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# The use of eyedrops in cystinosis: Panel discussion

I.Casteels
University Hospitals Leuven, Belgium

# Importance of early treatment of cystinosis

**1978: introduction of cysteamine**
**1994: FDA approval as Cystagon®**

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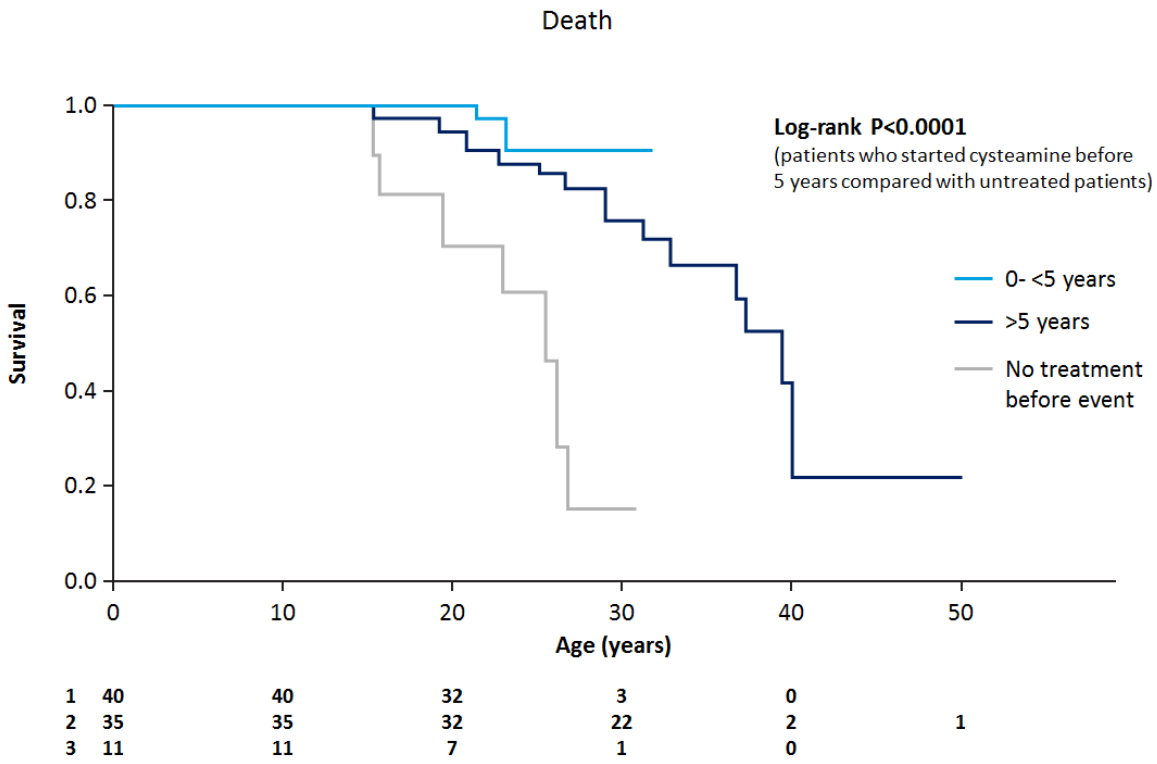
# Cysteamine therapy: better general prognosis

**Death according to the age at start of cysteamine treatment (before or after 5 years, or not treated)**




Brodin-Sartorius A, et al. Kidney International 2011;81(2):179–89.

