitivity and increased corneal thickness. In very young patients, visual acuity (VA) is usually not affected, however, in older patients where corneal complications are more common, these may lead to visual impairment.

2.1.5. Management

Virtually all cystinosis patients are treated by oral administration of cysteamine (Cystagon and Procysbi) aiming to reduce intracellular cystine accumulation, therefore delaying organ and tissue damage. While oral administration of cysteamine reduces intracellular cystine accumulation in non-corneal tissues, systemically administered cysteamine does not reach the cornea and has consequently no effect on corneal cystine deposits.

To dissolve cystine crystal deposits in the cornea, the established approach is to use eye drops solutions containing cysteamine. Currently, eye drop formulations at concentrations between 0.10% - 1.13% are prepared ex tempore, e.g. by pharmacies at local hospitals. A range of different posologies, including hourly instillations, are applied.

About the product

Cystadrops contains 0.55 % mercaptamine hydrochloride (5.5 mg/ml mercaptamine hydrochloride, equivalent to 3.8 mg/ml mercaptamine base). Mercaptamine is also known as cysteamine, and the two names are used interchangeably throughout this report. It is formulated with carboxymethylcellulose (CMC) to increase the residence time of the eye drops, and is to be administered 4 times per day. With time, the dose may be decreased to a minimum of one drop per day. The product also contains 0.01 % benzalkonium chloride (BAK) as a preservative.

Type of Application and aspects on development

This is a complete application in accordance with Article 8(3) of Directive 2001/83/EC with a known active substance, No. 726/2004 (Mandatory Scope) Annex 4: Orphan designated medicinal product.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as an eye drops solution containing 5.5 mg/ml of mercaptamine hydrochloride, equivalent to 3.8 mg/ml mercaptamine, as active substance.

Other ingredients are: benzalkonium chloride solution (BAK), carmellose sodium (CMC), citric acid monohydrate, disodium edetate, hydrochloric acid, sodium hydroxide and water for injections.

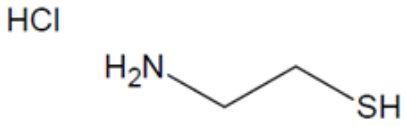
The product is available in glass vials sealed by bromobutyl rubber and an aluminium seal. A PVC dropper applicator with HDPE closure is supplied with each vial and is attached to the glass vial by the patient before first use.

2.2.2. Active Substance

General information

The chemical name of mercaptamine hydrochloride is 2-aminoethanethiol hydrochloride corresponding to the molecular formula $C_2H_7NS.HCl$. It is also known as cysteamine hydrochloride. It has a relative molecular mass of 113.6 g/mol and has the following structure:

Figure 1: Structure of Mercaptamine hydrochloride



It is a white crystalline powder. It is soluble in water and alcohol and insoluble in methylene chloride. The structure of mercaptamine hydrochloride has been confirmed by several techniques including elemental analysis, IR, MS, ^{13}C-NMR and ^{1}H-NMR. Mercaptamine hydrochloride has no chiral centre. Polymorphism is not considered relevant as mercaptamine hydrochloride is present in solution in the finished product.

Mercaptamine hydrochloride is not the subject of a monograph in the Ph. Eur.

Manufacture, characterisation and process controls

Two alternative manufacturers are used for the manufacture of mercaptamine hydrochloride. The information from both manufacturers has been provided in form of Active Substance Master Files (ASMFs). Detailed information on the manufacturing process of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory.

Well defined starting materials with acceptable specifications are used in each case. For one of the manufacturers, a major objection was raised relating to the acceptability of a proposed starting material. A new starting material was defined and acceptable information was provided regarding the manufacturing process, control of ingredients, discussion of carry-over of impurities and control of intermediates.

The synthetic routes have been shown to produce material of equivalent pharmaceutical quality ensuring similar performance *in vivo*.

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

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities for both synthetic routes were well discussed with regards to their origin and well characterised.

Specification

The active substance specification includes tests for appearance, identity (IR, HPLC), assay (HPLC), impurities (HPLC), appearance of solution (Ph. Eur.), pH (Ph. Eur.), water content (KF) and residual solvents (GC). For one manufacturer, tests for sulfated ash (Ph. Eur.) and heavy metals (ICP-MS) are also included. The finished product manufacturer controls the drug substance according to a consolidated specification which is in accordance with the specifications used by the active substance manufacturers.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. The methods used by the finished product manufacturer are the same as used by the drug substance manufacturers and have been validated by the respective manufacturers.

Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set for both manufacturers/synthetic routes.

Satisfactory information regarding the reference standards used for testing has been presented.

Batch analysis data of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Mercaptamine hydrochloride is packaged in glass vials with rubber stoppers. Acceptable specifications for the vials and rubber stoppers have been provided.

Stability data on production scale batches of active substance, stored in the intended commercial package, for up to 48 months under long term conditions at 5 ±3ºC and up to 6 months under accelerated conditions, at 25ºC / 60% RH, according to the ICH guidelines, were provided. Samples were tested for appearance, identity, assay, impurities and water content. The analytical methods used were the same as for release and are stability indicating. All tested parameters complied with the specifications.

The stability results indicate that the active substance manufactured by the proposed suppliers is sufficiently stable and the proposed retest periods and storage conditions are acceptable.

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical development

Cystadrops is a sterile eye drops solution to be marketed in amber glass vials containing 5 ml drug product. A PVC dropper applicator with HDPE closure is supplied with each vial and is attached to the glass vial by the patient before first use. The eye drops solution contains mercaptamine hydrochloride 5.5 mg/ml (0.55 % w/v) corresponding to mercaptamine 3.8 mg/ml and is formulated using excipients described in the current Ph. Eur. The excipients are: benzalkonium chloride solution (BAK), carmellose sodium (CMC), citric acid monohydrate, disodium edetate, hydrochloric acid, sodium hydroxide and water for injections.

The drug product contains both an antioxidant, disodium edetate, and a preservative agent, benzalkonium chloride (BAK). These have been satisfactorily justified. It has been shown that the amount of BAK at shelf-life is enough to fulfil the requirements of Ph. Eur. 5.1.3 Efficacy of Antimicrobial Preservation. The presence of BAK in the formulation is further discussed in section 2.6.1. In order to prolong the contact time between the cornea and the drug substance and thereby improve the efficacy of

the drug product and reduce the number of daily instillations, a viscous formulation was chosen. The viscosity agent used is carmellose sodium. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.2.1 of this report.

The final drug product cannot be terminally sterilised by autoclaving since the drug substance is sensitive to high temperatures and it cannot be sterilised by aseptic filtration since the carmellose sodium makes the solution so viscous that it cannot pass through a 0.22 µm filter. Therefore, the manufacturing process for the pilot batches used in the first and second clinical studies comprised; sterilising filtration of a solution the drug substance and excipients, sterilisation by autoclaving of a solution of carmellose sodium and excipients, then aseptic mixing of the two solutions. Following difficulties during scale up to production scale, another process in which carmellose sodium was sterilised by ethylene oxide (rather than by autoclaving) was initially proposed.

The CHMP raised major objections to this choice of ethylene oxide sterilisation process and, having failed ensure sterility by this process, the applicant reverted to the original process used for pilot scale batches and clinical batches, i.e. sterilisation of the carmellose sodium solution by autoclaving. The change in sterilization method for carmellose sodium required some adjustments in the composition, manufacturing process, in-process controls and drug product specification. The manufacturer performed complementary process validation activities to validate the manufacturing process steps while increasing the batch size. All changes were well described and justified and the final process is now more consistent with the one used for the clinical batches.

The final formulation and viscosity are similar in the clinical batches and the product proposed for marketing. A specification limit for viscosity was set based on the variability in the historical batches.The minimum effective drop size has been defined and shown to be consistently achieved. The solution is buffered and the basis for setting of the pH/buffer capacity of the solution has been adequately justified. It was considered possible that the low buffered pH and viscosity of the formulation are contributing factors to ocular irritation and inflammation. However, this has to be weighed against the benefits of a stable substance that stays at the eye for a longer time and allows longer intervals between the administration times (i.e. 4 times a day during waking hours compared to current situation; mercaptamine eye drop formulations prepared *ex tempore*, e.g. by pharmacies at local hospitals, which have a range of different posologies, including hourly instillations).

The primary packaging of the drug product is amber glass vials. Each vial is closed by a bromobutyl siliconised stopper and sealed with a flip off/tear off aluminium vial seal. Additionally, an individually packed PVC dropper applicator with HDPE closure is supplied with each vial and is attached to the glass vial by the patient before first use. The materials comply with Ph. Eur. and EC requirements. The vials, rubber stoppers and dropper applicators are sterilised before use and validation data for the sterilisation process has been provided where relevant. The performed usability test revealed some patients had difficulties when removing the closure and attaching the dropper applicator. This lead to a revision of the instructions for use in the package leaflet. Several subjects also had negative perception of usability of the container. Moreover, the process of opening the vial and attaching the dropper by patients, which has been shown to be difficult, could lead to microbiological and particulate contamination of the product. Difficulties in dispensing drops from the assembled vial/dropper were also reported. Inspection of product samples showed that container is not considered optimal in view of usability and assuring the microbiological quality of the drug product in-use. The CHMP concluded that the container closure system is not optimal, but considering the overall benefit/risk of the product, it could be used whilst awaiting the development of a new container closure system, preferably a plastic bottle with an integrated dropper

applicator already attached. The applicant has initiated a development plan for post approval development of a new container aiming for development of ready-to-use plastic bottles (with dropper already in place).

Manufacture of the product and process controls

The non-standard manufacturing process consists of four main steps: preparation of the buffer solution, mixing of carmellose sodium into a portion of the buffer solution to produce a gel followed by autoclaving, dissolution of the active substance and other excipients in the remaining buffer solution followed by sterile filtration, and mixing of the two solutions followed by clarifying filtration through a 40 µm filter.

The critical steps in the manufacturing process have been identified. In-process controls have been satisfactorily described and appropriate acceptance criteria are laid down. Bioburden is measured on the gel and active substance solutions prior to sterilisation. Sterility of the gel is tested as per Ph. Eur. before it is combined with the active substance solution. A clarifying filtration through a 40 µm filter is then performed before the product is filled into vials. The filters used have been acceptably described and validated.

Since the drug substance is sensitive to oxidation, the filling in glass vials is performed under nitrogen bubbling.

Process validation has been performed on three commercial scale batches. All results were acceptable and the process was shown to be robust and reproducible. No unit showed microbiological growth in the media fill tests on three batches. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process.

Product specification

The finished product specifications include appropriate tests for this kind of dosage form; appearance (visual), pH (Ph. Eur.), viscosity (Ph. Eur.), osmolality (Ph. Eur.), identification (mercaptamine hydrochloride, benzalkonium chloride and disodium edetate) (HPLC / UV), assay (mercaptamine hydrochloride, benzalkonium chloride and disodium edetate) (HPLC / UV), impurities (HPLC / UV), efficacy of antimicrobial preservation (Ph. Eur.) and sterility (Ph. Eur.).

The in-use specifications include appearance, pH, viscosity, osmolality, assay (mercaptamine hydrochloride, benzalkonium chloride and disodium edetate) and impurities.

The proposed specifications limits have been appropriately justified and are acceptable. The proposed limit for total impurities was accepted based on results for clinical batches and the limits for cystamine and any other impurity.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data has been provided for three commercial scale batches manufactured according to the new process. All tests in the release specification were carried out and all results were within the specification limits.

Stability of the product

Three months stability data has been provided for three commercial scale batches manufactured according to the new process and stored under long term conditions at 5ºC and under accelerated conditions at 25ºC / 60% RH according to the ICH guidelines.

All tests in the shelf-life specification were performed. The results were within the specification limits and in line with the batch analysis data except for the specified impurity, cystamine, where an increasing trend was seen.

Supporting data was provided for batches where carmellose sodium was sterilized by ethylene oxide and the manufacturing process and formulation were somewhat different and from clinical batches with the same composition and sterilisation method as for the commercial batches.

An in-use stability study was performed on two of the batches manufactured according to the proposed commercial manufacturing process. The level of cystamine impurity was higher than the limits in the release and shelf-life specifications and so a separate in-use shelf life specification with wider limits for cystamine content has been accepted. Every day for 7 consecutive days, two drops were sampled from each bottle four times a day. All results obtained after 7 days' use comply with the specifications regardless of in-use conditions (room temperature, refrigerator or mixed room temperature/ refrigerator). It was shown to be important (e.g. with respect to viscosity) for the correct use of the product that it is administered at room temperature. Accordingly, the SmPC includes an instruction for the patient to bring Cystadrops to room temperature before the first administration. When discussing the in-use stability of the product, the CHMP considered that requiring storage at 2-8°C during the in-use period and requiring a patient to bring the product back to room temperature before each administration of the product would not be ideal in terms of usability and patient compliance. For that reason, the CHMP preference was for an in-use period with storage at room temperature.

Based on the overall provided data, and following discussion of the issues outlined above, the CHMP concluded that the shelf-life of the unopened vial should be limited to 6 months when stored at 2-8°C and that an in-use shelf-life of 7 days after opening, when stored at or below 25°C, was acceptable.

In order to provide assurance of appropriate in-use quality of the product, the in-use stability of batches that are currently on long term stability should be investigated at the 6 month and subsequent test intervals. Before a longer shelf-life can be accepted, new in use stability data should be provided at that latest time point.

Adventitious agents

No excipients derived from animal or human origin have been used.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The 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.

The active substance is manufactured by two different suppliers. The major objection that was raised requesting a redefinition of the starting material for active substance manufactured one of the suppliers was solved.

Initially, a major objection was raised during the procedure regarding the usability of the container closure system but it was subsequently decided, in view of the clarifications introduced in the Product Information and the improved usability of this product compared to current clinical practice (mercaptamine eye drop formulations prepared *ex tempore*, e.g. by pharmacies at local hospitals), that the proposed container can be approved. In addition, the applicant has undertaken to develop an alternative more user friendly container, preferably a plastic bottle with an integrated dropper applicator.

The finished product is sterilised partly by aseptic filtration and partly by autoclaving (carmellose sodium solution in buffer). The applicant first proposed to use ethylene oxide sterilisation of carmellose sodium for commercial batches but after a major objection was raised that sterility had not been acceptably proven, the applicant changed to autoclaving of the carmellose sodium solution and the major objection was solved.

The formulation has not been optimised for viscosity in relation to tolerability and dose delivery. It is possible that the low buffered pH and viscosity of the formulation are contributing factors to ocular irritation and inflammation. However, this has to be weighed against the benefits of a stable substance that stays at the eye for a longer time and allows longer intervals between the administration times (i.e. 4 times a day during waking hours compared to current situation; mercaptamine eye drop formulations prepared *ex tempore*, e.g. by pharmacies at local hospitals, which have a range of different posologies, including hourly instillations). The benefit of improved usability and patient compliance associated with easier and reduced dosing schedule was considered to outweigh the risk of potential irritation. Based on the available stability data, only six months' shelf-life for the unopened container stored at 2-8°C is supported at present, with a 7 day in-use shelf life when stored at or below 25°C. Before this shelf-life can be extended, more in-use stability data must be provided.

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. The application is recommended for approval from a pharmaceutical point of view.

2.2.6. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

1. The applicant should develop an alternative, more user-friendly container closure system, preferably a plastic bottle with an integrated dropper applicator.
2. The stability programme with the current container closure system should continue as planned and in-use stability studies should be carried out for the drug product at each intermediate time points as they are reached (i.e. at 6, 12 and 18 months).

2.3. Non-clinical aspects

2.3.1. Introduction

The non-clinical dossier was primarily comprised of published literature. The Applicant has provided an overview of data available for oral and topical formulations of mercaptamine. In support of the ocular

route of administration, ocular pharmacology, absorption and ocular tolerance studies were also conducted.

