25 April 2025
EMA/CHMP/130728/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Cystadrops

International non-proprietary name: Mercaptamine

Procedure No. EMEA/H/C/003769/II/0032

Note

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

Table of contents

List of abbreviations

AEs	adverse events
BAK	benzalkonium chloride
BCVA	best corrected visual acuity
CCCS	corneal cystine crystal score
CSR	clinical study report
EDS	Ehlers-Danlos syndrome
IVCM	in-vivo confocal microscopy
LADRs	local adverse drug reactions
OCT	optical coherence tomography
PASS	post authorisation safety study
PIP	paediatric investigation plan
SAEs	serious adverse events
SOC	system organ class
TEAE	Treatment Emergent Adverse Events
VA	visual acuity

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Recordati Rare Diseases submitted to the European Medicines Agency on 30 September 2024 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II and IIIB

Extension of indication to include treatment of children from 6 months of age for Cystadrops, based on final results from study CYT-C2-001. This is an open-label, single-arm, multicenter study to assess the safety of Cystadrops in pediatric cystinosis patients from 6 months to less than 2 years old. As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 2.1 of the RMP has also been submitted. In addition, the MAH took the opportunity to update Annex II of the PI and the list of local representatives in the Package Leaflet.

The variation requested amendments to the Summary of Product Characteristics, Annex II and Package Leaflet and to the Risk Management Plan (RMP).

Information relating to orphan designation

Cystadrops, was designated as an orphan medicinal product EU/3/08/578 on 23.01.2017. Cystadrops was designated as an orphan medicinal product in the following indication: Treatment of cystinosis.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included (an) EMA Decision(s) P/0019/2022 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0019/2022 was completed.

The PDCO issued an opinion on compliance for the PIP P/0019/2022.

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 MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no other authorised medicinal product for a condition related to the proposed indication.

Protocol assistance

The MAH received Protocol Assistance from the CHMP on 19 June 2012.

(EMEA/H/SA/2335/1/2012/PA/III). The Protocol Assistance pertained to quality (validation and stability), clinical aspects (design of the randomised 3 months study [0.10% Vs 0.55%], including the proposed paediatric population and overall program for MAA) and significant benefit (proposed evidence) in relation to paediatric development of the dossier, for the indication treatment of corneal cystine crystals deposits in cystinosis.

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: N/A

Timetable	Actual dates
Submission date	30 September 2024
Start of procedure:	2 November 2024
Rapporteur preliminary assessment report circulated on:	20 December 2024
PRAC Rapporteur preliminary assessment report circulated on:	20 December 2024
PRAC members comments	23 December 2024
PRAC Outcome	16 January 2025
CHMP members comments	20 January 2025
Joint Rapporteurs updated assessment report circulated on:	23 January 2025
Request for supplementary information (RSI) and extension of timetable adopted by the CHMP on:	30 January 2025
MAH's responses submitted to the CHMP on:	24 February 2025
Rapporteur preliminary assessment report circulated on:	25 March 2025
Joint Rapporteurs preliminary assessment report circulated on:	28 March 2025
PRAC Outcome	10 April 2025
CHMP members comments	14 April 2025
Rapporteur updated assessment report circulated on:	16 April 2025
CHMP Opinion	25 April 2025

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

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.

Claimed therapeutic indication

Cystadrops is currently indicated for the treatment of corneal cystine crystal deposits in adults and children from 2 years of age with cystinosis. With the current variation, the MAH sought an extension of the indication to include treatment of children from 6 months of age.

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.

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.

Clinical presentation, diagnosis

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.

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.

Eye drop solutions containing cysteamine can be used to reduce corneal cystine crystal accumulation.

2.1.2. 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. The product also contains 0.01% benzalkonium chloride (BAK) as a preservative.

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

The recommended dose is one drop in each eye, 4 times a day during waking hours. The recommended interval between each instillation is 4 hours. The dose could be decreased progressively (to a minimum total daily dose of 1 drop in each eye) depending on the results of ophthalmic examination (such as, corneal cystine crystal deposits, photophobia). The dose should not exceed 4 drops a day in each eye.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

The current variation relates to the extension of the indication of Cystadrops from 6 months to 2 years.

On 29 May 2008 the applicant submitted to the European Medicines Agency (EMEA) an application for a Paediatric Investigation Plan including a deferral and a waiver (EMEA-000322-PIP01-08-M06).

A positive Opinion of the Paediatric Committee on compliance (EMA/PDCO/334580/2023) with the Paediatric Investigation Plan (EMEA-C-000322-PIP01-08-M06) was granted in September 2023.

2.1.4. General comments on compliance with GCP

Study SCOB2, an open-label, single-arm, multicenter study to assess the safety of Cystadrops in paediatric cystinosis patients from 6 months to less than 2 years old was performed in compliance with Good Clinical Practice (GCP) as claimed by the applicant.

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

The Applicant has submitted a justification for not updating the ERA submitted in 2014, as the variation application concerns only the extension of the paediatric population from 6 months to 2 years of age. It is agreed that the addition of the very few patients ≤2 years will not meaningfully change the environmental exposure to mercaptamine why no further update is considered needed.

2.2.2. Discussion on non-clinical aspects

No new non-clinical data have been submitted in this application, which is considered acceptable.

The Applicant has submitted a justification for not updating the ERA submitted in 2014, as the variation application concerns only the extension of the paediatric population from 6 months to 2 years of age. It is agreed that the addition of the very few patients ≤2 years will not meaningfully change the environmental exposure to mercaptamine why no further update is considered needed.

2.2.3. Conclusion on the non-clinical aspects

There are no non-clinical objections to the approval of this extension of indication.

The updated data submitted in this application do not lead to a significant increase in environmental exposure further to the use of mercaptamine.

Considering the above data, mercaptamine is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

- Tabular overview of clinical studies

The clinical development for the initial MAA for Cystadrops consisted of 2 studies: one open-label, single-arm 5-year study where the dosing frequency was adapted based on response (study OCT-1) and one randomised, controlled superiority 3-months trial vs. a standard of care formulation of cysteamine (CH 0.10%) (study CHOC).

To support the current variation, the MAH submitted the final results of study CYT-C2-001, an open-label, single-arm, multicenter study to assess the safety of Cystadrops in paediatric cystinosis patients from 6 months to less than 2 years old (see Table 1). The previous studies are included for reference.

Table 1. Previous studies and final results of study CYT-C2-001

Study ID (Country)	Study Design and Objectives	Population	Treatment schedule	Duration of treatment
OCT-1	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.	60 months
CHOC study	Open label, randomised, comparative trial. The study had 2 parallel treatment-arms: CYSTADROPS and CH 0.10%. Primary objective: superiority of CYSTADROPS versus CH 0.10% for efficacy (primary endpoint = change in IVCM total score). Secondary objective: safety of CYSTADROPS (LADRs, AEs and SAEs; ocular parameters).	Patients of either sex and of any age, with corneal cystine crystal deposits, treated by topical cysteamine. Total enrolled: 32	The study had 2 parallel treatment arms: CYSTADROPS 0.55% and CH 0.10%. Both 4 instillations/eye/day for a period of 90 days.	3 months
Study ID (Country)	**Study Design and Objectives**	**Population**	**Treatment schedule**	**Duration of treatment**
CYT-C2-001	Single-arm, open-label, interventional, multicenter trial, lasted for 90 days (3 months). Primary objective: Safety of Cystadrops as measured by the incidence of: • Serious ocular adverse events (ocular SAEs) • Serious ADRs (SADRs) related to Cystadrops • All Adverse Events (AEs) that required temporary discontinuation/withdrawal of treatment (IMP) or unscheduled/emergency ophthalmic visit(s). Secondary Objective: Efficacy of Cystadrops by measuring ophthalmologic assessments (CCCS, photophobia and Best Corrected Visual Acuity [BCVA].	Patients aged from 6 months to less than 2 years old. Total enrolled: 5 Mean (± SD) age at inclusion: 18.0 (±4.7) months. Range: 13-23 months.	The treatment investigational product was Cystadrops (cysteamine or mercaptamine hydrochloride) 3.8 mg/mL eye-drop solution. 1 drop in each eye, 4 times a day during waking hours with a recommended interval between each instillation of 4 hours.	3 months

2.4. Clinical efficacy

2.4.1. Main study(ies)

Study CYT-C2-001

Open-label, single-arm, multicenter study to assess the safety of Cystadrops in pediatric cystinosis patients from 6 months to less than 2 years old.