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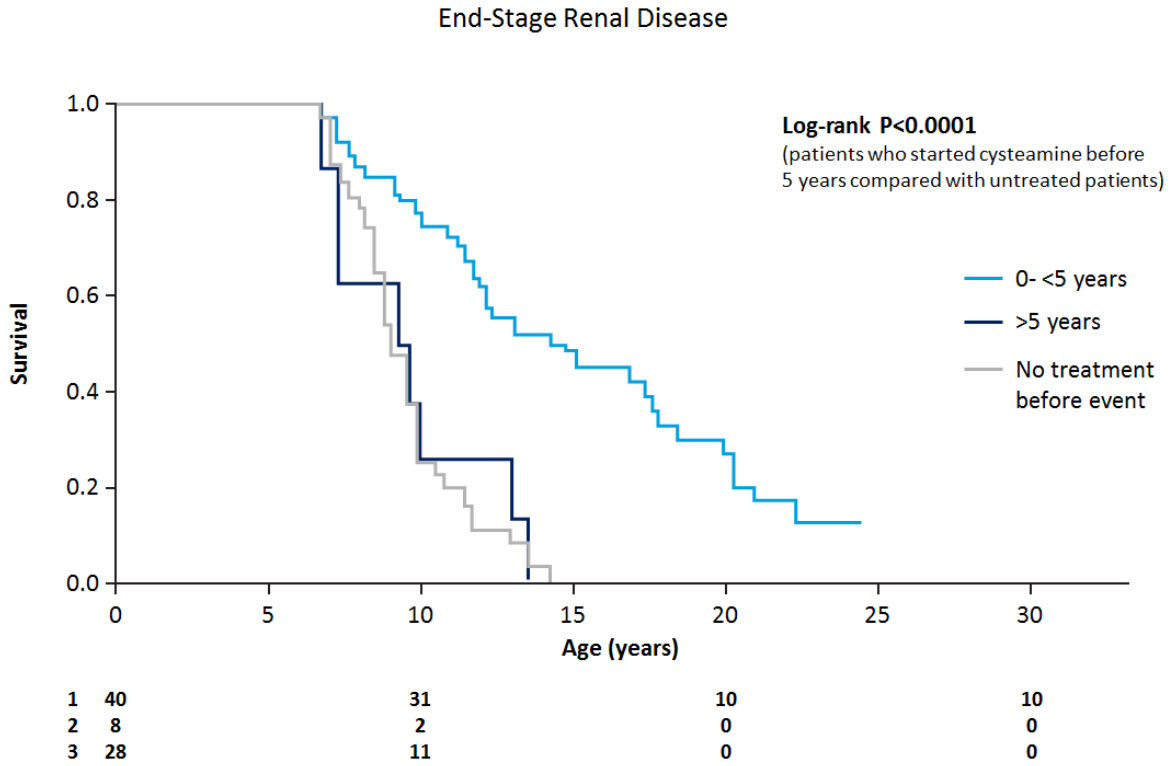
# Cysteamine decreases incidence of ESRD

## ESRD according to age at start of cysteamine treatment




ESRD, end-stage renal disease.

Brodin-Sartorius A, et al. Kidney International 2011;81(2):179–89.

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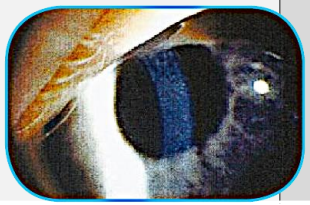
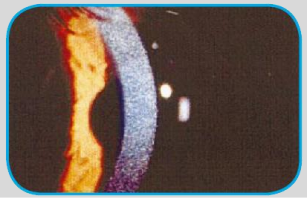
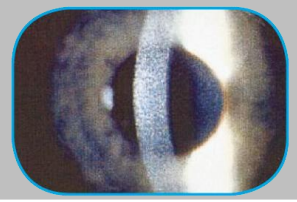
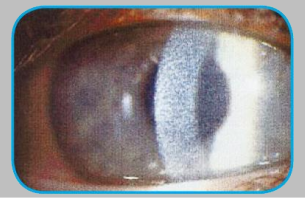
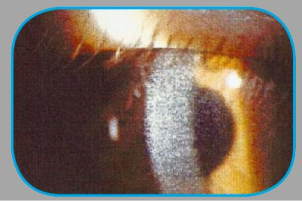
# Renal and extra-renal sequelae

| | <1 year | 1–2 years | 3–4 years | 7–10 years | Puberty | 2nd & 3rd decades of life |
|---|---|---|---|---|---|---|
| **Age-dependent general signs and symptoms** | Failure to thrive, rickets, growth disorders, light hair and blue eyes in Caucasian patients[1] | | | Severe symptoms, thyroid insufficiency (50%)[2] | Delayed sexual maturation, Hypogonadism[3] | Symptomatic CNS involvement (2%), CNS calcification (15%), myopathy (20%), diabetes mellitus, liver disease, male hypogonadism (70%), pulmonary dysfunction (100%)[3,4] |
| **Age-dependent nephrological signs and symptoms** | Fanconi syndrome at 6 to 12 months (95%)[2] | Polyuria, polydipsia[5], progressive reduction of the glomerular filtration rate, Fanconi syndrome[3] | Progressive renal failure; final stage of renal insufficiency in the first decade of life (ESRD)[5] | Progressive renal failure; final stage of renal insufficiency in the first decade of life[6] | Terminal renal failure (prevalence chronic renal failure 95%), kidney transplant[2] | |