2.3.2. Pharmacology

Primary pharmacodynamic studies

The primary pharmacodynamics of cysteamine was explored in *in vitro* and *in vivo* studies. Free cysteamine is able to enter lysosomes and to participate with cystine in a disulfide interchange reaction to form cysteine and cysteine-cysteamine mixed disulfide. These two compounds can exit the cystinotic lysosome by using transporters other than the defective cystinosin.

A study to support the clinical efficacy of the Cystadrops 0.55 %, eye drops formulation was conducted in Ctns-/- mice. No clear benefit could be shown following three months of three times daily instillations. When the frequency of instillations was increased to 6 times daily a possible effect (reduction of time-dependent increase in number of cysteine crystals) was observed.

In the literature, it has been reported that a treatment regimen of 4 ocular drops/day with a 0.55% cysteamine solution for 1 month in 5 months old Ctns-/- mice showed a clear effect of cysteamine treatment. These data indicates that cysteamine drops could have an effect on the corneal cysteine crystals deposits in cystinosis.

Secondary pharmacodynamic studies

It is well established that cysteamine has several other pharmacological/biological effects distinct from its intralysosomal cystine depleting activity. The most important effects can be ascribed to its a) antioxidant effect occurring as a result of increased intracellular glutathione levels b) inhibition of transglutaminase 2 and c) depletion of tissue somatostatin and prolactin.

Safety pharmacology programme

No studies were conducted as Cystadrops is a locally acting product.

Pharmacodynamic drug interactions

No studies were conducted, as systemic exposure from the applied eye drops is expected to be very low.

2.3.3. Pharmacokinetics

From published studies in rats and mice, orally administered cysteamine appears to be rapidly absorbed, and is eliminated rapidly from plasma and tissue. Ocular administration of cysteamine is unlikely to result in noteworthy systemic exposure.

A series of studies were performed in order to choose the optimal formulation of Cystadrops. Cysteamine could be assayed in the cornea up to 3 hours post administration in the presence of N acetyl cysteine. The elimination half-life of cysteamine from the ocular tissue appeared to be in the range of 1 hour. Overall, the best formulation seemed to be the 0.55% cysteamine/CMC medium viscosity formulation.

2.3.4. Toxicology

The ocular tolerance of the clinical and commercial Cystadrops formulations have been characterized in one pivotal GLP-compliant study, one non-GLP full study and in one non-GLP pilot study. In addition, the

Applicant performed a literature search covering the period up to the year 2013. No other new toxicity studies were submitted.

Repeat dose toxicity

General toxicity studies via ocular administration with cysteamine were not conducted as this is locally acting product.

Genotoxicity

Cysteamine is not considered to be genotoxic, as shown by the results of Ames test and *in vivo* mouse micronucleus assay.

Carcinogenicity

Cystadrops is intended to treat the local ocular symptoms only. Systemic effects from ocularly administered cysteamine are considered negligible in patients with concomitant oral exposure when considering that the proposed daily clinical ocular dose (1 drop up to 4 times daily in each eye) is 1000-fold lower than the highest recommended daily oral dose of the approved Cystagon hard capsules. Carcinogenicity studies using ocular administration are not considered feasible. Therefore, the lack of carcinogenicity studies is accepted.

Reproduction Toxicity

The observed reduced female fertility in rats at the high dose as reported in literature is not considered relevant for ocular administration of Cystadrops since the systemic exposure is anticipated to be low. Similarly, the observed developmental toxicity and teratogenic effects in rats with NOAEL at 75 mg/kg/day following oral administration are not considered relevant for ocular administration.

Local Tolerance

Cystadrops administered three times a day during three months to rabbits was macroscopically and microscopically well tolerated. When administered six times a day during three months, the treatment was less well tolerated and was not tolerated when it was administered nine times a day during two weeks. For the animals treated nine times a day, food and water consumption were decreased. On ocular examination moderate to severe conjunctival redness, slight to moderate conjunctival chemosis, slight to moderate cornea opacity, slight to severe conjunctival congestion and cornea vascularisation were observed along with pathological findings on conjunctivae, cornea epithelium, cornea stroma and eyelids.

In the study bridging the Cystadrops formulation used in clinical trials with the formulation to be marketed, the findings were similar in animals treated with the two different formulations. The formulation itself induces very slight conjunctival and corneal changes that appear to regress over time. No clear difference in ocular tolerance was seen between Cystadrops itself and the vehicle.

2.3.5. Ecotoxicity/environmental risk assessment

Mercaptamine is a natural substance and the use of Cystadrops will not alter its concentration or distribution in the environment. Therefore, Cystadrops is not expected to pose a risk to the environment.

Table 1: Environmental risk assessment

Substance (INN/Invented Name): Mercaptamine Hydrochloride			
CAS-number (if available): 156-57-0			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}		-2.14	Not PBT
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	-2.14	Not B
	BCF		
Persistence	DT50 or ready biodegradability		
Toxicity	NOEC or CMR		
PBT-statement :	Not PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	0.000011	µg/L	> 0.01 threshold N

2.3.6. Discussion on non-clinical aspects

While presented ocular pharmacology study does not show conclusive efficacy, the rationale for development of Cystadrops for the treatment of ocular manifestations of cystinosis is appropriate. It is unclear which instillation frequency of the Cystadrops formulation is optimal, or if the Cystadrops formulation is equally effective as other cysteamine formulations. However, the evaluation of clinical efficacy and dosage regimen is based on the available clinical data.

No further information has been provided relating to the disposition of cysteamine after ocular administration, and it is considered that additional valuable data relating to the ocular (and potential systemic) distribution/elimination of cysteamine could have been generated in the rabbit pharmacokinetic studies. However, the absence of these data is considered acceptable.

The lack of safety pharmacology studies for this ocular formulation is accepted based on the low anticipated systemic exposure of cysteamine. The lack of non-clinical drug-drug interaction studies is accepted.

The main cysteamine-related toxicity reported in published safety pharmacology and toxicology studies were effects on the CNS and GI, as well as on reproductive and developmental systems. While existing non-clinical cysteamine toxicity data cannot be considered to be complete, clinical safety has been established through long-term oral use in patients with cystinosis.

In general, the ocular repeated dose toxicity of cysteamine should have been evaluated in at least one species for at least six months in order to support chronic ocular use. However, no ocular repeated dose toxicity study has been submitted. This was justified by claiming that different cysteamine formulations have been extensively used in cystinosis patients. With reference to the submitted clinical data, the lack of further non-clinical data was accepted.

Cysteamine in its commercial formulation elucidated ocular irritation and inflammation in rabbits, primarily consisting of slight conjunctival redness, congestion and chemosis. Corresponding effects were also observed in the clinic where a high incidence of generally transient reactions like stinging, blurring, irritation, itching, redness was reported in association with instillation of the eye drops. It is not

considered likely that generation of new *in vivo* non-clinical data will add further reassurance relating to the ocular tolerance of Cystadrops. As the proposed clinical safety measures are considered adequate to address the tolerability concerns, it is considered that no further non-clinical data are required.

The excipients used in the Cystadrops drug product have well-established use in ocular formulations, and are considered acceptable.

2.3.7. Conclusion on the non-clinical aspects

Overall, the non-clinical data were considered by the CHMP sufficient to support the application for a marketing authorisation for Cystadrops in the treatment of corneal crystals in cystinosis. The CHMP furthermore concluded that Cystadrops was not expected to pose a risk to the environment.

2.4. Clinical aspects

2.4.1. Introduction

GCP

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

- Tabular overview of clinical studies

Study ID (Country)	Study Design and Objectives	Population	Treatment schedule	Study status; Type of report
OCT-1 (France, 2 centres)	Open-label, single-group. Initially planned for a period of 6 months; extended to 60 months. Primary objective: safety Secondary objectives: 1) identification of lowest effective dose and 2) efficacy An adaptive, dose-response included	Male and female cystinosis patients, ⩾ 3 y of age, with corneal cystine crystal deposits. Total enrolled: 8 Mean (± SD) age at inclusion: 12.1 (± 4.6) yrs; 4 patients <12 y, 3 patients 12 to < 18 y, 1 patient ⩾ 18 y.	Run-in: usual treatment with CH 0.10% (3 – 6 instillations/eye per day). Treatment period: treatment with Cystadrops was initiated at the same dosing frequency Dose adaptation up to Month 48.	Complete; Full
CHOC (France, 2 centres)	Open-label, randomised, comparative 3-months. Treatment arms: Cystadrops and CH 0.10%. Primary objective: superiority of Cystadrops vs.CH 0.10% for efficacy Secondary objective: safety	Male and female cystinosis patients, ⩾ 2 y of age, with corneal cystine crystal deposits. Total enrolled: 32 Mean age (± SD) at inclusion: 17.1 (± 13.0) y; 13 patients <12 y, 6 patients 12 to < 18 y, 12 patients ⩾ 18 y.	4 instillations/ eye/day for 90 days	Complete; Full

2.4.2. Pharmacokinetics

No studies were performed, nor has the applicant reviewed data available for systemically administered cysteamine.

2.4.3. Pharmacodynamics

Mechanism of action

Patients with the autosomal recessive lysosomal storage disease, cystinosis, lack a functional cystine carrier, resulting in intracellular accumulation of cystine. Cysteamine is an amino thiol that converts cystine to cysteine and cysteine-cysteamine mixed disulphide, both of which can pass through the lysosomal membrane without a functional carrier and then eliminated from the cells.

Due to the lack of corneal vascularisation, systemic administration of cysteamine has no therapeutic effect on corneal cystine crystals and local treatment is needed.

Primary and Secondary pharmacology

No studies were performed.

The absence of corneal cystine crystals deposits in healthy subjects does not allow the performance of a pharmacodynamic study in this population. In *in vitro* experiments, a rapid reduction in intra-lysosomal cystine levels of 90 – 95% has been shown in cultured fibroblasts and peripheral leukocytes (Thoene et al, 1976) and corneal stromal cells (Kaiser-Kupfer et al, 1987) for concentrations of cysteamine > 0.1 mM. This is approximately 50-fold less than the concentration of cysteamine contained in Cystadrops.

2.4.4. Discussion on clinical pharmacology

No pharmacokinetic studies have been performed. The vast majority of patients with cystinosis has systemic manifestations of the disease and are already treated with oral cysteamine in the range of 1 (small children) to 2 grams (older children and adults) per day. This is to be compared with the approximately 2 mg/day administered by the ocular route. Thus, the additive systemic exposure is expected to be negligible and the absence of pharmacokinetic studies was accepted by the CHMP. There is also no concern in special populations including subjects with hepatic or renal impairment or in the elderly.

From the non-clinical data, it was shown that cysteamine resided in rabbit corneal tissue up to one hour after administration of a single dose of 0.55% cysteamine solution including CMC, albeit at lower concentrations that used in the clinical formulations. Even though the rabbit cornea may not be fully relevant (no cystine deposits, lower blinking frequency) it is acknowledged that corneal absorption and residence time cannot be evaluated in patients.

No pharmacodynamic studies have been performed and none are requested as the mechanism of action of cysteamine is well characterised. The addition of cysteamine eye drops on top of oral cysteamine-treatment is further not likely to give a relevant contribution to a risk for systemic secondary pharmacological effects or systemic pharmacodynamic interactions. With regards to the potential for local, ocular interactions, the recommendation in the SmPC to allow 10 minutes between administrations of different eye drops is considered acceptable.

More than 90 mutations of the CTNS gene have been reported which produce different phenotypes. All but one patient in the two conducted studies were diagnosed with infantile nephropathic cystinosis which is the most common (95%) form with the most rapid progression rate. Although recognising the need for topical treatment once cystine accumulates in the cornea, a less frequent dosing may be sufficient in the more slowly progressing forms. Due to the rarity of the disease, the difficulties in evaluating this are however acknowledged. In any case, during the course of study OCT-1 (see below), the dosing frequency was reduced in all patients and one out of the eight included subjects maintained the reduction in crystals

with one instillation per day throughout the 5-year study period. The potential to decrease the dosing frequency based on treatment response as proposed in the SmPC is therefore a pragmatic approach which is considered reasonable.

2.4.5. Conclusions on clinical pharmacology

The CHMP was of the view that the available information from the scientific literature were sufficient to support the application for Cystadrops in the treatment of corneal crystals in cystinosis from a clinical pharmacology perspective. Given the local route of administration and that no significant systemic exposure is expected, the CHMP considered that the lack of specific pharmacodynamics or pharmacokinetic studies was acceptable.

2.5. Clinical efficacy

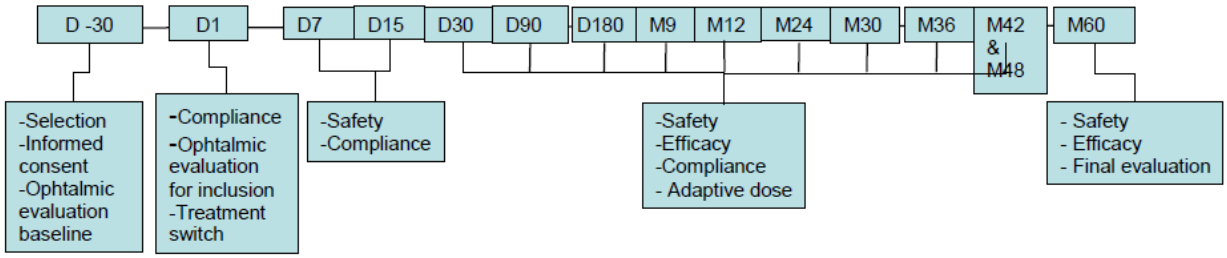
2.5.1. Dose response study

Study OCT-1: Adaptive dose regimen of Cystadrops for cOrneal Crystal deposiTs and ocular manifestations in nephropathic cystinosis

Methods

The study was an open-label non-randomised phase I-IIa study to evaluate dose-response and safety over a period of 5 years.

Figure 2: Study schematics



The study included subjects from 3 years of age with confirmed cystinosis with corneal deposits.

After the 30 day run-in period on their previous treatment (cysteamine eye drops 0.10%, 3-6 times/day), subjects received Cystadrops at the same frequency as with the 0.10% formulation (range 3-6 times/day, median 4 times/day. The number of daily eye drops was increased (only in case of a previous reduction of the number of daily instillations), remained stable or decreased based on worsening, no change or improvement in the amount of crystal deposits. The decision to adapt the dose regimen was taken by the ophthalmologist. The criterion for worsening or improvement was based on his subjective evaluation following the results of all ophthalmic examinations performed during the visit. Two formulations were tested, one with 4.10% (up to 15 September 2009) and one with 5.20 % CMC.

The primary efficacy endpoint was the absolute change in total score of the corneal cystine crystal density measured by IVCM using the Rostock Cornea Module of the Heidelberg Retina Tomograph (HRT/RCM) in the central cornea (7 corneal layers i.e. 2 layers in the epithelium, Bowman's membrane, superficial, medium and deep stroma and the endothelium) at each visit up to Month 60 of study treatments. Both eyes were analysed. IVCM images, 5-10 per corneal layer, were evaluated and scored in an open fashion. A single score was established for each layer.

Crystal density was rated on a 0-4 point scale from no (score 0) to 75-100% of deposits in the image (score 4) in each of 7 corneal layers, i.e. the maximal total score was 28.

Secondary ocular imaging endpoints: Crystal thickness (in µm and as percentage of corneal thickness) assessed by HRT in the central corneal region and by optical coherence tomography (OCT, with software for analysis of the anterior segment). The corneal cystine crystal score (CCCS) was assessed by slit-lamp and (score 0.00 to 3.00).

Secondary ocular clinical criteria: Photophobia (slit-lamp for each eye individually with a gradual increase in the light intensity, rated by investigator, 0 -5 point scale), visual acuity (VA, logMAR scale), and contrast sensitivity (Galinet chart, LogMar scores)

Statistical methods and analysis populations:

This was an open study and all patients received treatment in both eyes.

A realistic sample size for this study was defined as 8 nephropathic cystinosis patients, taking the rarity of the disease and the pilot status of the study into account.