Methods

This was a single-arm, open-label, interventional, multicenter trial, conducted in Europe to provide information regarding safety, and if assessable, efficacy of Cystadrops in paediatric patients with infantile nephropathic cystinosis aged from 6 months to less than 2 years old.

Patient participation was expected to last 90 days (3 months). Study visits included the following visits:

- The Inclusion visit (Day 1) during which parents or legally acceptable representatives were given 3 months' worth of treatment and a "Welcome pack". Investigators checked patients' inclusion/exclusion criteria, performed ophthalmic assessments, and collected demographics data, medical history, previous ophthalmic medications.
- A telephone call at Day 30 (+/- 4 days), during which Investigators assessed treatment compliance, collected concomitant ophthalmic medications and safety data.
- In case, parents or legally acceptable representatives contacted the Investigator during the study to express concerns regarding drug safety, unscheduled/emergency visits or telephone calls could be set up and recorded. During this visit, Investigators were to assess treatment compliance, performed ophthalmic assessments, and to collect information on concomitant ophthalmic medications and safety data.
- An EOS visit at Day 90 (+/- 4 days) during which parents or legally acceptable representatives were asked to bring back all unused and/or partially used vials of treatment. Investigators were to assess treatment compliance, performed ophthalmic assessments, and to collect information on concomitant ophthalmic medications and safety data. In addition, the patient termination form was to be completed.

Post-trial access (PTA) to the investigational medical product (IMP)

Considering that (1) patients could be adversely impacted by treatment discontinuation; (2) there was no alternative medicinal product available on the market; and (3) there was no alternative approved access to the investigational medicinal product (IMP, Cystadrops) before the patient was 2 years old, a procedure for post-trial access (PTA) to the IMP was set up when needed. Consequently, IMP could be provided by the site to parents and legally acceptable representatives of patients below 2 years of age at the time of EOS visit (Day 90) free of charge until the patient reached 2 years of age. Decision to offer continuation of treatment with the IMP was to be made by the Investigator for each patient at EOS visit (Day 90) based on an individual medical benefit/risk assessment for the concerned patient. Parents or legally acceptable representatives were to specifically consent to this PTA to IMP and related procedures. During the PTA to IMP period, only SADR were collected.

The schedule of assessments is shown below (Table 2).

Table 2. Schedule of assessments and procedures

	Inclusion	Treatment Period		End-of-study	Optional PTA to IMP[h]
Study Procedure	**Day 1**	**Day 30[d] [+/- 4 days]**	**Unscheduled/ Emergency visit(s) telephone call**	**Day 90 [+/- 4 days]**	**IMP delivery visit(s)[g]**
Informed consent	X	-	-	X[e]	-
Inclusion/exclusion criteria	X	-	-	-	-
Demographics	X	-	-	-	-
Medical history	X	-	-	-	-
Treatment compliance	-	X	X	X	-
Ophthalmic assessments[a]	X	-	X	X	-
Adverse event assessments	←	—	—	→	
SAE assessments[b]	←	—	—	—	→
Previous and Concomitant ophthalmic medications[c]	←	—	—	→	-
Study completion	-	-	-	X[f]	-
IMP delivery	X	-	-	X[g]	X[e]

IMP= Investigational Medicinal Product; PTA= Post-Trial Access; SAE=Serious adverse event

a. Ophthalmic assessments include: corneal cystine crystal score (CCCS), photophobia, and best corrected visual acuity (BCVA) of both eyes. Considering that these ophthalmic assessments can be difficult to perform in infants and toddlers and/or could cause them unnecessary distress, feasibility to measure and collect efficacy assessments was deferred to Investigators based on their clinical judgment.
b. For patients granted with PTA to Cystadrops®, Serious ADRs (Adverse Drug Reaction related to IMP) were to be collected from EOS visit (Day 90) until the last visit of the PTA to IMP period.
c. Ophthalmic medications received during the month preceding inclusion in the study were recorded
d. Day 30 visit was to be done over the telephone by the Investigator.
e. For patients who continued the treatment through PTA to IMP.
f. For patients who prematurely discontinued the study, Investigator was to complete the Patient Termination Form at the time of discontinuation. Otherwise, this form was to be completed the day of the EOS visit (Day 90).
g. Parents and legally acceptable representatives were requested to come to the study site to refill their IMP prescription. Visit frequency depended on site practice and Cystadrops® shelf-life. Last visit to the study site was to occur during the month the patient reaches 2 years of age.
h. If Investigator considered IMP beneficial for the patient, parents and legally acceptable representative of patients below 2 years of age at time of EOS visit (Day 90) could be provided with IMP free of charge at the site until the patient reaches 2 years of age.

Study participants

Inclusion criteria

Patients were to meet all inclusion criteria to be eligible for study participation.

1. Patient aged from 6 months to less than 2 years old.
2. Cystinosis diagnosed patients confirmed by the physician and with presence of corneal cystine crystal deposits assessed during ophthalmic examination.
3. Evidence of a signed and dated informed consent document indicating that parents/ legally acceptable representatives had been informed of all pertinent aspects of the study (if required by regulation).
4. Parents/ legally acceptable representatives who were willing to comply with regular visits and ophthalmic exams.

Exclusion criteria

Patients were not eligible for study participation if they met any of the exclusion criteria or were discontinued at the discretion of the Investigator in consultation with the medical monitor if they developed any of the exclusion criteria during the study.

1. Contraindications to any of the Cystadrops components.
2. Participation in another ophthalmic investigational study or intent to participate during the course of the study.
3. Any medical condition that would, in the opinion of the Investigator, interfere with the evaluation of the study objectives.

Treatments

The treatment investigational product was Cystadrops (cysteamine or mercaptamine hydrochloride) 3.8 mg/mL eye drop solution.

The same dose and regimen indicated in adults and children from 2 years of age with cystinosis was administered to the patients below the age of 2 included in this study: 1 drop in each eye, 4 times a day during waking hours with a recommended interval between each instillation of 4 hours. If the parents/legally acceptable representatives missed an instillation, the treatment was to be continued with the next instillation at the same dose and to not double doses to make up for the missed doses. The dose was not to exceed 4 drops a day in each eye.

Information related to prior ophthalmic medications received during the month preceding IMP initiation and concomitant ophthalmic medications received from IMP initiation was collected (name of product, start and stop dates, dose, and regimen) until EOS visit (Day 90).

Objectives

The primary objective of the study was to assess the safety profile of Cystadrops over a 90-day period as measured by the incidence of:

- Serious ocular adverse events (ocular SAEs)
- Serious ADRs (SADRs) related to Cystadrops
- All Adverse Events (AEs) that required temporary discontinuation/withdrawal of treatment (IMP) or unscheduled/emergency ophthalmic visit(s)

The secondary objective was to assess the efficacy of Cystadrops by measuring ophthalmologic assessments (CCCS, photophobia and Best Corrected Visual Acuity [BCVA]) after 90 days of treatment with Cystadrops when possible, considering the age of the patients.

Outcomes/endpoints

Primary (safety) endpoints

Occurrence of the following safety criteria between signature of the ICF and the End Of Study (EOS) visit (Day 90):

- Ocular treatment emergent SAEs
- Serious adverse drug reactions (SADRs) related to Cystadrops
- All AEs that required temporary discontinuation/withdrawal of treatment (IMP) or unscheduled/emergency ophthalmic visit(s)

Secondary (efficacy) endpoints

Ophthalmic assessments included corneal cystine crystal score (CCCS), photophobia, and best corrected visual acuity (BCVA) of both eyes. The assessments were to be collected at the inclusion visit (Day 1), EOS visit (Day 90) and possibly during unscheduled/emergency visit(s), if applicable.