1. Gahl WA, et al. New York: McGraw-Hill 2000;5085–108; 2. Gahl WA, et al. NEJM 2002;347(2):111–21; 3. Elenberg E, et al. Medscape 2013; Available from: http://emedicine.medscape.com/article/981650-overview;
4. Wilmer MJ, et al. Pediatric Nephrology 2011;26(2):205–15;
5. Emma F, et al. Nephrology, Dialysis, Transplantation 2014;29(Suppl 4):87–94;
6. Tsilou E, et al. Survey Ophthalmology 2007;52(1):97–105.

# Ocular complications of cystinosis

| <1 year | 1–2 years | 3–4 years | 7–10 years | Puberty | 2nd & 3rd decades of life |
|---|---|---|---|---|---|
| No signs before the age of 1, initially asymptomatic[1] | Corneal crystals visible after 16 months, no symptoms yet[1] | Accumulation of corneal crystals, crystal deposits in the anterior and increasingly in the posterior periphery; pigmentary mottling; early photophobia[1] | Crystals in the entire periphery of the stroma and in the endothelium; progressive photophobia (prevalence 50%), blepharospasm[1] | Superficial punctate keratopathy, macula anomalies; the feeling of a foreign body in the eye and pain[1] | Filamentous and band keratopathy, neovascularization of the corneal periphery, crystals in the entire corneal stroma structures[2]; decreased visual acuity, reduced color vision and reduced peripheral and night vision, retinal blindness, corneal transplant[1] |
| |  |  |  |  |  |


1. Tsilou E, et al. Surv Ophthalmol 2007;52(1):97–105;
2. Emma F, et al. Nephrology, Dialysis, Transplantation 2014;29(Suppl 4):87–94.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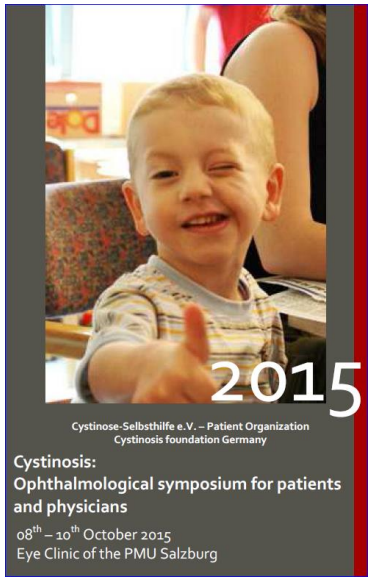
# Literature - clinical experience - expert opinions