Descriptive statistics were used for all demographic, safety and efficacy endpoints. As the IVCM score is calculated for each eye, the reference unit for the analysis was the eye. Model-based analysis using Generalised Estimating Equation (GEE) was used to take into account the correlation between eyes. Inferential tests were applied to compare the absolute change from baseline (Day 1) for the IVCM total score, as response to Cystadrops treatment.

The full analysis set (FAS) includes all patients/eyes who received at least one dose of Cystadrops and who have a baseline assessment and at least one ocular measurement post-dose. Due to the limited number of subjects, no per protocol set (PPS) was defined.

Rules for imputation of missing data were developed prior to database lock and were detailed in the SAP. The SAP was dated 13 February 2014.

Conduct

The study recruited 8 patients from 2 centres in France and was conducted between February 2008 and April 2013.

The study was initially planned as a 6 months study (Feb 2008). The study was amended 5 times and prolonged 4 times, finally to 60 months. The algorithm for treatment adaptation was included in July 2008.

Of the 8 patients (16 eyes), all completed day 180 and all completed the 5-year study. Compliance based on patient diary card recordings ranged from 98% to 100%.

Results

All included patients were diagnosed with infantile nephropathic cystinosis. The patient population included 1 adult, 3 paediatric subjects aged 12-17 and 4 aged 7-12 years, with a mean disease duration of 10.6 (±4.2) years. All subjects received concomitant systemic treatment for nephropathic cystinosis. The mean baseline IVCM corneal crystal score was 11.4 (±2.9), photophobia was 2.5 (±0.9) while VA was close to normal.

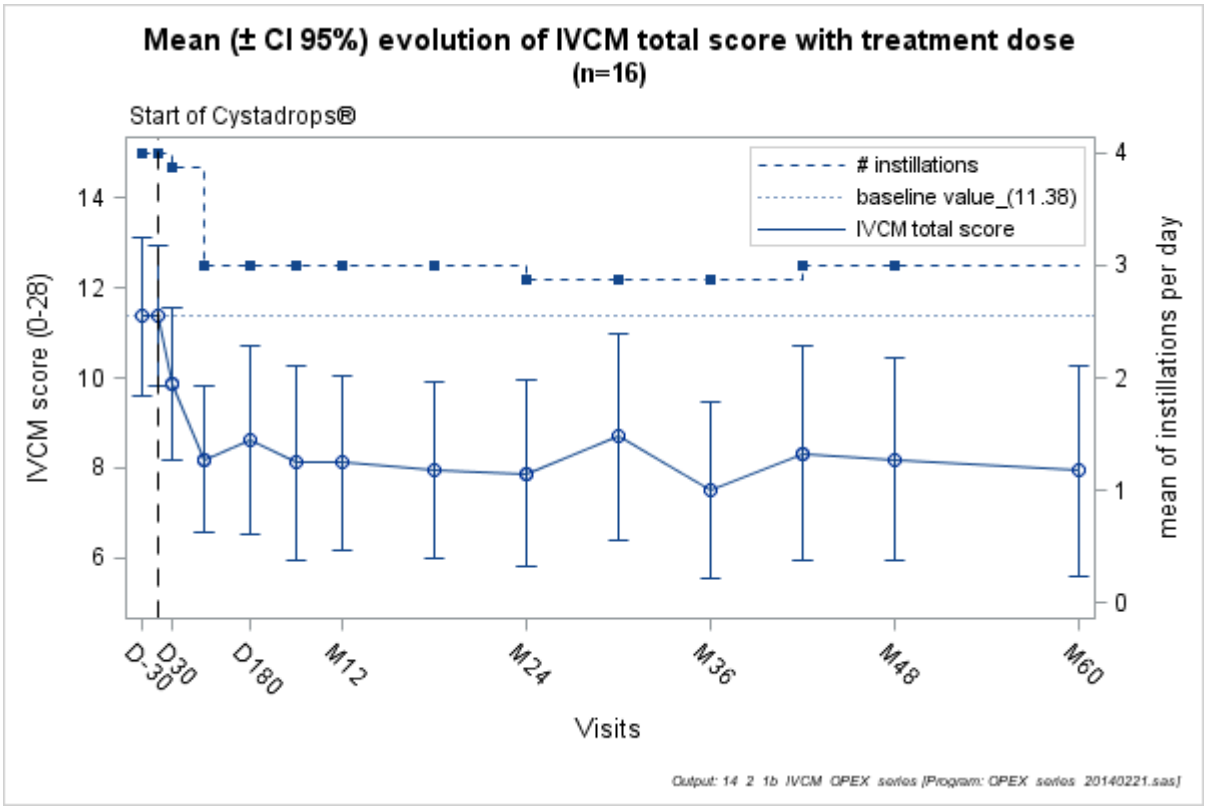
Following the run-in period, subjects received a median of 4 instillations/eye/day (range 3-5). At Day 30, the number of instillations was decreased by one for 1 patient. At Day 90, the prescribed number of instillations was decreased by 1 for all patients (median 3 instillations/eye/day, range 2-4). After Day 90, one subject maintained the reduction in corneal crystals with one instillation per day.

The mean change in IVCM total score from baseline (Day 1) at each visit to month 60 are summarised in the Table and Figure below. Using the GEE model, the absolute mean change in IVCM total score from baseline was statistically significant vs. baseline at all time-points.

Table 2: IVCM total score and change from baseline at each visit. N= 16 eyes at each time-point.

Time-point	IVCM total score µm (SD)	Absolute change from baseline (SD)	% change from baseline (SD)
Day 1	11.4 (2.9)	-	-
Day 30	9.9 (3.2)	-1.5 (2.4)	-11.8 (25.1)
Day 90	8.2 (3.1)	-3.2 (1.8)	-28.6 (17.5)
Day 180	8.6 (3.9)	-2.8 (2.3)	-25.8 (18.6)
Month 9	8.1 (4.1)	-3.2 (2.4)	-30.8 (19.8)
Month 12	8.1 (3.6)	-3.2 (2.1)	-30.2 (16.9)
Month 18	7.9 (3.7)	-3.4 (1.8)	-32.5 (18.1)
Month 24	7.9 (3.9)	-3.5 (2.1)	-33.1 (20.8)
Month 30	8.7 (4.3)	-2.7 (2.7)	-25.9 (24.3)
Month 36	7.5 (3.6)	-3.9 (2.3)	-35.8 (21.6)
Month 42	8.3 (4.5)	-3.1 (2.8)	-29.5 (25.4)
Month 48	8.2 (4.2)	-3.2 (3.0)	-29.6 (27.0)
Month 60	7.9 (4.4)	-3.4 (2.8)	-32.7 (25.4)

Figure 3: IVCM total score from D-30 to M60 (mean ± 95%CI) combined with treatment dose – FAS eye population (N = 16)



The absolute mean change in IVCM total score from the Day 1 baseline was statistically significant ($p < 0.05$ using a GEE model) at each time point from Day 30 onwards.

Mean photophobia scores, over time are provided in the Table below.

Table 3: Change in photophobia from baseline at each visit. N= 16 eyes at each time-point.

Time-point	Photophobia (SD)
Day 1	2.5 (0.9)
Day 30	2.6 (0.8)
Day 90	2.0 (0.9)
Day 180	2.2 (1.3)
Month 9	2.2 (1.0)
Month 12	2.2 (0.8)
Month 18	2.2 (1.0)
Month 24	1.5 (0.5)
Month 30	1.8 (0.9)
Month 36	1.4 (0.8)
Month 42	2.0 (1.0)
Month 48	1.6 (1.0)
Month 60	1.6 (0.9)

Crystal deposits were also evaluated by corneal layer. The largest reduction of deposits was observed in the stromal layers which gives indirect evidence of a penetration of cysteamine through the corneal epithelium. VA and contrast sensitivity remained fairly stable over time.

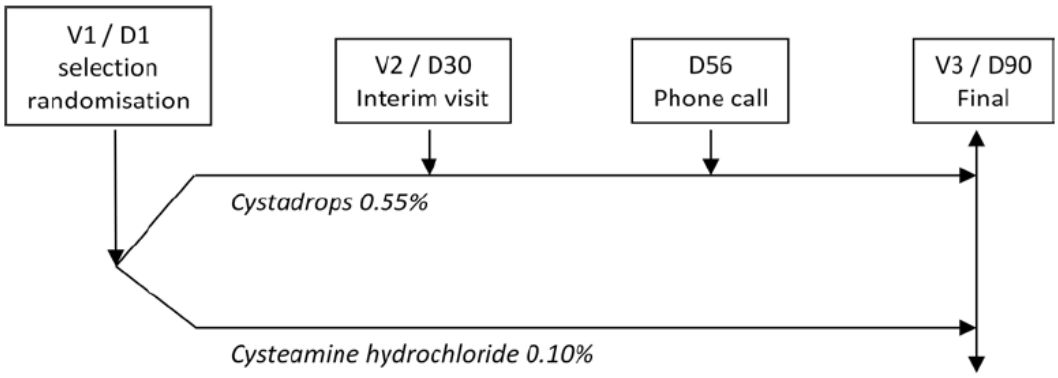
2.5.2. Main study

Study CHOC: Cysteamine Hydrochloride for nephrOpathic Cystinosis

Methods

This was an open-label (scoring of primary efficacy masked), randomised, 3 month superiority trial comparing Cystadrops and cysteamine HCl eye drops solution 0.10% (CH 0.10 %).

Figure 4: Schematics of main study CHOC.



Study Participants

The study included subjects diagnosed with cystinosis based on white blood cells cystine concentration (> 1.5 nmoles half-cystine/mg protein) and presence of corneal crystal deposits. Subjects less than 2 years of age were excluded as conduct of confocal microscopy may not be feasible in this population. Other exclusion criteria included uncontrolled hepatic, cardiovascular or neurologic disease, cancer, pregnancy or breastfeeding.

Treatments
Cystadrops and the comparator (CH 0.10%), were both administered 4x/day to each eye for the duration of the study. The comparator was the standard of care used in France at the time of study. The formulation of Cystadrops in this study contained 5.20 % CMC.

Objectives
The primary objective was to compare the efficacy of Cystadrops vs. CH 0.10% in terms of superiority in patients with nephropathic cystinosis. The secondary objective was to evaluate the safety profile of Cystadrops in patients with nephropathic cystinosis.

Outcomes/endpoints
The primary efficacy endpoint was the change in IVCM total score (crystal density) at day 90 compared to baseline, see study OCT-1 above. As in OCT-1, scores for 7 layers of the central cornea are summarised (score 0-4 for each layer). In this study, at each site visit, approximately 200 IVCM images of all layers are acquired in the central cornea of each eye.

Secondary endpoints were photophobia, crystal thickness and CCCS. In children which could not undergo evaluation with IVCM (not included in the primary analysis), the secondary endpoints were to be analysed. Exploratory analyses were to be repeated for each subgroup: children (< 18 years) and adults (≥ 18years).

VA and contrast sensitivity were included among the safety endpoints but presented among the efficacy endpoints below.

Sample size
The sample size was based on the change in IVCM total score in study OCT-1 and based on the following assumptions: no changes in the CH 0.10% treatment group, a mean reduction of 3.0 points in the Cystadrops treatment group and an SD of 2.0. With a 2-sided alpha of 0.05 and a power of 90% taking a drop out of 10% into account, the sample size was estimated to 12 patients per treatment arm.

Randomisation
The unit of randomisation was the patient and the unit of analysis was the eye. Randomisation was stratified according to IVCM status (done /not done) and age class (≤11, 12-17, ≥18).

Masking
Patients were not masked to treatment due to the different viscosities of the formulations. Physicians and the study coordinators were not masked to the patient's treatment allocation while scoring of IVCM images was made by an independent masked reader.

Statistical methods
A GEE model was applied for the primary endpoint with treatment arm as effect and IVCM total score at baseline as covariate. The structure of the variance-covariance matrix for the primary efficacy analysis was autoregressive. A parametric Analysis of Covariance (ANCOVA) was used to analyse the change at Day 90 from baseline for the secondary efficacy criteria. The correlation between paired eyes was taken into account as repeated measurements within the subject in the model.

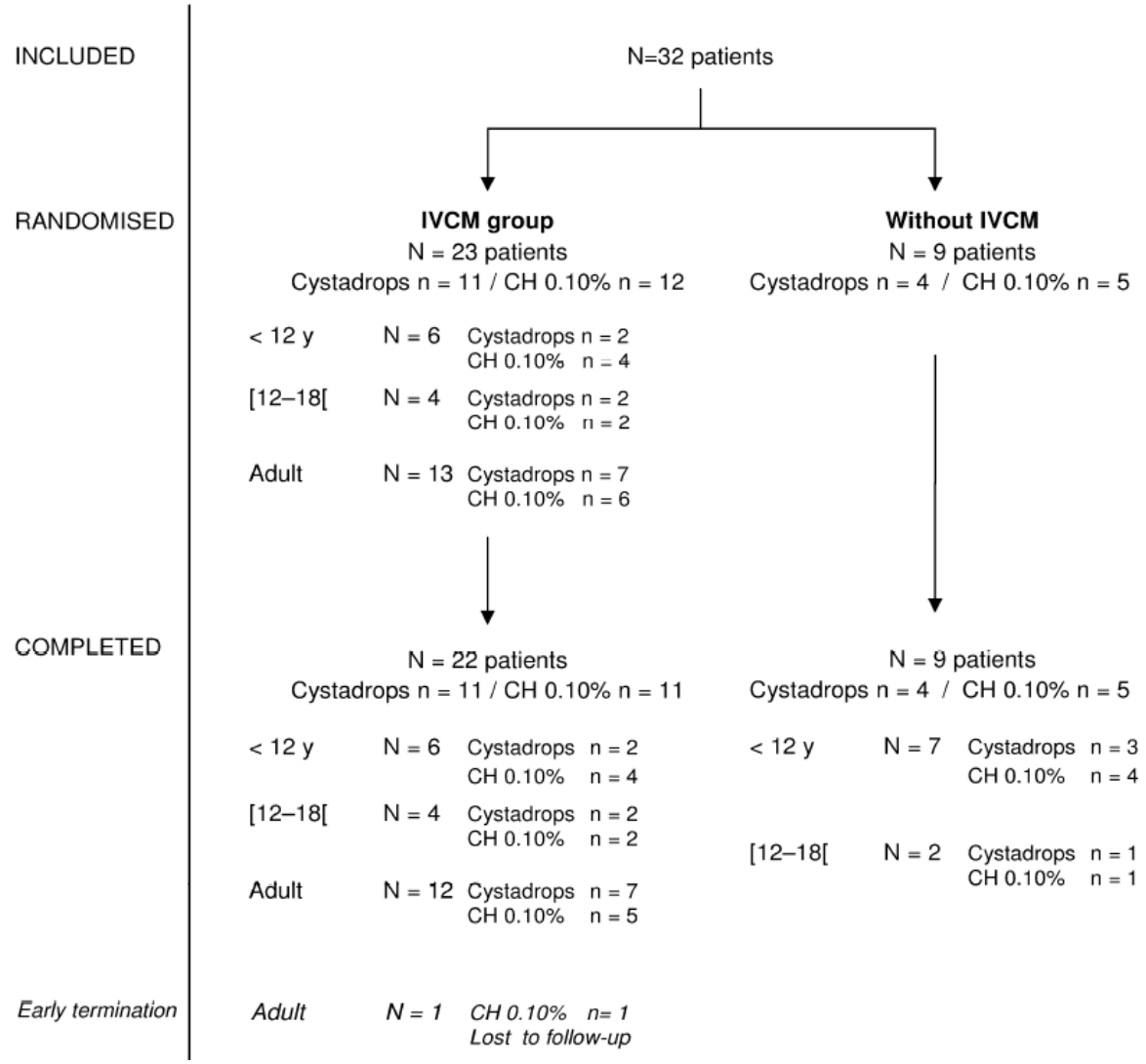
Three analysis populations were defined in this study, the Safety Set (SS) and the FAS including all patients/eyes who received at least one dose of a study product and the PPS including all patients/eyes of the FAS who did not meet any major protocol deviations which may affect efficacy assessments.