Ophthalmologic assessments were consistent with those generally used for the management of patients with this disease and utilize widely accepted measures. However, considering that these ophthalmic assessments could be difficult to perform in infants and toddlers and/or could cause them unnecessary

distress, feasibility to perform these assessments was deferred to Investigators based on their clinical judgment.

The secondary efficacy endpoints included the following:

- Change from Day 1 (Inclusion) to Day 90 (EOS) in Corneal Cystine Crystal Score (CCCS),
- Change from Day 1 (Inclusion) to Day 90 (EOS) in photophobia score
- Change from Day 1 (Inclusion) to Day 90 (EOS) in best corrected visual acuity (BCVA)

Corneal Cystine Crystal Score

The density of corneal cystine crystals was to be assessed during slit-lamp examination by the Investigator, using the classification of Gahl et al. (Gahl et al, 2000, Table 3) called Corneal Cystine Crystal Score. This score ranges from 0.00 (clarity at the center) to 3.00 (greatest recognizable crystal density) in 0.25 increments. The Investigator was to take pictures of the cornea and keep them in medical file as source data. A decrease in CCCS over time corresponds to an improvement.

This classification system, created by Gahl and colleagues in 2000, is primarily based on the appearance and density of corneal cystine crystals observed through slit-lamp examination. This classification categorizes corneal cystine crystals into distinct grades based on their visibility:

Table 3. Gahl et al. classification

Score	Description
0.00	No crystals visible
0.25	Very few crystals
0.50	Few scattered crystals
0.75	Diffuse haziness; crystals difficult to individualize
1.00	Crystals easily seen, cornea still transparent
1.25	Crystals more numerous, some haziness of cornea
1.50	Dense crystal accumulation, significant haziness
1.75	Crystal deposits cover most of anterior cornea
2.00	Crystals throughout entire cornea, significant opacity
2.25	Dense crystal deposition, cornea becoming opaque
2.50	Cornea opaque, crystals difficult to visualize
2.75	Cornea completely opaque, crystals barely visible
3.00	Cornea completely opaque, crystals not visible

This classification helps in monitoring disease progression and guiding treatment decisions. Gahl's classification correlates well with other clinical markers of cystinosis severity, such as visual acuity and the presence of corneal complications. It has been widely used to assess the degree of crystal accumulation in patients with nephropathic cystinosis.

Photophobia score

The overall photophobia score for the two eyes was to be rated from 0 to 5 by the Investigator according to the cystinosis photophobia scale (Liang 2015, Table 4). A decrease in photophobia score over time corresponds to an improvement.

Table 4. Evaluation of photophobia

	Clinician-assessed evaluation of photophobia scaling
Grade 0	No photophobia under the slit-lamp beam even with the largest slit
Grade 1	Photophobia to moderate slit-lamp beam light
Grade 2	Photophobia to the lightest slit-lamp beam
Grade 3	Photophobia with inability to tolerate the blue slit-lamp beam
Grade 4	Photophobia requiring dark glasses. The patients is unable to open the eyes inside the illuminated consultation room
Grade 5	The patient is unable to open the eyes even inside the dark room

Reference: Liang H, Baudouin C, Tahiri Joutei Hassani R, Brignole-Baudouin F, Labbe A - Invest Ophthalmol Vis Sci. 2015 May; 56(5):3218-25.)

Photophobia in cystinosis shows a significant correlation with the density of corneal crystals. As corneal crystal deposition progresses with age, photophobia tends to increase correspondingly. It's important to note that while crystal density is a major factor, photophobia in cystinosis is also associated with other corneal changes:

1- Infiltration of inflammatory cells.

2- Corneal nerve damage.

3- Changes in corneal sensitivity.

All these are considered as late complications.

However, assessing photophobia in children aged 6 months to 2 years can be challenging due to their limited ability to communicate.

BCVA

BCVA was to be assessed in LogMAR units. A decrease in BCVA (in logMAR) over time corresponds to an improvement in visual acuity.

BCVA (in logMAR) is an accurate and standardized method of testing visual acuity, however testing visual acuity in children [even healthy individuals] of 6 months – 2 years of age is challenging.

Sample size

The planned number of patients was 5.

Randomisation

Not applicable.

Blinding (masking)

Not applicable.

Statistical methods

No formal hypotheses were tested. Continuous variables were to be summarized with standard descriptive statistics including means, standard deviations, medians and range. Categorical variables were to be summarized with frequencies and percentages.

Results

Participant flow

In total, 5 patients were enrolled in the study. All patients completed the study.

Recruitment

A total of 4 sites were initiated and participated in the study. In total, 5 patients were enrolled in the study: 1 patient was enrolled in Belgium, 1 in France, 2 in Italy, and 1 in the UK.

Conduct of the study

In total, 4 minor protocol deviations were reported in 3 patients: the time window of 90 days was not respected for 3 patients (98, 100, and 102 days with respective treatment duration 96, 99 and 87 days) and the protocol-prescribed dose was not followed for 1 patient (3 drops instead of 4 drops per day throughout the study period).

Baseline data

Patient demographic and baseline characteristics in the Safety (SAF) population are described in Table 5 below.

Table 5. Demographic and baseline characteristics (Safety Population)

Reference unit: Patient	All patients N=5
Country	
Belgium	1 (20.0%)
France	1 (20.0%)
Italy	2 (40.0%)
United Kingdom	1 (20.0%)
Sex	
Female	3 (60.0%)
Male	2 (40.0%)
Age at inclusion, in months	
N	5
Mean (SD)	18.0 (4.7)
Median	16.0
Min - Max	13.0 - 23.0
Age category at inclusion(1)	
Infant	5 (100.0%)
Age at visit D90, in months	
N	5
Mean (SD)	21.0 (4.7)
Median	19.0
Min - Max	16.0 - 26.0
Age category at visit D90(1)	
Infant	3 (60.0%)
Child	2 (40.0%)

(1) Infant: from 1 month to 23 months
(1) Child: from 24 months to 11 years

Numbers analysed

All 5 enrolled patients were included in the Safety Analysis Set (SAF population -patients who received at least one dose of the IMP) and 5 patients and 10 eyes were included in the Evaluable Set (patients/eyes who received at least one dose of the IMP and for whom both Inclusion visit [Day 1] and Day 90 were completed). No patients were excluded from the efficacy analyses.

Outcomes and estimation

Primary endpoint

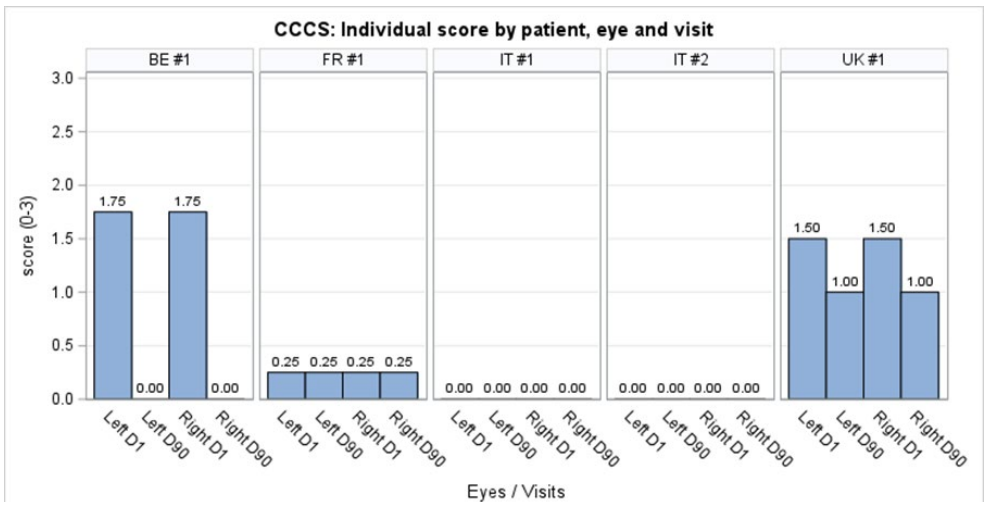
Safety results are described in section 2.5 (Clinical Safety).