**Need for a standardized protocol in eye care in cystinosis patients!**

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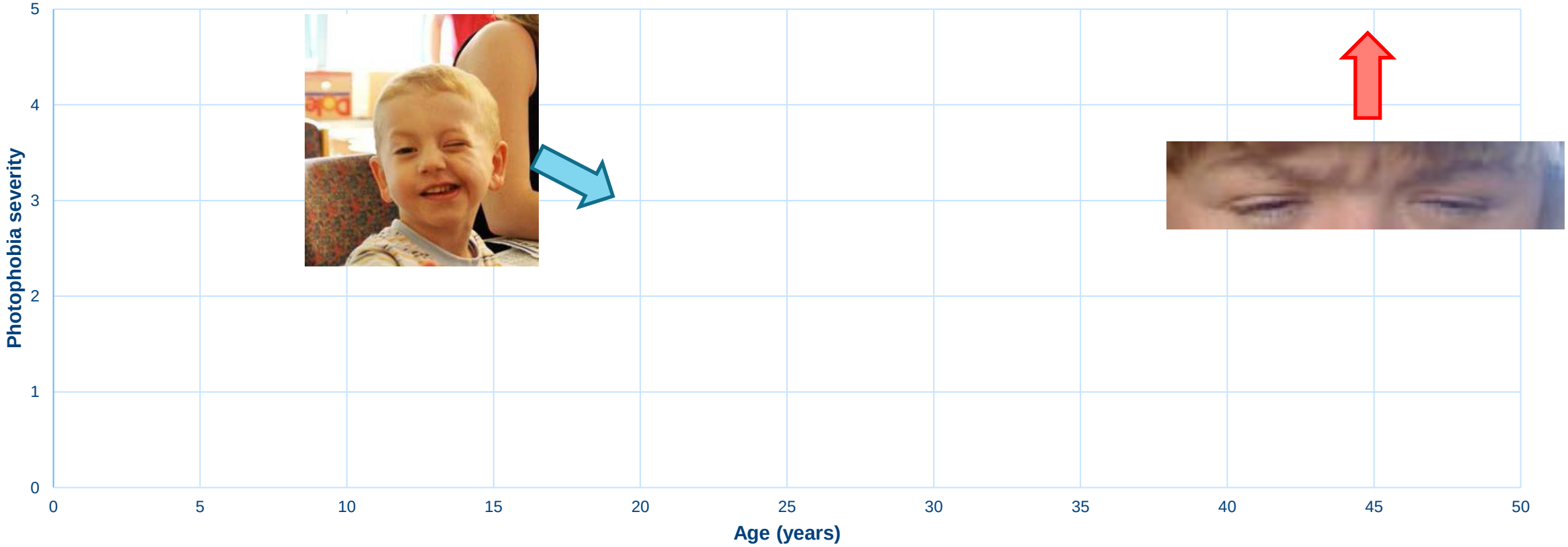
# Reality in daily practice UZ Leuven

## … *progressive* symptoms…




- **Photophobia**

Peeters Freya, et al. "Ophthalmic Outcome in a Belgian Cohort of Cystinosis Patients Treated with a Compounded Preparation of Cysteamine Eye Drops: Retrospective Analysis." *Ophthalmology and Therapy* (2019): 1-11.

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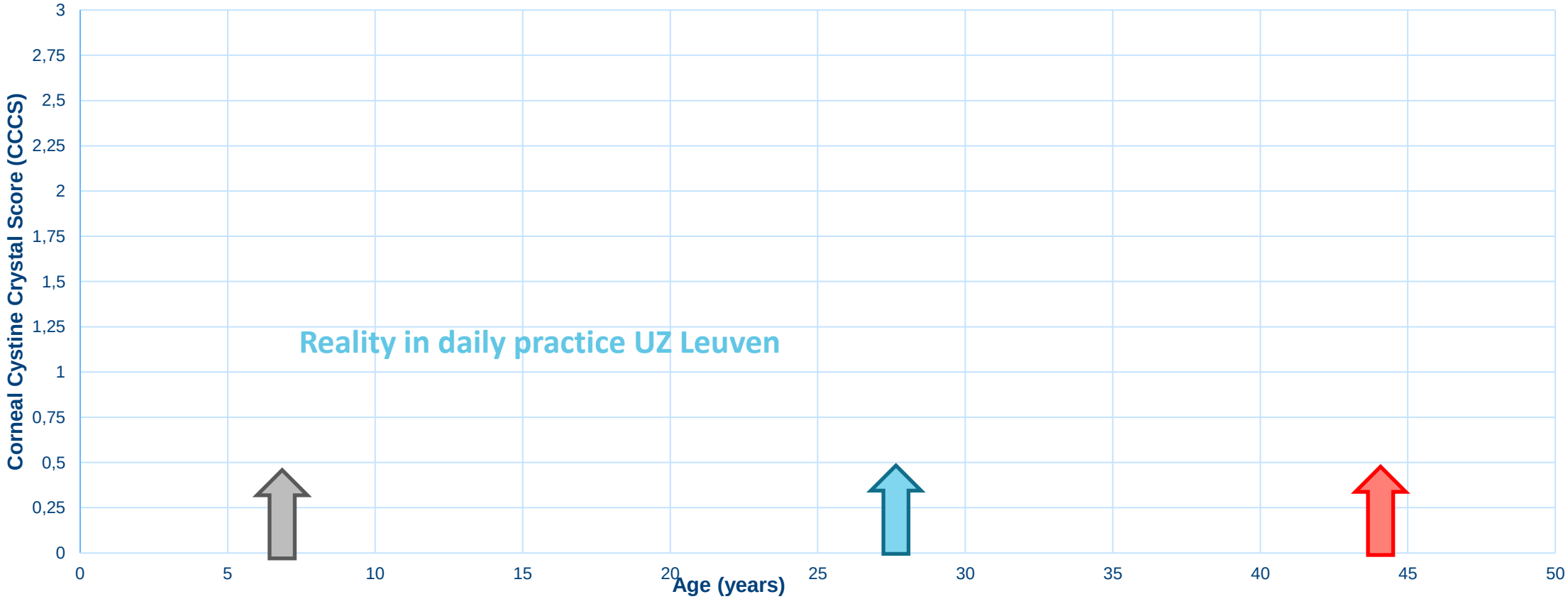
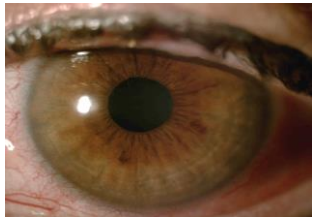
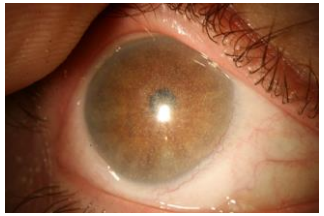
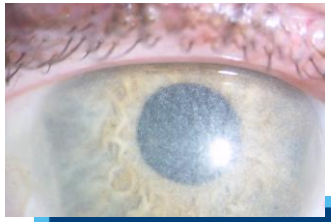
# Reality in daily practice UZ Leuven