Rules for imputation of missing data were developed prior to database lock and were detailed in the SAP. No interim analysis was planned and none was performed.

Results

Participant flow

Figure 5: Participant disposition by ICVM status



Recruitment
Over a period of less than 6 months (09 January 2013 to 28 June 2013), 32 subjects were included in 2 French centres.

Conduct of the study
No significant protocol amendments were made. The protocol version used during the study was dated 20 December 2012. The majority of protocol deviations were related to compliance to treatment.

Numbers analysed
One patient (CH 0.10% arm) was reported as lost to follow-up after randomisation. The remaining 31 patients completed the study. The mean duration of treatment was 89.6 ± 14.5 days, and the mean number of days on treatment was 85.5±14.5. The mean number of daily instillations was 3.5 and 4.1 in the Cystadrops and CHOC treatment arm, respectively.

Baseline data
All included patients were diagnosed with infantile nephropathic cystinosis except for one adult patient in the Cystadrops arm who was diagnosed with late-onset nephropathic cystinosis. All but this subject and one additional subject on dialysis after rejection of 2 renal transplants were treated with systemic cysteamine treatment at inclusion. All subjects were treated with topical cysteamine (CH 0.10%) at inclusion and all were co-treated with topical ocular treatments e.g. dry-eye treatments, anti-infectives or anti-inflammatory treatment.

Main baseline demographics and disease characteristics are summarised in the table below.

Table 4: Baseline demographics and main disease characteristics– Study CHOC

Demographic variable /Disease characteristics /Treatment	**Cystadrops N= 15**	**CH 0.10% N=16**
Age Years		
Mean (SD)	19.2 (15.15)	15.1 (10.3)
Range	2.9-62.6	3.5-36.0
⩾ 18 years (N)	7	5
12-17 years (N)	3	3
<12 years (N) [1]	5	8
Sex N		
Male	7	8
Female	8	8
Duration of disease Years		
Mean (SD)	15.9 (11.0)	13.8 (10.8)
Age at diagnosis Months		
Mean (range)	38 (5-360)	16 (5-46)
Visual acuity LogMar		
Mean (SD)	0.24 (0.36)	0.16 (0.30)
Range	0.1-1.0	0.1-1.0
Contrast sensitivity		
Mean (SD)	0.57 (0.37)	0.44 (0.30)
Range	0.15-1.40	0.05-1.30
Photophobia (by investigator)		
Mean (SD)	1.9 (1.2)	1.7 (1.0)
Range	0-4	0-4
Total IVCM corneal crystal deposit score N patients (eyes) [2]	**N=11 (22)**	**N=12 (20)**
Mean (SD)	10.6 (4.2)	10.8 (3.5)
Range	(3.2-19.0)	(4.2-16.2)
IVCM corneal crystal deposit score not conducted, N patients	4	5
Cystinosis Corneal Crystal Score, Eyes)	**N=30**	**N=32**
Mean (SD)	2.3 (0.56)	2.0 (0.50)

Demographic variable /Disease characteristics /Treatment	Cystadrops N= 15	CH 0.10% N=16
Range	1.50-3.00	1.00-3.00

[1] Included 5 children were 2 in the Cystadrops treatment arm were <6 years of age
[2] Measurement could only be performed in one eye for two patients (both in CH 0.10% arm) due to amblyopia (unable to focus) and corneal transplant surgery. Data of one the corneal layers was missing for 3 subjects in the Cystadrops treatment arm.

Outcomes and estimation

Primary endpoint

The total IVCM score change from baseline at Day 90 is displayed below.

Table 5: Primary efficacy criterion: IVCM total score change from baseline at Day 90 –SS/FAS eye population with IVCM test done at baseline

Descriptive Statistics	Cystadrops (N=22)	CH 0.10% (N=20)	ALL (N=42)	P-value
Absolute IVCM change from baseline				
N[a]	20	17	37	
Mean ± SD	-4.60 ± 3.12	-0.455 ± 3.38	-2.70 ± 3.82	<0.0001[b]
Min ; Max	-11.0 ; -0.600	-7.60 ; 6.50	-11.0 ; 6.50	
Med. (Q1 ; Q3)	-4.13 (-5.47 ; -2.45)	-1.20 (-2.20 ; 1.35)	-2.40 (-4.60 ; -0.750)	
Relative IVCM change from baseline (%)				
N[a]	20	17	37	
Mean ± SD	-40.4 ± 16.0	-0.679 ± 33.0	-22.2 ± 32.0	
Min ; Max	-64.7 ; -8.33	-46.9 ; 63.1	-64.7 ; 63.1	
Med. (Q1 ; Q3)	-43.6 (-52.9 ; -34.1)	-10.6 (-24.7 ; 16.7)	-29.7 (-46.2 ; -10.6)	

Source: Table 14.2.1.1.3 and Table 14.2.1.1.4
a N = eyes with paired Day 1 (baseline)/Day 90 results. Paired data not available for 5 eyes in the SS/FAS eye population; 2 eyes for Patient 0204 (IVCM total score could not be calculated due to missing individual scores at baseline), 2 eyes for Patient 0106 (IVCM not done at Day 90) and 1 eye for Patient 0111 (IVCM not done at Day 90)
b GEE model

The difference in absolute change in IVCM total score between the 2 treatment arms (control minus Cystadrops) at Day 90 was estimated to be 3.84 ± 0.89 (95% CI 2.11, 5.58).

Table 6: Primary efficacy criterion: IVCM total score change from baseline at Day 90 –PPS eye population with IVCM test done at baseline

Descriptive statistics	Cystadrops (N=18)	CH 0.10% (N=15)	P-value
Absolute IVCM change from baseline			
N (eyes)	18	14	
Mean ±SD	-4.29 ± 2.96	-0.82 ± 3.43	p = 0.0002
Relative IVCM change from baseline			
N (eyes)	18	14	
Mean ±SD	-40.0 ± 16.5	-2.59 ± 34.9	

Source: Table 14.2.1.4.3, Table 14.2.1.4.2
GEE model

Secondary endpoints

Endpoints evaluating corneal crystals

- *IVCM score by corneal layer*

In the Cystadrops arm, the mean IVCM score decreased in all corneal layers. A trend towards a decrease was observed also in the CH 0.10% group. The day 90 change compared to baseline is summarised below.

Table 7: Absolute IVCM change from baseline to day 90 in the corneal layers

	Cystadrops N=22	**CH 0.10% N=20**
N (eyes observed)	20	17
Epithelium Mean ±SD	-0.95 ± 1.15	-0.20 ± 0.85
Basal epithelium Mean ±SD	-0.46 ± 0.60	-0.20 ± 0.67
Bowman's layer Mean ±SD	-0.53 ± 0.68	-0.06 ± 0.76
Superficial stroma Mean ±SD	-0.82 ± 0.73	-0.05 ± 0.92
Medium stroma Mean ±SD	-1.02 ± 0.76	0.07 ± 1.16
Deep stroma Mean ±SD	-0.73 ± 0.90	-0.02 ± 0.85
Endothelium Mean ±SD	-0.10 ± 0.45	0.00 ± 0.00

Source Table 14.2.1.1.2

- *Cystinosis Corneal Crystal Score (CCCS) and Crystal thickness*

In the Cystadrops arm, the mean CCCS as measured by slit lamp was lower at Day 90 than at baseline, whereas in the CH0.10% arm, the mean score was higher at Day 90 than at baseline. Also crystal thickness (measured with OCT) was lower at Day 90 than at baseline in the Cystadrops arm while in the CH 0.10% arm, mean crystal thickness had increased Day 90 compared to baseline, see Table below.

Table 8: Cystinosis Corneal Crystal Score and Crystal thickness from baseline at Day 90

Descriptive statistics	Cystadrops (N=30)	CH 0.10% (N=32)	P-value
Absolute CCCS change from baseline			
N (eyes)	30	31	
Mean ±SD	-0.59 ± 0.52	0.10 ± 0.24	0.0015
Absolute change in crystal thickness from baseline			
N (eyes)	28	29	
Mean ±SD	-46.3 ± 55.3	10.6 ± 43.6	0.0031

Source: Table 14.2.2.1.14, Table 14.2.2.1.15, Table 14.2.2.1.17 and Table 14.2.2.1.18.
ANCOVA

Clinical endpoints

- *Photophobia rated by the investigator and patient*

On average, the mean photophobia score decreased with respect to baseline in the Cystadrops arm but not in the CH 0.10% arm.

Table 9: Photophobia by investigator and patient. Absolute change from baseline at Day 90 – Eye population

Descriptive Statistics	**Cystadrops (N=30)**	**CH 0.10% (N=32)**	**P-value**
Investigator rating			

N (N missing)	30 (0)	31 (1)	
Mean ± SD Range	-0.63 ± 0.76 -2 ; 0	0.06 ± 0.44 -1 ; 1	0.0048[1]
Patient rating			
N (N missing)	30 (0)	31 (1)	
Mean ± SD Range	-0.27 ± 0.58 -2 ; 0	0.23 ± 0.72 -2 : 2	na[2]

Source: Table 14.2.2.1.2, Table 14.2.2.1.3, Table 14.2.2.1.8 and Table 14.2.2.1.9.
[1]ANCOVA
[2] The ANCOVA did not converge

A reduction in photophobia was observed also at day 30. In the PPS eye population (Investigator's grading), the mean change in photophobia score was -0.38 ± 0.58 in the Cystadrops arm and 0.09 ± 0.29 in the CH 0.10% arm (p = 0.0320).

Key VA and contrast sensitivity outcomes are summarised in the table below.

Table 10: Visual acuity (LogMAR) and Contrast sensitivity. Absolute change day 90 vs. baseline – eye population.

Descriptive Statistics	Cystadrops (N=30)	CH 0.10% (N=32)
Visual acuity		
N (N missing)	22 (8)	29 (3)
Mean ± SD Range	-0.10 ± 0.15 -0.52, 0.16	-0.07 ± 0.15 -0.60, 0.2
Contrast sensitivity		
N (N missing)	22 (8)	27 (5)
Mean ± SD Range	-0.20 ± 0.27 -1.0, 0.1	-0.14 ± 0.20 -0.7, 0.15

Source Table 14.3.3.1.4, Table 14.3.3.1.2

Ancillary analyses

Sensitivity analyses of primary efficacy

Analysis of IVCM scores that included all eyes with complete IVCM baseline data imputing missing day 90 IVCM data by using the LOCF approach (day 30 scores, or if not available baseline IVCM scores) demonstrated that the same magnitude of reduction in corneal crystals in the Cystadrops treatment arm (-4.60) and a minimally increased improvement in the CH 0.1% treatment arm (from -0.46 to -0.63) compared to the primary analysis in the FAS was observed. Consistency was also observed in the PP population. For both, statistical significance remained. Sensitivity analyses including eyes were IVCM scores were missing in some corneal layers were also consistent with the primary analysis.

Subgroup analyses in the adult and paediatric populations

At day 90, the relative reduction in the IVCM total score vs. baseline was 44 and 36% for Cystadrops in the adult and the paediatric population, respectively. In the CH 0.10% treatment group, the corresponding changes were 2 and 0.15%. In adults, the difference in absolute change in IVCM total score between the 2 treatment arms (control minus Cystadrops) at Day 90 was estimated to be 5.09 (95% CI, 2.76, 7.42). A difference of similar magnitude was observed in the paediatric population but the GEE model did not converge.

With regards to CCCS and Crystal thickness, an outcome in favour of Cystadrops was observed in both adults and paediatric patients. For CCCS he mean changes in CCCS were, in the Cystadrops and CH 0.10% arms respectively, -0.59 ± 0.55 and 0.04 ± 0.20 in the paediatric eye population (p = 0.0201) and -0.59 ± 0.52 and 0.25 ± 0.28 in the adult eye population (p = 0.0254).

Regarding photophobia, similar trends but without statistical significance between treatment groups were observed in the adult and the paediatric population as observed for the full study population.

Summary of main study

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

Table 11: Summary of Efficacy for trial CHOC

Title: CHOC			
Study identifier	Cystadrops®/09/choc-study/EudraCT No: 2009-012-564-13		
Design	Open-label (scoring of primary efficacy masked) randomised 3 month superiority trial comparing Cystadrops and cysteamine hydrochloride eye drops solution 0.10% (CH 0.10%) recruiting patients from 2 centres in France.		
	Duration of main phase:		90days
	Duration of Run-in phase:		NA
	Duration of Extension phase:		NA
Hypothesis	Superiority		
Treatments groups	Cystadrops		4 times/day, 90 days, n=15 For IVCM (primary endpoint) n=11
	CH 0.10%		4 times/day, 90 days, n=17 For IVCM (primary endpoint) n=11
Endpoints and definitions	Primary endpoint	IVCM total score	Absolute change in total score of the corneal cystine crystal density measured by IVCM at day 90 vs. baseline. Score 0-28. All subjects (i.e. the youngest) not able to undergo IVCM.
	Secondary endpoint	Photophobia	Day 90 change from baseline assessed by investigator. Score 0-5
	Secondary endpoint	CCCS	Day 90 change from baseline. Corneal Cystine Crystal Score as measured by slit lamp. Score 0.00 to 3.00
	Secondary endpoint	Crystal thickness	Day 90 change from baseline. Crystal thickness as measured by OCT (µm)
	Other: Safety endpoint	Visual acuity	Day 90 change from baseline. (LogMar)
	Other: Safety endpoint	Contrast sensitivity	Day 90 change from baseline. LogMar score
	Other: Subgroup analysis – Adult/ paediatric	IVCM total score	Absolute and percentage change in total score of the corneal cystine crystal density measured by IVCM at day 90 vs. baseline. Score 0-28
Database lock	Not known		
Results and Analysis			
Analysis description	**Analyses of Primary endpoint**		
Analysis population and time point description	Full analysis set (FAS): All randomised subjects/eyes receiving at least one treatment Per protocol set (PPS): All patients/eyes of the FAS who did not meet any major protocol deviations		
Descriptive statistics	Treatment group	Cystadrops	CH 0.10%

and estimate variability	No of eyes	20	17
	Primary analysis: IVCM total score (SD) (FAS)	-4.60 (3.12)	-0.46 (3.38)
Effect estimate per comparison GEE model	Treatment difference ±SD, (95% CI)	3.84 ±0.84 (2.11, 5.56)	
	P-value	<0.0001	
Descriptive statistics and estimate variability	No of eyes	18	14
	Primary endpoint: IVCM total score (SD) (PPS)	-4.29 (2.96)	-0.82 (3.43)
Effect estimate per comparison GEE model	Treatment difference ±SD, (95% CI)	3.48 (1.67, 5.29)	
	P-value	0.0002	
Analysis description	**Analyses of Secondary endpoints** (FAS)		
Descriptive statistics and estimate variability Effect estimates ANCOVA	Treatment group	Cystadrops	CH 0.10%
	No of eyes	30	31
	Secondary endpoint: Photophobia (SD)	-0.63 (0.76)	0.06 (0.44)
	Treatment difference, (95% CI)	0.69 (0.23; 1.14)	
	P-value	<0.0048	
	Treatment group	Cystadrops	CH 0.10%
	No of eyes	30	31
	Secondary endpoint: CCCS (SD)	-0.63 (0.76)	0.06 (0.44)
	P-value	0.0015	
	Treatment group	Cystadrops	CH 0.10%
	No of eyes	28	29
	Secondary endpoint: Crystal thickness (SD)	-46.3 (55.3)	10.6 (43.6)
	P-value	0.0031	
Analysis description	**Analyses of Other endpoints** (FAS)		
Descriptive statistics and estimate variability	Treatment group	Cystadrops	CH 0.10%
	No of eyes	22	29
	Safety endpoint: Visual acuity (SD)	-0.10 (0.15)	-0.07 (0.15)
	No of eyes	22	27
	Safety endpoint: Contrast sensitivity (SD)	-0.20 (0.27)	-0.14 (0.20)
Analysis description	**Subgroup analyses of primary endpoint** (FAS)		
Descriptive statistics and estimate variability Effect estimates GEE model	Treatment group	Cystadrops	CH 0.10%
	No of eyes	12	6
	Subgroup analysis: IVCM total score (SD). Adults	-4.98 (3.29)	-0.40 (3.51)
	P-value	<0.0001	
	No of eyes	8	11
	Subgroup analysis: IVCM total score (SD). Paediatric	-4.03 (2.95)	-0.48 (3.49)

	P-value	NS
Notes	Open label study, but primary endpoint evaluated in a masked fashion. However, selection of images for the masked evaluation appeared non-masked.	