Secondary endpoints (efficacy analyses)

1- <u>CCCS Corneal Cystine Crystals Score</u>

An individual bar graph of CCCS values overtime is presented in Figure 1 below.

Figure 1. Ophthalmic assessment: CCCS – Evaluable Eye Population



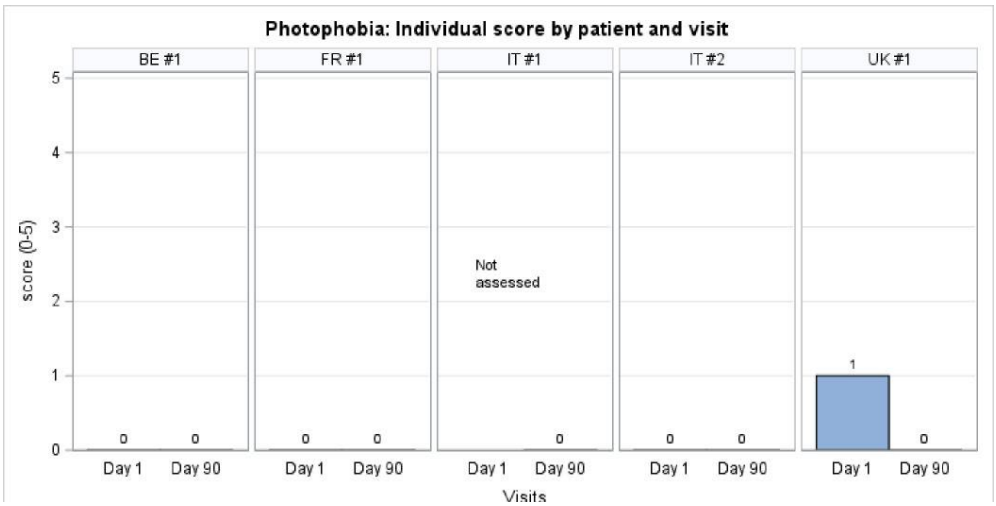
It should be noted that at time of inclusion, patients were expected to have crystals deposits (central or peripheral), while CCCS assessment by Gahl is only assessing central crystals.

CCCS could be considered the most relevant investigation of efficacy of Cystadrops in this young patient population. CCCS measurements were performed in all patients. Three of the 5 patients had a central CCCS above 0 in both eyes at Day 1, and in two of these patients, the CCCS had decreased in both eyes at Day 90, from 1.75 (crystals covering most of the anterior cornea) to 0 (no crystals) and from 1.5 (dense crystal accumulation, significant haziness) to 1.0 respectively. This is considered to provide support for the efficacy of treatment.

2- <u>Photophobia</u>

An individual bar graph of photophobia values over time is presented in *Figure 2* below.

Figure 2. Ophthalmic Assessment Photophobia – Evaluation Patient Population



At Day 1, photophobia was rated grade 0 (no photophobia under the slit-lamp beam, even with the largest slit) in 3 patients (60.0%), grade 1 (photophobia to moderate slit-lamp beam light) in 1 patient (20.0%). One patient was not assessed for photophobia at Day 1.

At Day 90, photophobia was rated grade 0 (no photophobia under the slit-lamp beam, even with the largest slit) for all 5 patients (100.0%).

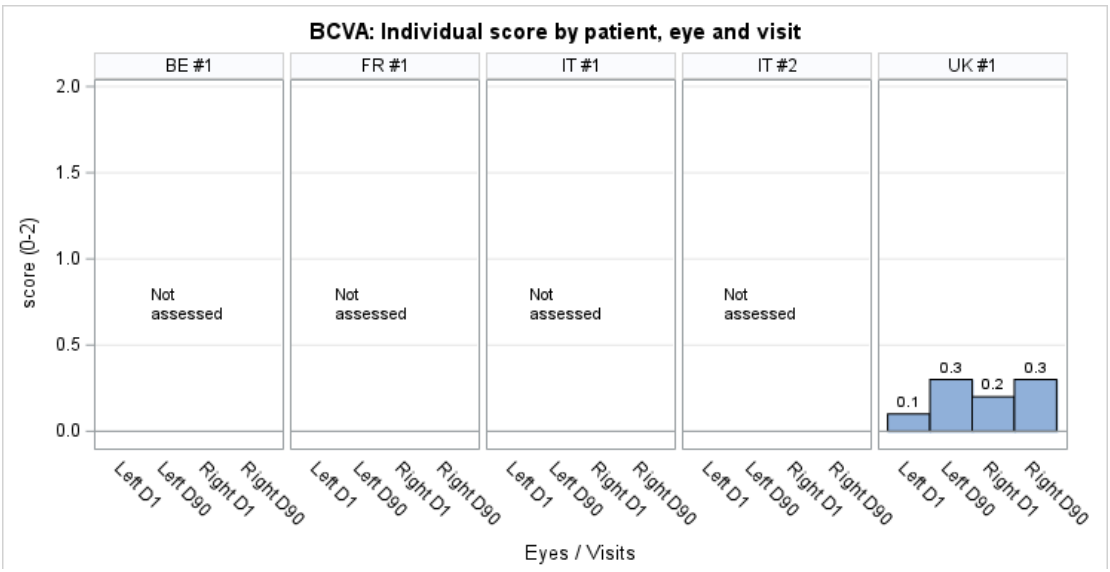
Photophobia is a symptom occurring later in ocular cystinosis, mostly in children older than 12 years of age, this is reflected in the results obtained in this study in that only one child had the symptom at Day 1 and photophobia resolved at the end of the study.

3- Best Corrected Visual Acuity (BCVA)

BCVA was assessed in 1 patient (2 eyes) at Day 1 and at Day 90. At Day 1, BCVA (in logMAR) was 0.2 for the right eye and 0.1 for the left eye. At Day 90, BCVA was 0.3 for both eyes.

An individual bar graph of BCVA values overtime (each eye) is presented below:

Figure 3. Ophthalmic Assessment: BCVA - Evaluable Patient Population



Visual assessment in children below 2 years of age can be challenging due to the limited attention span, inability to communicate verbally, the individual variations in developmental maturity at this age and cooperation issues, which make it difficult to perform a reliable testing of visual acuity.

In addition, interpreting the results of some tests like preferential looking could be difficult as it depends on the child's interest. Testing monocular vision can be challenging as the infant may object to having one eye occluded. It is therefore accepted that MAH cannot present adequate data on BCVA for patients of this age.

Ancillary analyses

Not applicable.

Summary of main study(ies)

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

2.4.2. Discussion on clinical efficacy

Cystinosis is a rare autosomal recessive disorder, characterized by the buildup of cystine within cells across various organs. Ocular involvement mainly characterised by deposition of cystine in the cornea.

The buildup of corneal crystals begins in infancy and is evident on slit-lamp examination in all nephropathic cystinosis patients by 16 months of age. There is progressive accumulation of corneal crystals with age, though at a variable rate. By the age of 12 years, most affected corneas show marked crystal formation.

Deposition of the crystals begins in the peripheral cornea, progressing towards the centre with age. The increase in crystal density culminates with a hazy cornea. The prevention of cystine accumulation in the cornea should therefore start at an early age, this would consequently preserve vision and avoid further complications.

Cystadrops (mercaptamine hydrochloride, also known as cysteamine hydrochloride) is currently authorised for the treatment of corneal cystine crystal deposits in adults and children from 2 years of age with cystinosis.