## ….corneal crystal deposition accumulates…







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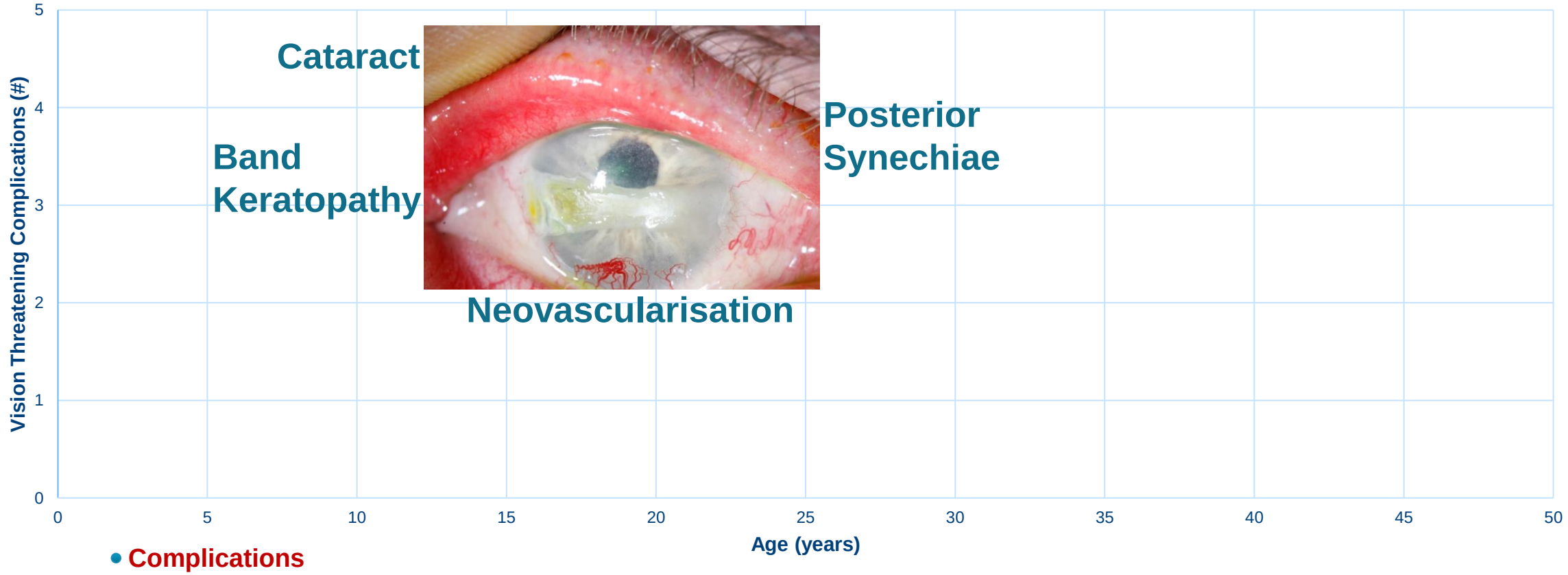
# Reality in daily practice UZ Leuven