Clinical studies in special populations

NA

Supportive studies

The Applicant supported this MAA with information about the NPU programme (see further details in Safety section) and published literature.

Supportive efficacy data from a number of published studies with various formulations of cysteamine eye drops as summarised in the table below. Together, they include 64 subjects of whom 50 have been treated with cysteamine eye drops at a concentration of 0.5 or 0.55%.

Table 12: Summary of published efficacy data

Reference	Design	Cysetamine	Comparator	Dose	Duration	Age	N	Results
Kaiser-Kupfer et al. 1990	Double masked, RCT 1 treated, 1 control eye	0.1 ⇨0.5 % (increased during study)	Saline	1 drop/ hour during waking hours	47 Mo	Gr 1: <4 Y Gr 2: 4-31 Y	Gr 1: 18 Gr 2: 11	10 patients: Marked clearing of crystals vs. control. 15 patients: No marked differences. 4 patients withdrew.
MacDonald et al. 1990	Double masked, placebo controlled	0.3%	Saline	1 drop 4x/day	7 Mo	33 Mo - 21 Y	4	No reduction in crystals or effect on VA.
Jones et al. 1991	Case report	Cysteamine 0.5 %		1 drop/ hour during waking hours	3 Mo	2 Y	1	Virtually complete clearance of crystals and diminution of photophobia

Bradbury et al. 1991	Double masked, RCT	0.2 %	Saline	6x/day	6 Mo	8-16 Y	6 (1 patient withdrew 2 weeks after treatment start)	Cysteamine group: Decrease in crystal density scores. Improvement in photophobia, pain, blepharo-spasm, VA (n= 5) and contrast sensitivity (n=3)
Gräf et al. 1992	Case report	0.1% OD 0.5% OS	OS untreated for 26 w	6 - 8 drops/d	26 w (OD), 12 w (OS)	2 Y	1	Clearance of crystals after 26 and 12 weeks with cysteamine 0.1% and cysteamine 0.5%, respectively
Blanksma et al. 1996	Not reported	5mg/ml in 0.5% hydroxyl-propyl-methylcellulose and BAK 0.01%	No control	5x/day	6 Mo	Not reported	3	Relief from photophobia. In 2/3 patients, measurable decrease in glare.
Tsilou et al. 2003	Double masked RCTs	New formulation (NF) 0.55% cysteamine with monosodium phosphate 1.85%, EDTA 0.10% and 0.01% BAK	Standard formulation (SF) 0.55% cysteamine with 0.01% BAK	1 drop/hour during waking hours	1 Y	2-11 Y	16	Reduction in the CCCS of ≥ 1.00 after 1 year: SF 47%, NF 7%

VA – visual acuity, OD – right eye, OS – left eye

In addition, five clinical trials have been conducted by Sigma-Tau for the development of a cysteamine topical eye drops formulation containing an ingredients' composition close to Cystadrops, especially in terms of active substance concentration. Together, they mention 63 subjects whereof 42 have been treated with cysteamine eye drops at a concentration of 0.5 %, although the available data was limited. These studies are the following:

- Study 86-EI-0062A in which 2 patients were treated with 0.1% cysteamine. There was a positive effect of cysteamine eye drops, which was very well tolerated.
- Study 86-EI-0006213-1 in which 19 patients in a double masked controlled trial were treated with 0.1% cysteamine. In terms of efficacy there was a 1.0 unit decrease in CCCS or failure to have a 1.0 unit increase when the baseline score was less than 1.0 CCCS. This resulted in no statistical difference (P=0.13) between treated and placebo eye. As to safety, three patients reported itching and irritation in both placebo and treated eye.
- Study 86-EI-00662B-2: In this double blind study 8 patients were treated with the current 0.5% strength Cysteamine. From an efficacy standpoint there was a 1.0 unit decrease in CCCS which resulted in a statistical difference (P=0.013) between treated and placebo eye. Seventeen (17)

patients reported AE's with the two groups (pain and redness were the most common AE's). The rate of AE's was equal between the two groups. There was no report of photophobia or corneal erosions.

- Study 92-EI-0230: In this double masked study 20 patients received either 0.5% cysteamine or 0.5% cysteamine with Benzalkonium (preservative). Both regimes were equally effective in preventing crystal formation in the one year follow-up period (patients had little crystal formation CCCS <1.0) One AE was reported occurring in both eyes (stinging and burning).
- Study 94-EI-0016: In this double masked study 14 patients received either 0.5% cysteamine or 0.5% cystamine. The study was stopped by the DATA Safety review board based on the planned preliminary analysis indicating no efficacy with cystamine. Three patients reported AE's and the most common were burning redness occurring in both treatments.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

Two studies, both conducted in France, form the basis for the clinical development programme. The studies recruited adult and paediatric subjects with almost exclusively nephropathic cystinosis with corneal cystine crystal deposits, i.e. subjects overall corresponding to the targeted indication.

The choice of comparator in the pivotal trial, a standard of care formulation of cysteamine (CH 0.10%) used in France, and the superiority design is overall endorsed. Due to the difficulties procuring a suitable 0.55 % cysteamine eye drop comparator, no third treatment arm was included which is unfortunate since a comparison of efficacy and tolerability with a non-viscous 0.55% formulation would have been of value. In view of the rarity of the condition, the overall clinical programme is considered reasonable. However, with regards to the pivotal CHOC study, the CHMP recommended that subjects should be treated for at least 6 months to demonstrate a sustained response to treatment. Even though study OCT-1 was 5 years in duration, only 8 subjects were included. To address the concern relating to the absence of longer-term data which was of major concern, the Applicant has provided further support for sustained efficacy and long-term safety the NPU programme, which was found reassuring.

One critical issue identified by the CHMP was that the product proposed for marketing was not tested in the clinical setting. For marketing, the concentration of the viscosity enhancing excipient CMC in Cystadrops was intended to be 2.43%. In the major part of the pilot and in the pivotal studies, the concentration of CMC in Cystadrops was 5.20%. However, by changing the method for sterilisation (see Quality), the now to be marketed formulation is very similar to that used in the clinical trial with the concentration of CMC being back to 5.2%. The CHMP concern was thus addressed.

The open-label design of OCT-1 where the patient was his/her own control in determining the lowest effective dose was acceptable for an initial study with focus on safety. The study involved patients who were responders to CH 0.10% on a regimen between 3-6 drops/eye/day and the dose adjustment was based on the clinical response. Although a mean regimen of 3 instillations/eye/day was reached with Cystadrops treatment, a decision was nevertheless made to use a regimen of 4 instillations/eye/day in the pivotal CHOC Study as this was the mean dosing frequency during the three initial months of OCT-1.

Both studies were open-label. In CHOC the evaluation of primary efficacy (i.e. scoring of images) was made by a masked, independent evaluator, however images for scoring were selected by a non-masked ophthalmologist immediately after the reading to select good-quality and representative images. There is thus a potential for a selection bias and leaves the study without any truly masked evaluations, which adds uncertainty to the magnitude of the effect size. While recognised that the different viscosities of

Cystadrops and CH 0.1% would hamper patient masking, it is unfortunate that attempts to mask the evaluating physician (secondary efficacy and safety) were not made in CHOC and consequently, the subjective assessments will be less robust.

In both studies, the primary endpoint "the absolute change in total score of the corneal cystine crystal density measured by IVCM" is considered acceptable and was previously agreed by the CHMP in the scientific advice as the main clinical endpoint, photophobia is prone to subjectivity.

Crystal scores from 7 corneal layers of different thickness (10 µm to close to 500 µm) were summarised, but the rationale for giving equal weight to the layers was not clear. The Applicant referred to a published methodology and has also presented re-calculated the ICVM outcomes weighing each corneal layer according to the relative thickness of each layer. The weighted IVCM total scores were higher than the un-weighted ICVM total scores, but importantly, the two curves of IVCM total scores are parallel over time. Consequently, the non-weighed evaluation does not affect the overall outcome. At each visit in OCT-1, 5-10 IVCM images were acquired from each corneal layer. In study CHOC, almost 30 rather than 5-10 images were captured for each layer. The Applicant has explained that a large number of images were captured to obtain 5-10 good quality pictures for reading. However, these images were selected by the physician that was unmasked to the patient's treatment assignment, resulting in a potential for a selection bias. However, corneal crystals were also evaluated with OCT and slit lamp. Since the outcome obtained with the IVCM was consistent with the secondary evaluations of corneal crystals, this issue is not considered major.

The evaluation with IVCM was not feasible in all patients, notably in the youngest paediatric subset and it was pre-specified that efficacy in these subjects will be evaluated outside the primary IVCM efficacy population through the secondary efficacy analyses. This was endorsed by the CHMP.

The evaluation of corneal crystals was complemented with evaluations of the key clinical endpoint in corneal cystinosis, photophobia. In addition, VA and contrast sensitivity have been evaluated which is considered adequate although in CHOC these evaluations were presented only in the safety section. These evaluations are considered of relevance for the understanding of the patient benefit. Even though photophobia is the main clinical manifestation, with progression of the disease, VA becomes generally impaired and if vision is negatively affected by the crystals, a reduction in these would logically lead to an improvement in VA. Similarly, as contrast sensitivity could be affected by glare, a reduction in corneal crystals may have a positive effect on contrast sensitivity as well although this relation seems not fully investigated.

Efficacy data and additional analyses

Bearing in mind the rarity of the disease and that only 2 centres participated in the CHOC study, the inclusion and follow-up of 32 subjects within less than 6 months appeared relatively rapid. This has been attributed to the fact that French cystinosis patients are well informed and that physicians involved in OCT-1 were asked to accelerate the recruitment to CHOC. This resulted in a rapid enrolment of all but the last few patients.

In cystinosis, phenotypic severity varies according to mutations within the CTNS genes and adequate reassurance has been provided that the condition can be considered genotypically and phenotypically homogeneous across Europe. Therefore, the data generated within a French cohort can be considered to be applicable to the wider geographical patient population.

The studies recruited a limited but adequate patient population with 8 subjects in OCT-1 and 32 subjects in CHOC. It is recognised that it would be difficult to conduct a placebo-controlled study with the CH 0.10 % formulation available and that this formulation was suitable to provide assay sensitivity in CHOC. However, from OCT-1, it remains unclear whether the patients were unusual in their response since

subjects remained stable on 3-5 daily instillations of CH 0.1 % during the 30 day run-in phase although CH 0.1 %is frequently recommended to use hourly during waking hours. It is on the other hand acknowledged that no improvement was observed during the run-in period and also that OCT-1 was an exploratory study.

In CHOC, 4 subjects in each treatment arm had no photophobia at baseline. The overall baseline VA indicated a mild vision loss, although somewhat worse compared to study OCT-01 and a few subjects presented with 1.0 LogMar (i.e. 0.1) at least in one eye.

In OCT-1, the IVCM total score (primary endpoint) was reduced with an average of 30%, however, the variability was high. After 90 days on treatment, no further reduction was observed. The reduction in crystal deposits was maintained with a mean decrease from 4 to 3 instillations of Cystadrops per day. In CHOC, the corresponding reduction after 3 months was 40% in the Cystadrops treatment arm without any change in the comparator arm. The reduction from baseline was clearly significant ($p<0.0001$) and supported by sensitivity analyses. This is a change of a magnitude that may be clinically relevant, taking into account on the effect on photophobia and other clinical outcomes.

In CHOC, while the unit of randomisation was the patient, the unit of analysis was the eye. The analyses performed based on "eye" may be appropriate, but for sensitivity purpose, the Applicant has re-analysed the primary endpoint and the key clinical endpoint of photophobia with the patient as the unit. Also in the analyses with the patient as the unit, the IVCM total score as well as photophobia remained significantly in favour of Cystadrops. These outcomes thus support a statistically significant effect also when the analysis was conducted with the same unit as used for randomisation, i.e. the patient.

The secondary outcomes related to crystal deposits support the decrease observed in the primary evaluation, i.e. for evaluation with the IVCM as an endpoint as well as regarding the reduction of crystal deposits. The CCCS and Crystal thickness was significantly lower in the Cystadrops treatment arms compared to the control ($p=0.0015$ and 0.0031, respectively).

In the subset of patients (n=9, mean age 7-8 years) that could not undergo the IVCM, the effect on CCCS was similar as in the FAS, but the Crystal thickness in these subjects was lower both at baseline and the reduction was similar in both treatment arms (7-8) and limited compared to the Cystadrops arm in the FAS in CHOC (-46). Also photophobia was lower at baseline, but an overall higher reduction in the Cystadrops treatment arm over CH 0.1 % was observed. Overall, consistency with the FAS has been demonstrated also in this subset of patients.

Regarding the key clinical endpoint of photophobia, in OCT-1, it tended to improve with treatment (-0.5 units at month 3, -0.9 units at month 60 vs. 2.5 units at baseline), but the effect seemed to have a slow onset and variability was high. In CHOC, at 3 months, there was a mean reduction with 0.6 units (from 1.8) in the Cystadrops treatment arm vs. no change in the comparator arm ($p=0.048$). The evaluation of photophobia seems to provide further support of a clinically relevant effect of treatment. It was however not clear what this reduction means to the patients. To obtain a better understanding of the effect, the Applicant was asked to provide responder analyses describing the proportions of eyes (with photophobia at baseline) that reduce their photophobia score with ≥1 or ≥2 units in the 2 treatment arms. Of the approximately 85% of eyes presenting with photophobia at baseline, at day 90, 19 and 35 % in the Cystadrops arm reduced their photophobia with 2 and 1 units (scale 0-5), respectively, versus 0 and 7 % in the CH 0.10% treatment arm. With the caveats concerning the unmasked design of the study, the difference between treatment arms is clear and thus seems to support a meaningful benefit of treatment.

In OCT-1, there were no effects on VA, which was not expected since most subjects had normal or close to normal VA at baseline. An improvement in VA was however demonstrated in both treatment groups in CHOC. The mean improvement was 5 vs. 3.5 letters in the Cystadrops vs. the CH 0.10% treatment

groups. It is acknowledged that only a mild visual impairment was observed at baseline although slightly worse (mean 4 letters) in the Cystadrops treatment arm. In responder analyses (proportions with gain of ≥15, ≥10 and ≥ 5 letters), the improvement in VA seemed modest and overall similar between treatment arms. It is however acknowledged that few subjects were included in these analyses. With the caveat of being a non-controlled compassionate use programme without structured follow up, it is noted that of the 18 subjects with an impaired VA in the NPU programme, a larger improvement appeared to be reached after a longer than 3 months treatment duration. Thus, besides the overall low degree of VA impairment at baseline, the CHOC study may have been too short to detect any meaningful effects.

Contrast sensitivity is an unproven endpoint but it would be expected that it would be affected by glare from the corneal deposits. In OCT-1, there were no changes in contrast sensitivity and in CHOC, there was an improvement vs. baseline in both treatment arms without any differences between treatment arms (33-35% improvement vs. baseline). The Applicant has not been able to explain why the reduction in corneal crystals did not translate into an expected improvement in contrast sensitivity. It can only be speculated, but it is possible that study CHOC was too short or that another chart than the Galinet chart could have been more sensitive to detect changes in this population.

To address the concerns of lack of controlled long-term data, information from the French NPU programme on corneal crystals, photophobia and VA has been provided for 53 of the 106 subjects (16 subjects 2 - 6 years old) who had undergone the baseline and at least one follow-up visit. The initial treatment period (3 months, period 1) and the longer-term effect (3-16 months, period 2) were evaluated, the latter with data from the last visit. Overall, a sustained treatment effect of Cystadrops was indicated. Even if this evaluation likely is prone to some subjectivity due to the non-masked evaluations, the proportion of eyes with severe crystal densities at baseline was reduced from 50 to 30 % with time and as a consequence, the proportions with mild CCCS increased.