MAH has committed to conduct a study to assess Cystadrops safety and efficacy in patients from 6 months to less than 2 years old (study CYT-C2-001) as part of the agreed Paediatric Investigational Plan (PIP) adopted by the Paediatric Committee (PDCO) on 21 July 2017.

The current variation relates to the extension of the indication of Cystadrops to include infants from 6 months of age. In support, the MAH submitted the final results of study CYT-C2-001. The study was conducted in 5 patients (10 eyes) and the patients were observed for 90 days. Given the extreme low incidence rate of cystinosis the small number of patients is acceptable and comparable to the two previous studies with Cystadrops that recruited 8 subjects in OCT-1 and 32 subjects in CHOC, respectively.

The efficacy of Cystadrops was assessed by measuring CCCS (corneal cystine crystal score), photophobia and BCVA. Considering the age of the patients BVCA could only be evaluated in one patient and the results were not conclusive. Photophobia was observed in only one patient before starting the treatment and resolved at the end of the study. It should be considered that photophobia is a late symptom of this

condition and rarely seen at this age. Accordingly, data relating to visual acuity and photophobia could not be used to support the efficacy assessment.

The CCCS assessed density of central corneal cystine crystals during slit-lamp examination using the classification of Gahl. The CCCS measurements were performed in all patients. Three of the 5 patients had a central CCCS greater than 0 in both eyes at Day 1, and in two of these patients, the CCCS had decreased in both eyes at Day 90, from 1.75 (crystals covering most of the anterior cornea) to 0 (no crystals) and from 1.5 (dense crystal accumulation, significant haziness) to 1.0 respectively.

Considering the difficulty in assessing BCVA in children at this age and the late development of photophobia in this condition, CCCS measurements are considered the most reliable objective finding to assess the efficacy of Cystadrops in the current study. Unlike the CHOC and OCT-1 studies which both used confocal microscopy IVCM in addition to slit-lamp evaluation and OCT for evaluation of corneal crystals, the CYT-C2-001 study used only slit-lamp and photography to evaluate CCCS; this is acceptable as the evaluation with IVCM is not feasible in this age group.

A comprehensive natural history study by Gahl et al. (2000) demonstrated that even those infants in the first year of life who had absent or minimal corneal crystals, showed linearly increased CCCS with age, such that every patient had visible crystals by 16 months of age, and plateaued at a maximum of 3.00 by early adolescence. According to Gahl and colleagues, in patients with the classic infantile form, the crystals are visible from the age of 16 months onwards but can be visible earlier by an experienced ophthalmologist.

There is a lack of standardised guidelines and recommendations for detecting ocular cystinosis, patient care and follow-up assessments. The Ophthalmology Cystinosis Forum held in Berlin in 2017, where Pinxten et al. produced a document to guide scheduling of follow-up visits and a protocol for ophthalmological examination based on the experiences of the authors, there was a clear emphasis on early detection, treatment, monitoring, and follow-up of ocular cystinosis.

Early treatment with, and strict adherence to, cysteamine has a considerable impact on the long-term prognosis of ocular cystinosis.

The descriptive results obtained in study CYT-C2-001, showing the resolution of central corneal cystine crystals in 2 of the 3 patients within a treatment period of 90 days, support the use of Cystadrops in patients with corneal cystine crystal deposits at the age of 6 months to 2 years.

2.4.3. Conclusions on the clinical efficacy

The available clinical data in this rare disease support the conclusion that Cystadrops exerts clinical efficacy in cystinosis patients with corneal cystine crystal deposits at the age of 6 months to 2 years.

2.5. Clinical safety

Introduction

Based on previous studies, the AE profile of Cystadrops is characterized 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 these clinical trials were transient (resolved within 1 hour or less).

The primary objective of the current study was to assess the safety profile of Cystadrops in paediatric cystinosis patients from 6 months to less than 2 years old over a 90-day period as measured by the

incidence of ocular SAEs, SADRs related to Cystadrops, and AEs that required temporary discontinuation/withdrawal of treatment or unscheduled / emergency ophthalmic visit(s).

Patient exposure

The prescribed dose at inclusion was 1 drop 4 times per day per eye for all 5 patients. The administered dose at inclusion was 1 drop 4 times per day per eye in 4 patients (80.0%) and 1 drop 3 times per day per eye in 1 patient (20.0%; reason for dose adjustment was "practical reasons / to ensure a better compliance").

Dose was adjusted in 1 patient (20.0%) at the time of inclusion. Cystadrops treatment was not interrupted in any patients during the study.

Missed instillations were reported in 3 patients (60.0%) during the study. The reason of missed instillations was difficulty in administration of Cystadrops in 2 (40.0%) patients (one patient missed 3 instillations and the other missed 40 instillations ["instillations missed during whole study/patient refused on occasions some instillations"]), and logistic reasons in one patient (20.0%; 3 missed instillations).

Patient exposure and treatment adherence is summarized in Table 6 below.

Table 6. Exposure and compliance (Safety Population)

Reference unit: patient	All patients N=5	
Prescription at inclusion		
1 drop 4 times/per day per eye	5	(100.0%)
Administration at inclusion		
1 drop 3 times/per day per eye	1	(20.0%)
1 drop 4 times/per day per eye	4	(80.0%)
Average daily dose (drop/day)		
N	5	
Mean (SD)	3.8 (0.4)	
Median	4.0	
Min - Max	3.0 - 4.0	
Reason for Adjustment		
PRACTICAL REASONS / TO ENSURE A BETTER COMPLIANCE	1	(20.0%)
Missed Instillations during study		
No	2	(40.0%)
Yes	3	(60.0%)
# Missed days		
0	4	(80.0%)
1	1	(20.0%)
# Missed instillations		
3	1	(20.0%)
7	1	(20.0%)
40	1	(20.0%)
Reason of missed instillations		
Difficulty to administer Cystadrops	2	(40.0%)

Other reason	1	(20.0%)
Exposure duration, in days		
N	5	
Mean (SD)	91.6 (5.5)	
Median	89.0	
Min - Max	87 – 99	
Compliance, in %		
N	5	
Mean (SD)	89.7 (14.9)	
Median	97.2	
Compliance by category		
< 80%	1	(20.0%)
80-120%	4	(80.0%)

Adverse events

No ocular SAEs, no SADRs related to Cystadrops, and no AEs that required temporary discontinuation / withdrawal of Cystadrops or unscheduled/emergency ophthalmic visit(s) or call(s) were reported during the study (see Table 7 below).

Table 7. Primary safety analysis: Overall Summary of Adverse Events (Safety Population

	Type of AEs	All patients N=5	
		NAE (1)	n (2) % (3)
Primary analysis*	Serious ocular TEAEs	0	0 (0%)
	Serious Drug-related TEAE**	0	0 (0%)
	AEs with temporary discontinuation/withdrawal of study drug	0	0 (0%)
	AEs requiring unscheduled/emergency ophthalmic visit	0	0 (0%)

(1)→Number·of·protocol·deviations¶

(2)····Number·of·patients·with·at·least·one·deviation¶

(3)····100*n/N¶

No new safety signals were detected during the study as all local AEs reported were consistent with the data listed in the Investigators' Brochure. No other reportable information (ORI) was reported during the study. Overall, 6 TEAEs were reported in 2 (40.0%) patients, including 5 TEAEs reported in 2 patients during the study (before Day 90).