## … and eventually to vision-threatening *irreversible* complications…




Peeters Freya, et al. "Ophthalmic Outcome in a Belgian Cohort of Cystinosis Patients Treated with a Compounded Preparation of Cysteamine Eye Drops: Retrospective Analysis." *Ophthalmology and Therapy* (2019): 1-11.

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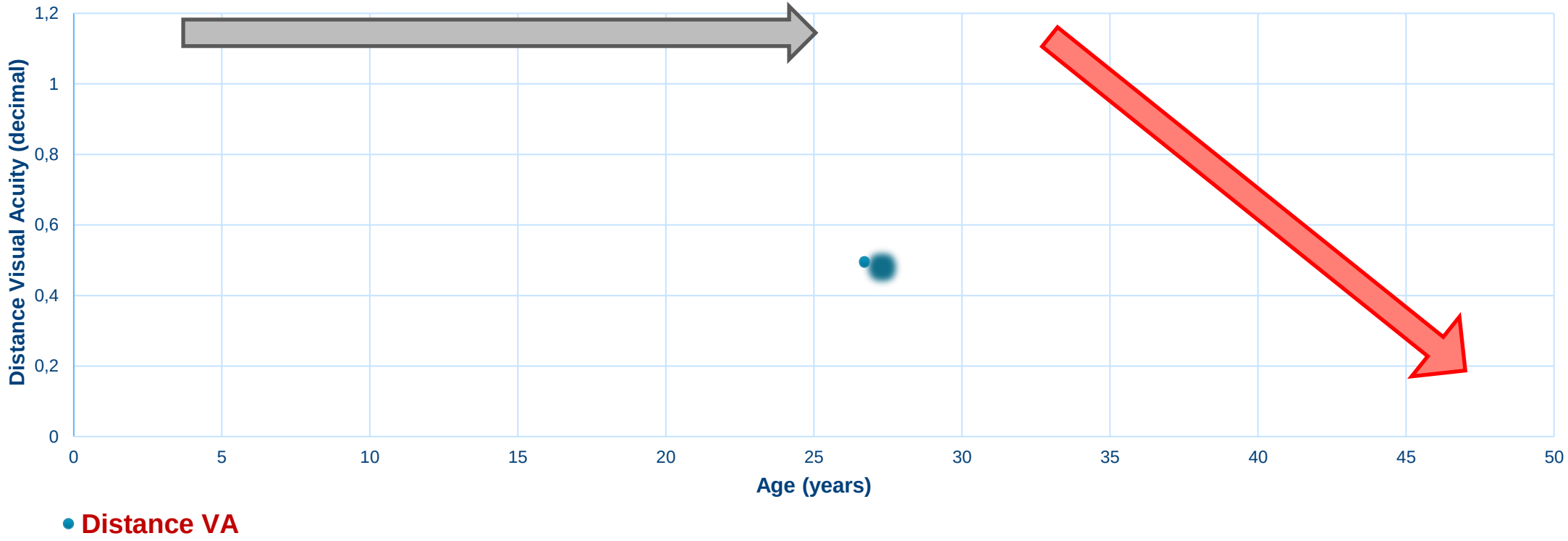
# Reality in daily practice UZ Leuven

## … resulting in *loss of functional vision…*




Peeters Freya, et al. "Ophthalmic Outcome in a Belgian Cohort of Cystinosis Patients Treated with a Compounded Preparation of Cysteamine Eye Drops: Retrospective Analysis." *Ophthalmology and Therapy* (2019): 1-11.

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# Statement 1

Patients with cystinosis should have regular eye check-ups.