In subgroup analyses of adult and the paediatric population, the outcomes of the IVCM total score as well as of secondary endpoints were consistent with those observed in the overall CHOC study population. Of the paediatric subset only two <6 years of age were treated with Cystadrops (0.55%). Thus, the treatment experience is limited in the youngest subset covered by the indication (2-6 years old). As study in children from 6 months of age (measure 2 of PIP) is still pending, this is adequately addressed in the SmPC. Adult patients were between 18 and 34 years except for one subject who was 62 years of age. Since there are no specific concerns regarding the older and elderly population, the absence of data in these populations is not considered necessary to be included in the SmPC.

Unfortunately, patients still have to instil eye drops quite frequently (starting with 4 instillations per day), especially considering that this is a life-long treatment. The Applicant has further explained the rationale for the 0.55 % cysteamine concentration in Cystadrops. Non-clinical data indicate that such concentration was tolerated, cysteamine eye drops at the 0.55 % concentration seem most commonly used in the EU and the 0.55 % NIH formulation has been made commercially available in the US. The Applicant pointed out that some of the hospital formulations used currently necessitate up to hourly instillations and has not considered developing a formulation that may reduce the initial dosing frequency to less than 4 times daily. While this is acknowledged, further future development of the formulation is encouraged. In any case, in study OCT-1, the dosing frequency could be reduced in patients whose corneal deposits were improving. After the first 3 months of treatment, the median number of daily instillations was reduced from 4 to 3 (range 2-4 instillations) per day with a maintained reduction in corneal crystals. During the remaining part of the study, one (out of 8) subjects maintained the reduction in crystals with one instillation per day. Even though the proposed dose reduction as outlined in section 4.2 of the SmPC is based on 8 patients from study OCT-1 only, it is a pragmatic approach that is considered reasonable.

A final issue is that the product is delivered in a glass vial and CHMP identified issues regarding the suitability of the vial and consequently a risk for medication error. In response to these concerns, the Applicant introduced improvements to Product Information and proposed a plan for a post-approval development of a different container closure system. This is further addressed in the Quality part of the assessment.

2.5.4. Conclusions on the clinical efficacy

The limitations of data should be put in context of the rarity of the disease as well as treatment with cysteamine eye drops being a standard of care in this condition. Data from the NPU programme support a benefit of treatment also in the longer term. Overall, the CHMP are of the view that the available clinical data are sufficient to conclude that Cystadrops exerts clinical efficacy in cystinosis patients with corneal cystine crystal deposits.

2.6. Clinical safety

The evaluation of safety was based on the pivotal 3-months CHOC study, the 5-year OCT-1 study and supportive safety data from two NPU programmes and publications. Focus of the evaluation was set on ocular safety.

Reporting of local and systemic adverse events (AEs) and serious AEs (SAEs) was defined to follow standard clinical trial practice. In addition, patients/parents were provided with daily diary cards where a number of signs and symptoms were exemplified to collect information on local adverse drug reactions (LADRs) after each instillation (including their duration and severity). In CHOC, other ocular symptoms were also reported through the diaries.

Patient exposure

The patient exposure is summarised in the Table below.

Table 13: Patient exposure (March 15, 2015)

	Patients enrolled	Patients exposed	Patients exposed to the proposed dose range	Patients with long term safety data
Active -controlled	32	31[2]	15	0
Open studies	8	8	8	8[1]
Total in clinical trials	**40**	**39**		
Post marketing	NA	NA	NA	NA
Named Patient Use (NPU) programme[3]	230	230	230	NR
NPU France[4]	106	106	106	NR
Total	**376**	**375**	**359**	**NR**
Published data[5]	54	54	46	50
Sigma-Tau studies[6]	63	63	42	NR

[1] 5-year data
[2] All subjects were exposed to cysteamine-containing eye drops, either Cystadrops (0.55%) or CH 0.10% (i.e. 0.10% cysteamine).
[3] Since 2011. In EU, Turkey, Middle East, Brazil, India and Russia.

[4] Since September 2013. Enrolling adults and children ⩾2 years. At data cut-off 52% of subjects were paediatric.
[5] Including different formulations of cysteamine eye drops where safety was reported, see also Supportive Efficacy data. Concentration range 0.5-0.55% cysteamine.
[6] information limited.
NA – not applicable, NR – not reported

In OCT-1, patients were exposed to a mean of 4 drops per day up to month 3 when a mean of 3 drops per day were administered. In CHOC, patients were administered mean 3.5 and 4.1 in the Cystadrops and CH 0.10% treatment arms, respectively. Information was provided in the patient diaries for 16,282 instillations with Cystadrops in the OCT-1 study and for 10,409 instillations (4644 with Cystadrops and 5765 with CH 0.10%) in the CHOC study.

Adverse events

An overview of AEs during the 5 years for OCT-1 and the 3 months for CHOC is displayed in the tables below.

Table 14: OCT-1 Summary of Adverse Events / Treatment Emergent Adverse Events - SS (N=8)

Type of AEs	**All patients**		**N=8**
	Events[1]	**Patients[2]**	**%[3]**
All AEs	73	7	(87.5%)
Severe AEs	14	4	(50%)
Serious AEs	48	6	(75%)
Deaths	0	0	(0%)
Drug-related AE**	3	2	(25%)
Serious Drug-related AE**	1	1	(12.5%)
AEs leading to temporary treatment discontinuation	0	0	0
AEs leading to treatment discontinuation	0	0	0

[1] No of Adverse Events
[2] No of patients with at least one adverse event
[3] 100*n/N
* TEAE = Treatment Emergent Adverse Event (AE which occurs or increases in severity after the first dose of Cystadrops)
AE and TEAE correspond to the same population
** AE with an investigator causality assessment either 'related' or 'unknown'

Table 15: CHOC Adverse events summary – SS/FAS population (N = 31)

Descriptive statistics	**Cystadrops (N=15)**		**CH 0.10% (N=16)**		**All (N=31)**	
	Patients	Events	Patients	Events	Patients	Events
All AEs	10 (66.7%)	54	13 (81.3%)	69	23 (74.2%)	123
Severe AEs	0	0	0	0	0	0
Serious AEs	2 (13.3%)	2	2 (12.5%)	2	4 (12.9%)	4
Deaths	0	0	0	0	0	0
Drug-related AEs	2 (13.3%)	4	1 (6.3%)	14	3 (9.7%)	18
Serious drug-related AEs	0	0	0	0	0	0
AEs leading to temporary treatment discontinuation	1 (6.7%)	1	1 (6.3%)	1	2 (6.5%)	2
AEs leading to treatment discontinuation	1 (6.7%)	1	0	0	1 (3.2%)	1

Study OCT-1

Ocular AEs

Treatment emerging ocular AEs, their severity and their relation are summarised below.

Table 16: OCT-1 Treatment emerging ocular AEs (N=8)

Preferred term	Patients n (%)	Severity	Related n (%)
All	2 (25%)		
Chalazion	1 (12.5%)	Mild	0
Corneal neovascularisation	1 (12.5%)	Moderate	1 (12.5%)
Dry eye	1 (12.5%)	Moderate	1 (12.5%)[1]
Hordeolum	1 (12.5%)	Mild	1 (12.5%)[1]
Papilloedema	1 (12.5%).	Mild	0

[1] Unknown, but regarded as a reasonably possible causal relationship

With regards to patient-reported diary-based ocular AEs (LADRs), all patients reported at least 1 LADR, see below. A total of 4,109 of LADRs were reported over the 5 years.

Table 17: OCT-1 Local adverse drug reactions at instillation (by patient) (N = 8)

Symptom	Preferred Term	Patients n (%)
All		8 (100%)
Stinging	Eye pain	7 (87.5%)
Blurred vision	Vision blurred	6 (75%)
Burning	Eye irritation	4 (50%)
Discomfort	Ocular discomfort	2 (25%)
Itching	Eye pruritus	2 (25%)
Sticky eyes	Abnormal sensation in eye	2 (25%)
Irritation	Eye irritation	1 (12.5%)
Irritation eyelid	Eyelid irritation	1 (12.5%)
Redness	Ocular hyperaemia	1 (12.5%)
Watering	Lacrimation increased	1 (12.5%)

In OCT-1, the exact symptom duration was collected. The maximum duration of LADRs was 17.5 seconds, with a median duration of 5 seconds. The mean pain score at the time of instillation (VAS 0-100 mm) was 27 at day 30 and tended to decrease with time with a mean score <20 from day 90 and onwards. At month 60, it was 7.

Systemic AEs

Several systemic AEs were reported in the study the majority related to the System Organ Class (SOC) of Surgical and medical procedures, Musculoskeletal and connective tissue disorders, Nervous system disorders. The Applicant regards none of them related to treatment.

Study CHOC

Ocular AEs

Table 18 summarises LARDs and treatment-emergent ocular AEs and their relationship to treatment. The majority of AEs were mild, one event each of conjunctival hyperaemia, allergic conjunctivitis and lacrimation increased (all Cystadrops treatment arm) were reported as moderate. None of the ocular TEAEs were reported as serious.

Table 18 CHOC –LARDs and Treatment-emergent ocular adverse events - Safety population (N = 31)

Symptom	System organ class	Preferred term	Relation-ship	Cystadrops (N=15) n (%)	CH 0.10% (N=16) n (%)
LOCAL ADVERSE DRUG REACTIONS					
Stinging	Eye disorders	Eye pain	Related	12 (80.0%)	8 (50.0%)
Redness		Ocular hyperaemia	Related	9 (60.0%)	7 (43.8%)
Burning		Eye irritation	Related	10 (66.7%)	4 (25.0%)
Blurred vision		Vision blurred	Related	9 (60.0%)	4 (25.0%)
Itching		Eye pruritus	Related	6 (40.0%)	4 (25.0%)
Other			Related	10 (66.7%)*	5 (31.3%)*
	Eye disorders	Eye pain	Related	3 (20.0%)	2 (12.5%)
		Lacrimation increased	Related	2 (13.3%)	1 (6.3%)
		Ocular hyperaemia	Related	3 (20.0%)	0 (0.0%)
		Abnormal sensation in eye	Related	2 (13.3%)	0 (0.0%)
		Eyelid oedema	Related	1 (6.7%)	1 (6.3%)
		Dry eye	Related	1 (6.7%)	0 (0.0%)
		Erythema of eyelid	Related	0 (0.0%)	1 (6.3%)
		Foreign body sensation	Related	1 (6.7%)	0 (0.0%)
	General disorders and adm site conditions	Instillation site discomfort	Related	7 (46.7%)	0 (0.0%)
		Product deposit	Related	3 (20.0%)	1 (6.3%)
		Instillation site pain	Related	1 (6.7%)	0 (0.0%)
		Instillation site complication	Related	0 (0.0%)	1 (6.3%)
All			Related	15 (100.0%)	12 (75.0%)**
ADVERSE EVENTS					
Non TEAE	Eye disorders			0 (0.0%)	0 (0.0%)
TEAE	Eye Disorders			5 (33.3%)	11 (68.8%)
		Ocular hyperaemia	Related	4 (26.7%)	5 (31.3%)
		Eye pain	Related	1 (6.7%)	3 (18.8%)
		Eye irritation	Related	2 (13.3%)	2 (12.5%)
		Vision blurred	Related	0 (0.0%)	3 (18.8%)
		Eye pruritus	Related	0 (0.0%)	2 (12.5%)
		Keratitis	Non related	0 (0.0%)	2 (12.5%)
		Conjunctival hyperaemia	Non related	1 (6.7%)	0 (0.0%)
		Conjunctivitis	Non related	0 (0.0%)	1 (6.3%)
		Conjunctivitis allergic	Non related	1 (6.7%)	0 (0.0%)
		Corneal neovascularisation	Non related	0 (0.0%)	1 (6.3%)
		Dry eye	Non related	0 (0.0%)	1 (6.3%)
		Lacrimation increased	Related	1 (6.7%)	0 (0.0%)
		Visual impairment	Related	1 (6.7%)	0 (0.0%)

*In CHOC Clinical Study Report, only patients with box "Other" ticked are included. In the table above, "Other" represents patients who ticked the box "Other" and those who did not tick the box "Other" but who described symptoms in the comment section of the patient diary.
**In CHOC Clinical Study Report patients who ticked "None" in the patient diary were not counted. One patient (patient 0204) ticked "None" but reported "Eyelid oedema" as an observation in the patient diary. This patient was not counted in the Clinical Study Report but was included in the table above.

With regards to patient-reported diary-based ocular AEs (LADRs), all patients in the Cystadrops arm and 11/16 patients in the CH 0.10% arm reported at least 1 LADR. In this study, patients were not asked to record the duration of any LADRs, only to indicate whether they lasted more or less than an hour. Overall, more than 98% of the LADRs at instillation were reported to have resolved in under an hour and most patients reported LADRs at instillation as mild or moderate in intensity.

Table 19: CHOC Local adverse drug reactions at instillation (by patient) (N = 31)

Symptom (Preferred Term)	Maximum intensity	Cystadrops (N=15)	CH 0.10% (N=16)
		n (%)	**n (%)**
All	any	15 (100.0%)	11 (68.8%)
	severe	5 (33.3%)	2 (12.5%)
	insufferable	2 (13.3%)	1 (6.3%)
Stinging (Eye pain)	any	12 (80.0%)	8 (50.0%)
	severe	4 (26.7%)	2 (12.5%)
	insufferable	2 (13.3%)	1 (6.3%)
Redness (Ocular hyperaemia)	any	9 (60.0%)	7 (43.8%)
	severe	0	0
	insufferable	0	0
Burning (Eye irritation)	any	10 (66.7%)	4 (25.0%)
	severe	2 (13.3%)	2 (12.5%)
	insufferable	0	1 (6.3%)
Blurred vision (Vision blurred)	any	9 (60.0%)	4 (25.0%)
	severe	2 (13.3%)	2 (12.5%)
	insufferable	0	0
Itching (Eye pruritis)	any	6 (40.0%)	4 (25.0%)
	severe	0	1 (6.3%)
	insufferable	0	1 (6.3%)
Other	any	3 (20.0%)	3 (18.8%)
	severe	1 (6.7%)	0
	insufferable	0	0

Additional analysis of ocular safety

There were no increases in corneal staining in any of the two treatment arms and there were also no indications of a worsened inferior staining that could be indicative of drug toxicity over time, rather corneal staining was reduced vs. baseline. There were no increases in intraocular pressure (IOP) and fundus examinations revealed no specific findings. Regarding VA and contrast sensitivity, there were some improvements vs. baseline in both treatment arms, as reported in Clinical Efficacy section.

Cysteamine has a chemical structure close to D-penicillamine, known to potentially interfere with the cross-linking of collagen fibres. Systemic administration of cysteamine has been associated with skin disorders resembling Ehlers-Danlos syndrome (EDS). Since the cornea, and more generally the anterior segment of the eye, are essentially composed of collagen fibres, topical cysteamine could lead to known ocular manifestations of EDS. The occurrence of a number of specific symptoms, megalocornea/glaucoma, ectopia lentis, keratoconus, microcornea, myopia, retinal detachment and blue sclera as "pre-defined serious ocular adverse events", was in consequence also to be reported.

There were 2 eyes (adult patient) in the Cystadrops dose group and 1 eye (adult subject) in the CH 0.10% dose group that showed abnormal corneal topography from day 30, but no baseline evaluations were conducted in these subjects. No subjects developed keratoconus.

Non-Ocular adverse events

The most frequently reported AEs coded to the SOCs "Infections and infestations", "Respiratory, thoracic and mediastinal disorders" and "Nervous system disorders". No systemic AEs were considered related to treatment.