All TEAEs were mild. The overall summary of adverse events is presented in Table 8 below:

Table 8. Summary of Adverse Events (Safety Population)

Type of AEs		All patients N=5		
		NAE (1)	n (2)	% (3)
AE*	**ALL**	**6**	**2**	**(40%)**
	Severe Adverse Events	0	0	(0%)
	Serious Adverse Events	0	0	(0%)
	Deaths	0	0	(0%)
	Drug-related AE**	3	2	(40%)
	Serious Drug-related AE**	0	0	(0%)
	AEs leading to study drug change	0	0	(0%)
All TEAE	**ALL**	**6**	**2**	**(40%)**
	Severe Adverse Events	0	0	(0%)
	Serious Adverse Events	0	0	(0%)
	Deaths	0	0	(0%)
	Drug-related AE*	3	2	(40%)
	Serious Drug-related AE*	0	0	(0%)
	AEs leading to study drug change	0	0	(0%)
TEAE - before D90	**ALL**	**5**	**2**	**(40%)**
	Severe Adverse Events	0	0	(0%)
	Serious Adverse Events	0	0	(0%)
	Deaths	0	0	(0%)
	Drug-related AE*	3	2	(40%)
	Serious Drug-related AE*	0	0	(0%)
TEAE - after D90	**ALL**	**1**	**1**	**(20%)**
	Severe Adverse Events	0	0	(0%)
	Serious Adverse Events	0	0	(0%)
	Deaths	0	0	(0%)
	Drug-related AE*	0	0	(0%)
	Serious Drug-related AE*	0	0	(0%)

(1) Number of protocol deviations

(2) Number of patients with at least one deviation

(3) 100*n/N

TEAEs are presented by SOC and PT in Table 9 below. Two patients experienced 3 TEAEs related to Cystadrops. Drug-related TEAEs consisted of eye pruritus (2 patients) and eye discharge (1 patient).

Table 9. Treatment emergent adverse events by SOC and PT – Safety Population

System Organ Class	Preferred Term	All patients N= 5		
		NAE (1)	n (2)	% (3)
ALL - before Day 90		**5**	**2**	**(40%)**
. Eye disorders		**3**	**2**	**(40%)**
	Eye discharge	1	1	(20%)
	Eye pruritus	2	2	(40%)
. Infections and infestations		**1**	**1**	**(20%)**
	Nasopharyngitis	1	1	(20%)
. Respiratory, thoracic, and mediastinal disorders		**1**	**1**	**(20%)**
	Cough	1	1	(20%)
ALL - after Day 90		**1**	**1**	**(20%)**
. Infections and infestations		**1**	**1**	**(20%)**
	Conjunctivitis	1	1	(20%)

(1) Number of Adverse Events

(2) Number of patients with at least one adverse event

(3) 100*n/N

Two patients had eye pruritis, which is already covered by the current SmPC.

Regarding eye discharge, this concerns one patient with conjunctivitis that did not require treatment but was considered at least possibly related to study drug by the investigator.

Serious adverse event/deaths/other significant events

None.

Laboratory findings

Not applicable.

Discontinuation due to adverse events

No patients were discontinued due to adverse events.

Post marketing experience

Post-Authorization Safety Study (PASS) CYT-DS-001

An international, single arm, open-label, longitudinal, post-authorization safety study to assess the safety of Cystadrops in paediatric and adult cystinosis patients in long term use is being performed. The study was designed as a descriptive and longitudinal single-arm study of patients treated with Cystadrops to evaluate the safety profile of Cystadrops in long-term use and in a real-world setting; especially to closely monitor and evaluate the important potential and identified risks as described in the risk management plan and to identify any new safety signals.

This study, currently ongoing, will support the analysis of the risk/benefit balance of Cystadrops. The latest interim study report presents results from an interim analysis performed on data from patients enrolled before 22 January 2024 (date of data cut-off). In total, 68 patients (out of approximately 70 patients planned) were enrolled in the study at time of data cut-off (Last Patient In: 20 February 2023): 22 in France, 12 in Germany, 29 in Italy, and 5 in the Netherlands. All 68 enrolled patients were included in the Safety Population.

Overall, 12 AEs occurred in 11 patients (16.2%) during the study. Of these 12 AEs, 6 ADRs suspected to be related to Cystadrops were reported in 5 patients (7.4%). ADRs consisted of abnormal sensation in the eye (4 AEs in 4 patients [5.9%]) and eye irritation (2 AEs in 2 patients [2.9%]). One ADR of abnormal sensation in the eye led to permanent discontinuation of Cystadrops.

Overall, the observed AEs were consistent with the known safety profile of Cystadrops. No new safety concerns were observed.

This post-authorization non-interventional study is included in the RMP as an additional pharmacovigilance activity. The data collection is projected to continue until March 2028 with a final CSR due within one year after database lock.

Overall post-marketing experience

The 7th PSUR assessment report for Cystadrops summarises the safety information collected from worldwide sources by the MAH from 19 January 2021 to 18 January 2024. Cumulatively, 28 subjects have been

exposed to Cystadrops in MAH-sponsored clinical trials. The estimated exposure from post-marketing experience was 4,812.9 patient-years during the reporting interval and 8,087.4 patient-years cumulatively.

According to the most recent PSUSA assessment conclusions, the review of data from cumulative and interval summary tabulations of adverse drug reactions from post-marketing data sources provided by the MAH did not identify any new safety concern leading to further actions. The most frequently reported ADRs remain in accordance with the current knowledge of the safety profile of Cystadrops or may be attributed to the underlying medical condition. The review of safety data from clinical trials, post-marketing experience, non-interventional studies and literature did not reveal any new safety information leading to further actions related to Cystadrops.

2.5.1. Discussion on clinical safety

The safety database generated by the CYT-C2-001 study is limited and consists of only 5 patients owing to the rarity of Cystinosis and because of the young age of patients included in this study (from 6 months to 2 years of age).

The Applicant has reported ocular and non-ocular AEs; the focus is on ocular safety as most 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, if any, is expected to be negligible.

The study reported no ocular SAEs, no SADRs related to Cystadrops, and no AEs that required temporary discontinuation / withdrawal of Cystadrops or unscheduled/emergency ophthalmic visit(s) or call(s).

It is mentioned that missed instillation in 2 (40.0%) patients was due to difficulty in administration of Cystadrops, and other reason in one patient (20.0%), it is not further explained where this was patient/ parent related or due to the fact that the bottle itself is tricky to use. Of note, increased risk of infection and medication error due to device assembly failure is already included in the RMP as a potential risk and will be further studied in the ongoing PASS.

The choice of benzalkonium chloride (BAK) as preservative has been previously discussed at the original approval of Cystadrops, as no new relevant safety information has emerged, no further actions are required.

The safety profile of Cystadrops has been previously evaluated in two other studies in different age groups, which included 8 patients from the OCT-1 study and 31 patients from the CHOC study, of whom 15 were treated with Cystadrops. The overall AE profile was predominated by a high incidence of generally transient reactions like stinging, blurring, irritation, itching, redness. These were transient and associated with instillation of the eye drops, and eventually occurred in all patients treated with Cystadrops as compared to 69% with placebo. In CHOC study the following ocular AE occurred in comparison to placebo; ocular hyperaemia (27% treated; 31% placebo), eye pain (7% treated; 19% placebo), eye irritation (13% treated; 12% placebo), vision blurred (0% treated; 19% placebo), pruritis (0% treated; 12% placebo), keratitis (0% treated; 12% placebo). In OCT-1 study 1% had a worsened corneal neovascularization (the relation to treatment was though considered uncertain).

In the current study, two patients experienced 3 TEAEs related to Cystadrops. Drug-related TEAEs consisted of eye pruritus (2 patients) and eye discharge (mild conjunctivitis) (1 patient).

Post Marketing Data

Cystadrops have been approved and used for treatment of ocular cystinosis in adults and children above 2 years of age since Jan 2017.

An international post-authorization safety study (CYT-DS–001) to assess the safety of Cystadrops in long term use is being performed. The study was designed as a descriptive and longitudinal single-arm study of patients treated with Cystadrops. This study, currently ongoing, will support the analysis of the benefit/risk balance of Cystadrops. The latest interim study report presents results from an interim analysis performed on data from patients enrolled before 22 January 2024 (date of data cut-off). Overall, the observed AEs were consistent with the known safety profile of Cystadrops. No new safety concerns were observed.

According to the most recent PSUSA assessment conclusions, the review of data from cumulative and interval summary tabulations of adverse drug reactions from post-marketing data sources provided by the MAH did not identify any new safety concern leading to further actions.

2.5.2. Conclusions on clinical safety

No significant new information on safety concerns has been identified during the study conducted on patients 6 months to 2 years of age. The safety profile of Cystadrops have been evaluated for many years, and the overall clinical safety profile is considered acceptable.

2.5.3. PSUR cycle

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.

2.6. Risk management plan

The MAH submitted/was requested to submit an updated 2.2 RMP version with this application.

The PRAC considered that the risk management plan version 2.2 is acceptable.

Safety concerns

Table 10. Summary of 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 EDLS • Increased risk of infection and medication error due to device assembly failure
Missing information	• Long term safety

BAK=benzalkonium chloride; EDLS=Ehlers-Danlos like syndrome.

Pharmacovigilance plan

Table 11. Ongoing and planned additional pharmacovigilance activities

Study title Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 3 – Required additional pharmacovigilance activities				
Study CYT-DS-001 Open-label, longitudinal post-authorisation safety study to assess safety of Cystadrops® in paediatric and adult cystinosis patients in long-term use. Ongoing	To assess and characterise the long-term safety of Cystadrops in paediatric and adult patients with cystinosis, who were followed-up for 5 years.	• Severe eye irritation • Punctate keratopathy and /or toxic ulcerative keratopathy (due to BAK) • Corneal neovascularisation • Ocular manifestation of EDLS • Increased risk of infection and medication error due to device assembly failure • Long-term safety	Ethics submission.	November 2018.
			Start of data collection.	January 2020.
			End of enrolment.	December 2021.
			End of data collection.	March 2028
			Study Progress Report.	Every 2 years
			Final Report of study results.	Approximately <1 year after database lock.

BAK=benzalkonium chloride; EDLS=Ehlers-Danlos like syndrome.

Risk minimisation measures

Table 12. Description of routine minimisation measures by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risk		
Severe eye irritation	Routine risk minimisation measures: SmPC Section 4.4 and 4.8. PL Section 2 and 4. Section 2 of the PL for Cystadrops recommends speaking to a doctor if abnormal eye sensation, stinging or pain in the eye occurs. Section 3 of the PL advises that patients remove excess medicine around the eye with a moist tissue to avoid potential irritation. Legal status: Subject to restricted medical prescription. Treatment should be supervised by a physician experienced in the management of cystinosis. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: PASS (Study CYT-DS-001).
Important potential risks		
Punctate keratopathy and/or toxic ulcerative keratopathy (due to BAK)	Routine risk minimisation measures: SmPC Section 4.4. As BAK has been reported to cause punctate keratopathy and/or toxic ulcerative keratopathy, Section 4.4 of the SmPC notes that monitoring is required. Legal status: Subject to restricted medical prescription on. Treatment should be supervised by a physician experienced in the management of cystinosis. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: PASS (Study CYT-DS-001).

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Corneal neovascularisation	Routine risk minimisation measures: Legal status: Subject to restricted medical prescription . Treatment should be supervised by a physician experienced in the management of cystinosis. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: PASS (Study CYT-DS-001).
Ocular manifestations of EDLS	Routine risk minimisation measures: Legal status: Subject to restricted medical prescription. Treatment should be supervised by a physician experienced in the management of cystinosis. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: PASS (Study CYT-DS-001).
Increased risk of infection and medication error due to device assembly failure	Routine risk minimisation measures: SmPC Section 6.6. PL Section 3. Section 6.6 of the SmPC and Section 3 of the PL include notes on how to use Cystadrops and advise that patients wash their hands carefully in order to avoid microbiological contamination of the content in the vial. Section 3 of the PL also includes a QR code linked to a video advising how to use Cystadrops. Legal status: Subject to restricted medical prescription. Treatment should be supervised by a physician experienced in the management of cystinosis. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: PASS (Study CYT-DS-001).

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Missing information		
Long-term safety	Routine risk minimisation measures: Legal status: Subject to restricted medical prescription. Treatment should be supervised by a physician experienced in the management of cystinosis. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: PASS (Study CYT-DS-001).

BAK=benzalkonium chloride; EDLS=Ehlers-Danlos like syndrome; PASS=post-authorisation safety study; PL=Package Leaflet; SmPC=Summary of Product Characteristics.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC have been updated. The Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to update Annex II of the PI and the list of local representatives in the Package Leaflet as detailed in the recommendations section above.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

Considering that the variation concerns the extension of the paediatric population from 6 months to 2 years of age and modifies only the section related to the indication in the package leaflet, the MAH considers that an update of the readability test is not relevant because the readability is not affected by this change.

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 and unmet medical need

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 (Cystadrops) which are approved for use in adults and children from 2 years of age. The original 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.

However, there is no available approved treatment for children below 2 years of age. This delay in treatment may lead to serious damage to the cornea and cause eventually unnecessary unfavourable visual prognosis.

3.1.3. Main clinical studies

To support the current variation, the MAH conducted an open-label, single-arm, multicenter study (Study CYT-C2-001) (see EMEA-000322-PIP01-08-M06) to assess the safety of Cystadrops in paediatric cystinosis patients from 6 months to less than 2 years old (n=5).

3.2. Favourable effects

CCCS

Cystinosis-diagnosed patients confirmed by the physician and with presence of corneal cystine crystal deposits assessed during ophthalmic examination were included. As per Gahl classification, the *central* assessment of CCCS in both eyes (right and left) was rated from 0 to 3 by the Investigator. A decrease in CCCS over time corresponds to an improvement. Three of the 5 patients had a central CCCS greater than 0 in both eyes at Day 1, and in two of these patients, the CCCS had decreased in both eyes at Day 90, from 1.75 (crystals covering most of the anterior cornea) to 0 (no crystals) and from 1.5 (dense crystal accumulation, significant haziness) to 1.0 respectively.

At Day 1, CCCS was 0 in 4 (40.0%) evaluable eyes, 0.25 in 2 (20.0%) evaluable eyes, 1.50 in 2 (20.0%) evaluable eyes, and 1.75 in 2 (20.0%) evaluable eyes. It should be noted that at time of inclusion, patients were expected to have crystals deposits (either central or peripheral), while CCCS assessment by Gahl is only assessing central crystals. At Day 90, CCCS was 0 in 6 (60.0%) evaluable eyes, 0.25 in 2 (20.0%) evaluable eyes, and 1.00 in 2 (20.0%) evaluable eyes.

Photophobia

As per the protocol photophobia scale, overall photophobia score for the two eyes was rated from 0 to 5 by the Investigator. A decrease in photophobia score over time corresponds to an improvement. At Day 1, photophobia was rated grade 0 (no photophobia under the slit-lamp beam even with the largest slit) in 3 patients (60.0%), grade 1 (photophobia to moderate slit-lamp beam light) in 1 patient (20.0%). One patient was not assessed for photophobia at Day 1. At Day 90, photophobia was rated grade 0 (no photophobia under the slit-lamp beam even with the largest slit) for all 5 patients (100.0%).

BCVA

The mean BCVA at the time of inclusion (Day 1) was 0.15 (logMAR) and 0.30 (logMAR) at Day 90. Some ophthalmological assessments cannot be performed in infants, and particularly the measurement of visual acuity, which led to the collection of data of 1 patient out of 5. A decrease in BCVA (in logMAR) overtime corresponds to an improvement in visual acuity. BCVA was assessed in 1 patient (2 eyes) at Day 1 and at Day 90. At Day 1, BCVA (in logMAR) was 0.2 for the right eye and 0.1 for the left eye. At Day 90, BCVA was 0.3 for both eyes.

3.3. Uncertainties and limitations about favourable effects

The present study had a single-arm, open-label design and included data from only 5 patients. Due to the very young, targeted population, the impossibility to perform some ophthalmological assessments such as visual acuity measurement did not allow to conclude on any potential impact of the treatment on BCVA as only 1 patient was evaluated. IVCM is not feasible for this age group and photophobia occurs usually later in the course of the disease. Accordingly, data relating visual acuity and photophobia could not be used to assess efficacy in this age group.