Supportive safety data

Two compassionate use programmes have together enrolled 359 subjects up to March 2015. All events were non-serious and considered as at least possibly related to treatment. There were no new AEs not observed in the clinical trials.

In the French NPU programme, as of 15 March 2015, a total of 106 patients (54 below 18 years of age) were included. Data from at least one follow-up visit was collected for 53 patients. For 4 patients, the AE resulted in a temporary treatment discontinuation.

Table 20: Listing of adverse events reported in the French NPU programme between September 24 2013 and March 15, 2015

SOC	Preferred term	[1]Event (%) (N= 24)	[2]Patients (%) (N= 106)
Eye Disorders	Eye irritation	9 (37.5%)	9 (8.5%)
	Eye pain	4 (16.7%)	4 (3.8%)
	Vision blurred	4 (16.7%)	4 (3.8%)
	Ocular hyperaemia	1 (4.2%)	1 (0.9%)
	Lacrimation increased	1 (4.2%)	1 (0.9%)
General disorders and administration site conditions	Product deposit	2 (8.3%)	2 (1.9%)
	Instillation site discomfort	3 (12.5%)	3 (2.8%)

[1] Number of adverse events. %= n*100/N.
[2] Number of patients with at least one adverse event. %= n*100/N.

Safety data collected through spontaneous reporting sources (by physicians or pharmacist) participating in other NPU programmes in Europe (Denmark, Sweden, Norway, Finland, Ireland, Island and Spain), or in the Middle East region, Brazil, India and Russia are displayed below. Approximately 230 cystinosis patients are part of these programmes.

Table 21: Individual case safety reports reported of the patients from the global NPU programmes

Case ID ***Reporter / country***	Events Reported (Preferred Term)
SWE-CLT-2012007 *Physician / Sweden*	Eye irritation
SWE-CLT-2013002 *Pharmacist / Finland*	Vitreous floaters
SWE-CLT-2013003 *Physician / Sweden*	Corneal deposits
OTH-CLT-2014004 *Physician / Russia*	Eye Irritation, hordeolum

Case report SWE-CLT-2013003 concerned a perceived increase in corneal deposits while the patient was receiving Cystadrops "twice daily". The dosage was increased to 4 times daily. The outcome was unknown. One patient in Russia experienced a non-serious related (de- and re-challenge) AE, hordeolum, and Cystadrops was stopped.

Published data

The data from 7 clinical trials reports were presented by the Applicant. The studies enrolled between 1 and 29 patients, for an overall total of 64 treated patients. Patients received a daily regimen consisting of 4 to approximately 12 drops (based on a frequency of one drop per waking hour) per eye. Use of cysteamine in these studies ranged from approximately 3 months to 4 years. In addition, 63 subjects were exposed to 0.1 or 0.5% of cysteamine eye drops in the Sigma-Tau studies.

No additional safety concerns were reported. Ocular symptoms were essentially limited to symptoms of irritation (burning, stinging, itching, pain and redness).

Serious adverse event/deaths/other significant events

Study OCT-1

There were 2 ocular SAEs, corneal neovascularisation and papilloedema, both bilateral in the same patient. Worsening of corneal neovascularisation was observed after 3.5 years of treatment and considered to be possibly related to study treatment. Papilloedema was reported one year after treatment initiation and was stable over the following years in study. The investigator considered this unlikely related to Cystadrops and finally reported a potential relationship with azathioprine.

There were no deaths in the study.

Study CHOC

Four patients experienced SAEs; 2 patients were in the Cystadrops treatment arm and 2 in the cysteamine hydrochloride 0.10% arm. These were gastroenteritis and fatigue (Cystadrops treatment arm), gastroenteritis and corneal graft rejection (CH 0.10% treatment arm). None were considered related to study treatment.

There were no deaths in the study.

Laboratory findings

In OCT-1, clinically significant out-of-range laboratory values were reported for 3 patients: creatineamia for 2 patients and hypokalaemia for 1 patient.

Safety in special populations

Although there are no data in subjects over 65 years in, there are no specific safety concerns regarding the elderly population.

A formal comparison of safety parameters between the adult and the paediatric age groups was not carried out. Analyses of LADRs in children < 18 years of age were performed in the CHOC study. The frequency of LADRs was similar between age groups, with a somewhat lower frequency in the paediatric population.

Safety related to drug-drug interactions and other interactions

Formal interaction studies on the use of Cystadrops with other ocular products have not been performed. However, it is common for cystinosis patients to have chronic corneal irritation and "dry eyes" syndrome, resulting in the potential need for other concomitant ocular formulations.

Discontinuation due to adverse events

No patients discontinued treatment in OCT-1. In CHOC, 1 patient permanently discontinued treatment due to allergic conjunctivitis and 2 subjects temporarily discontinued treatment due to dizziness (crystal detachment in inner ear) and due to a corneal graft rejection in the left eye. In the latter case, treatment was restarted in the right eye only.

Post marketing experience

Not applicable.

2.6.1. Discussion on clinical safety

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

Although it is recognised that treatment with eye drops containing cysteamine is a standard of care in corneal cystinosis, the safety database is limited and consists of 8 patients from the 5-year OCT-1 study and 31 patients from the 3-months CHOC study, out of which 15 were treated with Cystadrops. The long-term experience in a controlled setting is thus very limited. In the Cystadrops and CH 0.10% treatment arms in the CHOC study, eye pain (stinging 80 % vs. 50%), ocular hyperaemia (60% vs. 44%), eye irritation (burning 67% vs. 25%), vision blurred (60% vs. 25%) and eye pruritis (40% vs. 25%) were most frequently reported by the patients. Therefore, a major concern was raised regarding a potential increased risk of LADRs and other more serious AEs in the long-term with potential consequences for compliance to treatment. Although under-reporting is likely, also in this regard, the reporting from the ongoing NPU programmes gives some reassurance. For the 106 subjects included in the French programme, there was a structured follow-up. The type of AEs from these programmes seems consistent with those observed in the clinical trials and in the 57 patients treated for $\geqslant$6 months as well as in the 28 patients treated for $\geqslant$12 months, no new or worsening of AEs were reported after the initial 3 months of treatment and there were no serious or unexpected findings.

The efficacy data from NPU programme also indicate a maintained effect (mean of 7-8 months of treatment), which would not be expected in case of lack of compliance. There was also no evidence of development of local intolerance or an increased risk of LADRs or other more serious adverse events in relation to the viscosity and low pH of Cystadrops. Taking into account the data from the clinical and NPU programmes, the safety profile of Cystadrops was regarded to be acceptable. In addition, the Applicant has committed to conduct a 5-year Post-Authorisation Safety Study (PASS),

In addition to the NPU programmes addressed above, published data including 88 subjects exposed to relevant concentrations of cysteamine eye drops in various formulations also support the observed safety profile and provide additional long-term data. Although reassuring, as these are published data, a thorough assessment cannot be made and from some of these studies there are indications of under-reporting of AEs.

As only a relatively short-term comparison against the less concentrated formulation i.e. CH 0.10% was carried-out in the CHOC Study, it is not possible to characterise whether the patient-reported LADRs were due to the active compound as such or due to the high viscosity and low pH of the Cystadrops formulation.

The Applicant has reported ocular and non-ocular AEs, but focused on ocular safety. The vast majority of patients with cystinosis are treated with concomitant oral cysteamine at substantially higher doses (1- 2 grams/day) than given by the ocular route (approximately 2 mg/day). The additive systemic exposure is expected to be negligible and systemic reactions, if any, related to topical cysteamine are not expected to

be distinguishable from those obtained after systemic cysteamine treatment. Thus, the focus on evaluation of ocular safety was supported.

The overall AE profile was predominated by a high incidence of generally transient reactions like stinging, blurring, irritation, itching, redness etc. associated with instillation of the eye drops.

Treatment-emerging and treatment-related AEs in OCT-1 were reported in 2 subjects with one event each of aggravation of pre-existing corneal neovascularisation (possibly treatment-related), dry eye and hordeolum. All were mild to moderate. With regards to corneal neovascularisation, as this is also associated with corneal cystinosis, a firm conclusion on the relation to treatment cannot be drawn. Therefore, it is acceptable not to include this AE in the SmPC but only address it as a potential risk in the RMP. In addition, in OCT-1 study, one SAE of papilloedema was reported as SAEs. Papilloedema was not regarded to be treatment-related. It was agreed that it is more likely that it was caused by any (or the combination) of the concomitant drugs administered (azathioprine and cyclosporine).

In CHOC, the frequency of treatment-emerging AEs (investigator-reported) was overall higher in the CH 0.10% comparator group. In the Cystadrops and the CH 0.10% treatment arms, ocular hyperaemia (27 vs. 31%), eye pain (7 vs. 19%) and eye irritation (13 vs. 12%) were most frequently reported. Treatment-related AEs of eye pain, eye irritation, dry eye, visual impairment and lacrimation increased were reported for single patients in the Cystadrops arm. In addition, eye pruritus was reported in the CH 0.10% arm. There were also events, mostly single, of keratitis, conjunctivitis and dry eye (regarded non-related to treatment) in the CH 0.10% treatment arm. According to published data, keratitis, dry eye and visual impairment are potential manifestations of the disease while conjunctivitis and lacrimation increased has not been reported as related to cystinosis. The SmPC has now been updated accordingly to reflect the profile of Cystadrops.

As patients were instructed to report local reactions upon instillation and a number of such LADRs were listed in the patient diaries to guide the patients, it is not surprising that the rate of reporting was high with frequencies ranging from very common (>1/10) to common (>1/100). The LADRs were generally transient and as assessed in OCT-1, their intensity tended to decrease over the duration of the study. Also in CHOC, the LADRs were generally transient (98% resolved within 1 hour) with a few events of ocular hyperaemia and blurred vision lasting for more than 1 hour. Despite a fairly high rate of severe reactions, compliance was high indicating that patients could manage the reactions.

A number of patients presented with abnormal corneal topography however there was no evidence that this developed during treatment with Cystadrops (or CH 0.1 %). Evaluations of corneal staining, keratoconus, IOP and fundus examinations revealed no specific findings. While no worsening of corneal staining is reassuring, CHOC was rather short in duration and the choice of BAK as preservative in a formulation intended for life-long treatment in subjects (including the paediatric subset) with an impaired corneal health needed further justification. The Applicant has considered developing a non-preserved formulation of Cystadrops but explained, that since cysteamine is easily oxidised and then inactivated, the polymers in a single-dose cannot be permeable to oxygen. No appropriate alternative has been found. In addition, the available multi-dose containers that either includes a filter or silver spiral seems inappropriate (cannot be filtered or oxidation increases). It has been recognised that such development is difficult. The Applicant has also expressed a concern that efficacy could be reduced if BAK, a compound that is well known to work as a permeability enhancer, is removed. Further evaluation whether it would be possible to develop an alternative non-preserved formulation or a formulation with an alternative preservative would be desired. Initially, the effect of BAK could, for example, be investigated in *in vitro* permeability models (e.g. an in vitro corneal permeability model).

Cysteamine may have a potential to interfere with the cross-linking of collagen fibres resulting in disorders similar to that of EDS. Ocular manifestations of EDS (type VI) have been reported to include dry eyes, keratoconus, myopia (thin and fragile sclera), scleral rupture, retinal detachment, glaucoma, strabism and hyperextensible eye lids and any such events were to be reported in CHOC. Only OCT-1 has a sufficient duration to evaluate any potential risks of the development of EDS-like manifestations, however, this study was non-controlled and too limited in size. In addition, in wound healing and wound strength collagen and collagen fibres play critical roles and this is a patient population where corneal grafting is not uncommon**.** The potential risks of EDS-like ocular manifestations are addressed in the RMP and will be further evaluated in the proposed PASS.

In CHOC, there were 4 SAEs, gastroenteritis and fatigue (Cystadrops treatment arm), gastroenteritis and corneal graft rejection (CH 0.10% treatment arm). None of the SAEs were considered related to study treatment. Although it cannot be completely excluded that initiation of CH 0.10% 11 days after grafting could have contributed to the event, the event had characteristics of an acute rejection episode and the investigator's conclusion that it was not related to treatment is considered reasonable.

In OCT-1, 3 patients reported clinically significant changes in laboratory parameters: creatineamia and hypokalemia. These are considered likely related to the underlying disease, nephropathic cystinosis and thus unlikely to be related to treatment with Cystadrops.

As detailed in the discussion on efficacy, the treatment experience with the 0.55% formulation is limited in the youngest subset of the paediatric population (2-6 years old). Since there are no specific concerns regarding the older and elderly population, the absence of data in these populations is not considered necessary to include in the SPC. Similarly, the addition of cysteamine eye drops on top of oral treatment is not likely to contribute to a specific risk in subjects with renal or hepatic impairment as the additive systemic exposure over that obtained by oral cysteamine is expected to be negligible. As the dosing frequency is to be based on the response to treatment and there is no specific safety concern, the dose should not be adjusted in these subjects.

2.6.2. Conclusions on the clinical safety

The CHMP was of the view that the available safety data were sufficient to support the application for Cystadrops in the treatment of cystinosis. The CHMP concluded that the safety profile of Cystadrops was acceptable with the majority of adverse reactions being eye disorders and related to the instillation of the eye drops, while the risk of systemic exposure and adverse reactions was considered low. The safety profile was furthermore considered adequately reflected in the product information and all safety concerns were addressed in the RMP.

In addition, the Applicant has committed to conducting an open-label, longitudinal post authorisation safety study to characterise long term safety of Cystadrops in more detail.

2.7. Risk Management Plan

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

The PRAC considered that the RMP version 1.0 (dated 4 July 2014) could be acceptable if the applicant implements the changes to the RMP as described in the PRAC endorsed PRAC Rapporteur updated assessment report dated 8 January 2015.

The CHMP endorsed this advice without changes.

The applicant implemented the changes in the RMP as requested by PRAC and CHMP.

The CHMP endorsed the RMP version 1.3 (dated 30 September 2015) with the following content:

Safety concerns

Table 22: Summary of the safety concerns

Important identified risks	• Severe eye irritation
Important potential risks	• Punctate keratopathy and/or toxic ulcerative keratopathy (due to benzalkonium chloride) • Corneal neovascularisation • Ocular manifestations of Ehlers-Danlos like syndrome (EDLS) • Increased risk of infections and medication errors due to device assembly failure
Missing information	• Patients with other ocular co-morbidities • Patients receiving concomitant treatment with ophthalmic products containing benzalkonium chloride (BAK) • Long term safety

Pharmacovigilance plan

Table 23: on-going and planned studies in the Post-authorisation Pharmacovigilance Development Plan

Study/activity **Type, title and category (1-3)**	**Objectives**	**Safety concerns addressed**	**Status** **(planned, started)**	**Date for submission of interim or final reports (planned or actual)**
Open-label longitudinal Post Authorization safety Study to assess safety of Cystadrops® in paediatric and adult cystinosis patients in long term use (Category 3)	To evaluate the risk of Cystadrops® after long term use in cystinosis patients	- Ocular irritation - Punctate keratopathy and/or toxic ulcerative keratopathy (due to BAK) - Corneal neovascularisation - Ocular manifestations of EDLS - Long term safety	Planned	Study to be completed by 2021 (final report)

Risk minimisation measures

Table 24: Summary table of the risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risk		
Severe eye irritation	Wording in SmPC Section 4.4, 4.8 Other routine risk minimisation measures: - prescription only medicine - treatment should be supervised by a physician experienced in the management of cystinosis (SmPC Section 4.2)	None
Important potential risks		
Punctate keratopathy and/or toxic ulcerative keratopathy (due to benzalkonium chloride)	Wording in SmPC Section 4.4 Other routine risk minimisation measures: - prescription only medicine - treatment should be supervised by a physician experienced in the management of cystinosis (SmPC Section 4.2)	None
Corneal neovascularisation	- prescription only medicine - treatment should be supervised by a physician experienced in the management of cystinosis (SmPC Section 4.2)	None
Ocular manifestations of Ehlers-Danlos like syndrome (EDLS)	- prescription only medicine - treatment should be supervised by a physician experienced in the management of cystinosis (SmPC Section 4.2)	None
Increased risk of infections and medication errors due to device assembly failure	Wording in SmPC Section 6.6 Other routine risk minimisation measures: - prescription only medicine	None
Missing information		
Patients with other ocular co-morbidities	- prescription only medicine - treatment should be supervised by a physician experienced in the management of cystinosis (SmPC Section 4.2)	None
Patients receiving concomitant treatment with ophthalmic products containing benzalkonium chloride (BAK)	Wording in SmPC Section 4.4 Other routine risk minimisation measures: - prescription only medicine - treatment should be supervised by a physician experienced in the management of cystinosis (SmPC Section 4.2)	None

Long term safety	Wording in SmPC Section 4.8 - prescription only medicine - treatment should be supervised by a physician experienced in the management of cystinosis (SmPC Section 4.2)	None

The MAH is reminded that, within 30 calendar days of the receipt of the Opinion, an updated version of Annex I of the RMP template, reflecting the final RMP agreed at the time of the Opinion should be submitted to h-eurmp-evinterface@emea.europa.eu.