This is the first study describing the efficacy and safety of Cystadrops in cystinosis patients aged 6 months to less than 2 years. No comparison could be made to other studies for this age group.

3.4. Unfavourable effects

In the SAF population, 2 patients (40.0%) experienced 6 AEs. Out of 6 AEs, 5 events were reported during the study (before Day 90) and 1 event was reported after Day 90. Two patients (40.0%) experienced 6 TEAEs and 2 patients (40.0%) experienced 3 TEAEs that were considered at least possibly related to Cystadrops. This included 2 mild events of eye pruritus and 1 mild event of eye discharge. No serious TEAEs were reported during the study. No AEs leading to study drug change (increase/reduction of dose) or study drug discontinuation were reported. All TEAEs reported during the study were mild in severity.

3.5. Uncertainties and limitations about unfavourable effects

The safety database generated by the current study is very limited and consists of 5 patients, patients were followed up for 90 days. Long-term experience in this young age group is thus lacking.

3.6. Benefit-risk assessment and discussion

3.6.1. Importance of favourable and unfavourable effects

Cystadrops has been approved in the EU since 2016 for the treatment of adults and children above the age of 2 years. It has showed efficacy in reducing corneal crystals formation reducing patient-burden and alleviating their symptoms. In addition, the dosing frequency is regarded beneficial compared to other previous formulations, improving compliance.

A comprehensive natural history study by Gahl et al. (2000) demonstrated that even those infants in the first year of life who had absent or minimal corneal crystals, showed linearly increased CCCS with age, such that every patient had visible crystals by 16 months of age, and plateaued at a maximum of 3.00 by early adolescence. According to Gahl and colleagues, in patients with the classic infantile form, the crystals are visible from the age of 16 months onwards but can be visible earlier by an experienced ophthalmologist.

According to Shams et al (2014) the buildup of corneal crystals begins in infancy and is evident on slit-lamp examination in all nephropathic cystinosis patients by 16 months of age. There is progressive accumulation of corneal crystals with age, albeit at a variable rate. By the age of 12 years, most affected corneas evince marked crystal formation.

Deposition of the crystals begins in the peripheral cornea, progressing centripetally with age. The increase in crystal density culminates with a hazy cornea, which can occasionally be seen by the naked eye in older untreated patients.

The aggregation of corneal crystals is typically asymptomatic initially, though most patients develop photophobia within the first decade of life, with severity varying with ambient light levels, and some experiencing associated blepharospasm. Superficial punctate keratopathy, foreign body sensation, and pain have also been reported, predominantly in older patients. This is thought to be secondary to crystals interrupting Bowman’s membrane, inciting inflammation within the epithelium and basement membrane. There has also been documentation of loss of contrast sensitivity, decreased corneal sensation, increased glare, and corneal thickening in patients with nephropathic cystinosis.

As there is no spontaneous regress of crystal nor a fluctuation of symptoms in the natural course of the disease, there is a rational for treating infants with ocular cystinosis below the age of 2 years. However, there is currently no approved treatment for children with ocular cystinosis below 2 years of age. This lack of treatment options for young infants can potentially result in severe corneal damage and lead to poor visual outcomes. Delayed intervention in these cases may cause permanent vision impairment, as the child's visual system is still developing.

Although there is a lack of standardised guidelines and recommendations for detecting and treating ocular cystinosis, there is consensus that early treatment with, and strict adherence to, cysteamine has a considerable impact on the long-term prognosis of ocular cystinosis. This was agreed on during the Ophthalmology Cystinosis Forum held in 2017.

Early detection significantly improves the long-term prognosis of ocular cystinosis by enabling prompt initiation of treatment, which can prevent or delay many clinical manifestations of the disease. The impact of early detection and treatment on ocular cystinosis prognosis is substantial.

The MAH is now applying for an extension of the indication to include children from the age of 6 months.

The CYT-C2-001 study was an open-label, single-arm, multicenter study with the primary aim to assess safety of Cystadrops in paediatric cystinosis patients from 6 months to less than 2 years old (n=5).

The study results indicate that Cystadrops can reduce corneal crystals formation (CCCS) and photophobia in this patient group. Further, a reduction of corneal crystals is not expected without treatment.

In addition, the pathophysiology of the disease is expected to be similar in all age groups and therefore, an extrapolation of results in older age groups generated in the previously conducted CHOC study to children below the age of 2 years seems reasonable.

The treatment with Cystadrops was shown to be safe and well-tolerated as only a few mild AEs and no SAEs were reported in this study. Also, no AEs that required temporary discontinuation or withdrawal of Cystadrops nor unscheduled/emergency ophthalmic visit(s) were reported during the study. No new safety signals were detected.

These safety results are consistent with the previous 3-month CHOC study and the recommended dosing regimen is the same for all age groups. Also, an international post-authorization safety study (CYT-DS–001) to assess the safety of Cystadrops in long term use is being performed. The study was designed as a descriptive and longitudinal single-arm study of patients treated with Cystadrops with the aim to assess and characterise the long-term safety of Cystadrops in paediatric patients from 2 years of age and adults with cystinosis, to be followed-up for 5 years. Data collection started in January 2020 and the end of data collection is estimated to be in the first quarter of 2028. This ongoing study will provide additional safety data for Cystadrops. The latest interim study report presented results from an interim analysis performed on data from patients enrolled before 22 January 2024 (date of data cut-off). Overall, the observed AEs were consistent with the known safety profile of Cystadrops. No new safety concerns were observed.

According to the most recent PSUSA assessment conclusions, the review of data from cumulative and interval summary tabulations of adverse drug reactions from post-marketing data sources provided by the MAH did not identify any new safety concern leading to further actions.

Altogether, based on the existing knowledge in terms of the aetiology and pathophysiology of the disease, its manifestations and its progressive nature, as well as the mechanism of action of Cystadrops and the fact that the proposed treatment regimen is the same as in currently approved populations, it is viewed that a similar response to Cystadrops is to be anticipated in the age group of 6 months to 2 years of age as compared to older patients.

3.6.2. Balance of benefits and risks

The clinical data from study CYT-C2-001 in cystinosis patients aged 6 months – 2 years indicated that Cystadrops can reduce corneal cystine crystal deposits.

No new safety concerns were observed in study CYT-C2-001. Although the safety database for this young age group is very limited, the rarity of the disease should be taken into account. There is also support from the previously conducted studies in adults and children over 2 years of age where the safety profile was found to be acceptable.

Virtually all cystinosis patients are treated with oral administration of cysteamine to treat cystine accumulation in non-corneal tissues. Early detection significantly improves the long-term prognosis of ocular cystinosis by enabling prompt initiation of treatment, which can prevent or delay many clinical manifestations of the disease. The impact of early detection and treatment on ocular cystinosis prognosis is substantial. The standard approach to treat cystine crystal deposits in the cornea (outside Cystadrops) may otherwise include ex-tempore prepared eye drops solutions containing cysteamine.

The MAH was provided with comments to the product information, and these have been adequately addressed. Other concerns related to RMP have also been addressed.

The CHMP views that the current data, although limited, are sufficient to conclude that Cystadrops exerts clinical efficacy in cystinosis patients 6 months – 2 years of age with corneal cystine crystal deposits, and with acceptable safety.

3.7. Conclusions

The overall B/R of Cystadrops is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II and IIIB

Extension of indication to include treatment of children from 6 months of age for Cystadrops, based on final results from study CYT-C2-001. This is an open-label, single-arm, multicenter study to assess the safety of Cystadrops in paediatric cystinosis patients from 6 months to less than 2 years old. As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 2.2 of the RMP has also been submitted. In addition, the MAH took the opportunity to update Annex II of the PI and the list of local representatives in the Package Leaflet.

The variation leads to amendments to the Summary of Product Characteristics, Annex II and Package Leaflet and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I, II and IIIB and to the Risk Management Plan are recommended.

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

Risk management plan (RMP)

The Marketing authorisation holder (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.

In addition, 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.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0019/2022 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.