2.8. Pharmacovigilance

Pharmacovigilance system

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

2.9. Product information

2.9.1. User consultation

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

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Cystinosis is a rare genetic autosomal recessive disease. It is caused by a lysosomal transport defect resulting in the intracellular accumulation of cystine. Cystine accumulates within lysosomes, forming crystal deposits in many tissues, including the kidneys and the eyes, but also in bone marrow, lymph nodes, intestine, spleen, liver, pancreas, gonads, thyroid, muscles, and in the central nervous system.

Corneal cystine crystals that can be seen in the corneal epithelium and the stroma are specific characteristics of all phenotypes of cystinosis. They appear as a myriad of needle-shaped highly reflective opacities. By 1 year of age, cystine crystals can be evidenced in the cornea by slit lamp. By approximately 7 years of age, the entire peripheral stroma accumulates crystals, and by approximately 20 years of age, crystals can be seen in the entire corneal stroma.

The crystals are initially asymptomatic but photophobia, resulting from the diffraction of light by the cystine crystals, is common and develops within the first few years of life. Many patients begin wearing sunglasses in early childhood. Superficial punctate keratopathy and pain are occasionally observed, mostly in patients older than 10 years of age. Other more severe complications of crystal deposits are corneal erosions, loss of visual contrast sensitivity, increased glare disability, decreased corneal sensitivity and increased corneal thickness. In very young patients, visual acuity (VA) is usually not

affected, however, in older patients where corneal complications are more common, these may lead to visual impairment.

3.1.2. Available therapies

All cystinosis patients are treated by oral administration of cysteamine (Cystagon and Procysbi) aiming to reduce intracellular cystine accumulation, therefore delaying organ and tissue damage. While oral administration of cysteamine reduces intracellular cystine accumulation in non-corneal tissues, systemically administered cysteamine does not reach the cornea and has consequently no effect on corneal cystine deposits.

To dissolve cystine crystal deposits in the cornea, the established approach is to use eye drops solutions containing cysteamine, but there are no licenced treatment options in the EU. Currently, eye drop formulations at concentrations between 0.10% - 1.13% are prepared ex tempore, e.g. by pharmacies at local hospitals. A range of different posologies, including hourly instillations, are applied.

3.1.3. Main clinical studies

The clinical development of Cystadrops consisted of 2 studies: one open-label, single-arm 5-year study where the dosing frequency was adapted based on response and one randomised, controlled superiority 3-months trial vs. a standard of care formulation of cysteamine (CH 0.10%) used in France.

3.2. Favourable effects

In the pilot, single-arm study OCT-1, the absolute reduction in corneal crystals as measured with IVCM from baseline to 60 months was 3.4±2.8 units, which corresponds to an approximately 30% reduction vs. baseline. The reduction was observed from month 1 (-1.5±2.4 units, -13%) and remained fairly stable between month 3 to month 60. The dosing frequency was adapted based on treatment response and from month 3, the average number of instillations of Cystadrops was reduced from the initial mean of 4 to a mean of 3 drops per day which may explain the absence of a further reduction in crystals.

In the pivotal CHOC study, the absolute reduction in corneal crystals from baseline to month 3 as measured with the IVCM (primary efficacy) was 4.6±3.1 units (-40.4%) in the Cystadrops treatment arm and 0.5±3.4 units (-0.8%) in the CH 0.10% comparator arm (a standard of care, ex tempore formulation of 0.10% cysteamine). The difference between treatment arms was 3.8 ± 0.9 (95% CI 2.1, 5.6, $p<0.0001$). Superiority of Cystadrops over CH 0.10% was supported in the PPS (difference 3.5, 95% CI 1.7, 5.3, $p=0.0002$), in sensitivity analyses as well as in the analyses of CCCS ($p=0.0015$) and crystal thickness ($p=0.0031$). Further, the ICVM outcomes were consistent with the outcomes in the primary analysis when each corneal layer was weighed according to the relative thickness of each layer.

In OCT-1, there was a 0.9 unit (-36%) reduction in photophobia at month 60 vs. baseline. The reduction seemed slower in onset (-0.5 at month 3) compared to the reduction in corneal crystals. In CHOC, the reduction in photophobia from baseline to month 3 was 0.6 ± 0.8 units (-33%) in the Cystadrops treatment arm and a minimal increase of 0.06±0.44 units (+5%) in the CH 0.10% comparator arm ($p=0.0048$). The difference between treatment arms was supported in the PPS ($p=0.0320$). Between baseline and day 90 (in patients with photophobia at baseline), photophobia was reduced with 2 and 1 units (scale 0-5) in 19 and 35 % in the Cystadrops arm, respectively, versus 0 and 7 % in the CH 0.10% treatment arm.

In OCT-1, visual acuity and contrast sensitivity remained fairly stable. In CHOC, an improvement in visual acuity was demonstrated in both treatment groups. The mean improvement was LogMar -0.10 ± 0.15

(+5 letters) vs. LogMar -0.07 ± 0.15 (+3.5 letters) in the Cystadrops vs. the CH 0.10% treatment groups. In responder analyses, (proportions with gain of ≥15, ≥10 and ≥ 5 letters), the improvement in VA seemed modest and overall similar between treatment arms, but the level of visual impairment was limited at baseline. With regards to contrast sensitivity, there was a 33-35% improvement vs. baseline without any differences between treatment arms.

To further support a sustained effect of treatment, the Applicant has presented available efficacy data from 53 of 106 subjects with baseline and at least one follow up visits enrolled in the French NPU programme. After mean treatment durations of 7-8 months, the proportion of eyes with severe crystal densities (CCCS) at baseline was reduced from 50 to 30 % with time and as a consequence, the proportion of patients with mild CCCS increased. With regards to photophobia, the overall reduction seemed less pronounced compared to the CHOC study, however, after 7 months on treatment, the proportion of subjects with a $\geqslant$ 2 step reduction increased while the corresponding proportions with a $\geqslant$ 1 step reduction increased compared to the analysis made after 3 months. Finally, the number of subjects with a relevant gain in VA (≥15 letters) was increased from between month 3 and 8. In subjects with no photophobia or visual acuity reduction at baseline, progression was inhibited in the majority of patients. With the limitations of being a non-controlled compassionate use programme, efficacy seemed to be maintained, and potentially also increased with time, however, progression was not stopped in all patients.

3.3. Uncertainties and limitations about favourable effects

While the evaluation of primary efficacy was based on images evaluated by an independent and masked reader, images for evaluation were selected by an unmasked ophthalmologist. There is thus a potential for a selection bias which leaves the pivotal study without any truly masked evaluations. This is unfortunate and adds uncertainty to the magnitude of the effect size. However, the overall effect size seems convincing. Additional support for this conclusion is derived from the effect on photophobia and other clinical outcomes measured as secondary endpoints.

Support for sustained efficacy has been provided from the NPU programmes. However, these are data were collected from a non-controlled setting and the effect sizes observed should be interpreted with caution.

The experience in children 2-6 years of age is limited.

The dosing frequency generally recommended for the comparator, CH 0.10%, used in the CHOC study is every hour while awake and not 4 times/day. On one hand, it could be argued that since CH 0.10 % was administered only 4 times/day in the study, this dosing was suboptimal. On the other, a placebo-controlled study would be difficult to conduct in this condition, and CH 0.10 % would therefore be expected to provide assay sensitivity. Since superiority was aimed for, and demonstrated, this was achieved. While a different outcome may have been observed if CH 0.-10 % would have been administered hourly, there is a benefit also in being able to reduce the frequency of instillations.

3.4. Unfavourable effects

The AE profile of Cystadrops is dominated by very common or common local reactions such as eye pain, ocular hyperaemia, eye irritation, vision blurred and eye pruritus upon instillation. The vast majority of the reactions observed in clinical trials were transient (within 1 hour or less). Although almost half of the reactions were reported as severe at one or more of the instillations, compliance to treatment was high. This indicates that the patients could manage the reactions.

Further safety reporting from the NPU programmes has been provided. Between September 2013 and March 2015, a total of 28 non-serious AEs, at least possibly related to treatment were reported. The reporting supports the safety profile characterised in the clinical studies as there were no unexpected, not previously identified AEs. In the 57 patients treated for ⩾6 months as well as in the 28 patients treated for ⩾12 months, all AEs were reported during the initial 3 months of treatment. There are thus no signals indicative of an induction of local intolerance or an increased risk of LADRs or other more serious AEs in relation to the viscosity and low pH of Cystadrops.

3.5. Uncertainties and limitations about unfavourable effects

The safety database is limited and consists of 8 patients from the 5-year OCT-1 study and 31 patients from the 3-months CHOC study, of whom 15 were treated with Cystadrops. The long-term experience in a controlled setting is thus very limited and no conclusions can be drawn whether LADRs and potentially more serious AEs may increase during the long-term (chronic) treatment that is expected in corneal cystinosis and whether this may have potential consequences for compliance to treatment. While the additional safety reports provided from the NPU programmes support the safety profile from the clinical trials, it is likely that there is an under-reporting and there is still some uncertainty regarding the long-term safety profile. To further characterise the long term safety of Cystadrops, the Applicant will conduct a 5-year PASS with focus on local AEs, SAEs and potential ocular manifestations of EDS.

Treatment-emerging and treatment-related AEs of mild to moderate nature in OCT-1 were reported in 2 subjects with one event each of aggravation of pre-existing corneal neovascularisation (SAE), dry eye, hordeolum. As corneal neovascularisation also is associated with the disease, a conclusion on the relation to treatment cannot be drawn.

Cystadrops may interfere with the cross-linking of collagen fibres and there is a potential risk of serious complications similar to the ocular manifestations of EDS, e.g. dry eyes, keratoconus, myopia (thin and fragile sclera), scleral rupture, retinal detachment, glaucoma, strabism and hyperextensible eye lids. Collagen is also a key-player in wound healing and patients with EDS have an impaired wound healing. While no such events were reported in the studies and there are no literature data that indicate that corneal wound healing may be negatively affected by cysteamine containing eye drops, this is adequately addressed in the RMP.

The treatment experience is limited in the youngest subset of the paediatric population (2-6 years old).

It is not possible to determine whether the LADRs were due to the active compound or due to the Cystadrops formulation as the initially considered active comparator, a less viscous 0.55% formulation of cysteamine was not used.

3.6. Effects Table

Table 25: Effects Table for Cystadrops

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
IVCM total score	Mean change 5 y[1] Mean change 3 mo[2]	points	-3.4 -4.6	NA -0.45	Limited no of patients. Open label. In CHOC study treatment difference was 3.8 ± 0.9 (95% CI 2.1, 5.6, p<0.0001)	See discussion on Clinical Efficacy

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Photophobia	Mean change 5 y[1] Mean change 3 mo[2]	points	-0.9 -0.6	NA +0.06	In CHOC study treatment difference was 0.69 95% CI0.23; 1.14, p< 0.048)	
CCCS	Mean change 3 mo[2]	points	-0.6	+0.06		
Crystal thickness	Mean change 3 mo[2]	µm	-46.3	+10.6		
VA	Mean change 3 mo[2]	LogMar	-0.10	-0.07		
Contrast sensitivity	Mean change 3 mo[2]	LogMar	-0.20	-0.14	Non-validated chart	
Unfavourable Effects						
Ocular AEs[2], investigator reported	Ocular hyperaemia Eye pain Eye irritation Vision blurred Pruritus Keratitis	%	27 7 13 0 0 0	31 19 12 19 12 12	Very limited safety database with 39 subjects in clinical studies whereof 23 exposed to Cystadrops (15 in pivotal study CHOC)	See discussion on Clinical Safety
Ocular AEs[2], patient reported	Transient, local reactions at instillation, e.g. stinging, burning, irritation, redness	%	100	69		
Ocular SAEs[1]	Worsened corneal neovascularisation	Event	1	NA	Relation uncertain	RMP

[1] Pilot study – OCT-1, single arm
[2] Pivotal study – CHOC, controlled

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The 30 to 40% reduction in corneal crystals is supported by a similar mean relative reduction in key clinical endpoint, photophobia. Responder analyses of photophobia support a clinically relevant treatment effect. Data from the NPU programme has further provided indications of a sustained effect of treatment over time, however, also these data are rather limited, originate from a non-controlled setting and should thus be interpreted with caution.

In the EU, there is currently no approved medicinal product for the treatment of the corneal manifestations of cystinosis. While there are some uncertainties regarding the effect sizes due to the open-label design of the study, Cystadrops was superior over the 0.10% cysteamine formulation (CH 0.10%) that is part of the current standard of care in the EU. In subjects treated with CH 0.10%, there was no further disease progression, however, no reduction in either corneal crystals or photophobia was observed. The improvement demonstrated with Cystadrops was consistent and addresses an unmet medical need. The effect is thus considered of clear benefit to the patients.

Although the safety database is very limited, in context of the rarity of the disease as well as taking into account that the treatment with cysteamine eye drops is a standard of care in this condition, Cystadrops seems fairly well tolerated even though the incidence of transient, local reactions was very high. As the number of discontinuations was very low, it indicates that the patients find the local adverse reactions

manageable. Although the incidence of the patient-reported local reactions was higher with Cystadrops than with the CH 0.10% comparator, this is balanced against the superior efficacy obtained with Cystadrops.

Reporting from the compassionate use programmes as well as literature data support the safety profile in the clinical studies and there were no unexpected, not previously identified AEs. There are thus no signals indicative of an induction of local intolerance or an increased risk of LADRs or other more serious AEs in relation to the viscosity and low pH of Cystadrops. With the limitations of being a non-controlled compassionate use programme, the efficacy data provided from the French programme also give an indirect indication that compliance was not a critical issue over a 7-8 months (mean treatment duration of the 53 subjects with follow-up visits) since efficacy seemed to be maintained. In addition, the long-term safety profile will be characterised in more detail during 5-year Post Authorisation Safety Study.

3.7.2. Balance of benefits and risks

The CHMP is of the view that the clinical data is sufficient to conclude that Cystadrops exerts clinical efficacy in cystinosis patients with corneal cystine crystal deposits. The safety profile was found to be acceptable.

3.7.3. Additional considerations on the benefit-risk balance

The container closure system consisting of a glass vial and a separate dropper applicator is not optimal from a microbiological and user friendly point of view and may lead to a risk for contamination (increased risk for infection) and medication error. There have also been reports regarding problems during instillation. The Applicant has therefore introduced a number of clarifications in the Product Information which aim to mitigate these risks. In addition, a plan for post approval development of a new container (ready to use bottles with dropper already in place) has been agreed as a recommendation.

3.8. Conclusions

The overall B/R of Cystadrops is positive.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Cystadrops is not similar to Procysbi within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See appendix 1.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Cystadrops is favourable in the following indication:

Cystadrops is indicated for the treatment of corneal cystine crystal deposits in adults and children from 2 years of age with cystinosis.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Other conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Additional risk minimisation measures

N/A

Obligation to conduct post-authorisation measures

N/A

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0322/2013 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.