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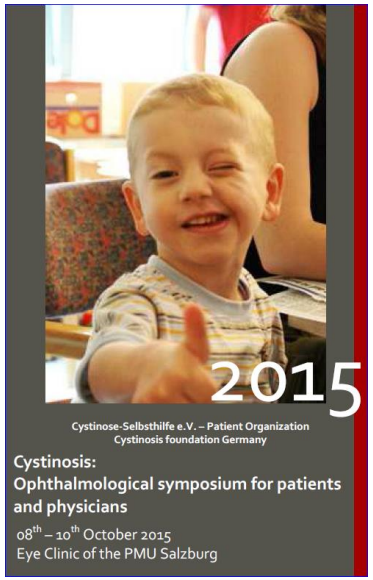
# Literature - clinical experience - expert opinions





Need for a standardized protocol in eye care in cystinosis patients!

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# University Hospitals Leuven
# 2015: Multidisciplinary cystinosis clinic

## Paediatric nephrologic department and ophthalmological department

Ophthalmol Ther (2017) 6:93–104
DOI 10.1007/s40123-017-0089-3

REVIEW

### Clinical Practice: A Proposed Standardized Ophthalmological Assessment for Patients with Cystinosis

Anne-Marie Pinxten · Minh-Tri Hua · Jennifer Simpson · Katharina Hohenfellner · Elena Levtchenko · Ingele Casteels

# Standardized clinical ophthalmological assessment for follow-up

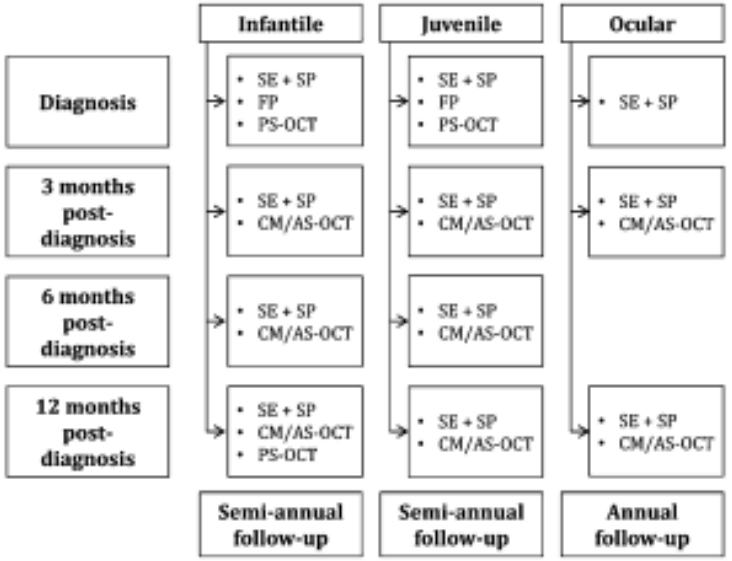


**Fig. 3** The standardized clinical ophthalmological assessment, a protocol for follow-up of patients with cystinosis. *AS-OCT* anterior segment optical coherence tomography, *CM* confocal microscopy, *FE* fundus examination, *FP* fundus photography, *SE* standard examination, *PS-OCT* posterior segment optical coherence tomography, *SP* split-lamp photography. Standard examination (SE) includes history, visual acuity, tonometry and slit-lamp examination

# Statement 2

Oral cysteamine is not effective
in the treatment of corneal crystals.

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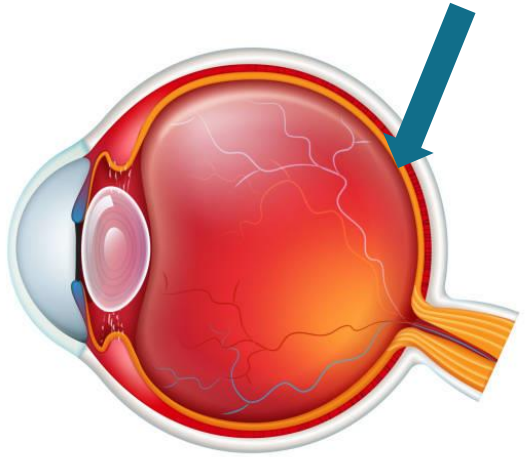
# Effect of oral cysteamine on the eye?

Oral administration of cysteamine reduces *systemic* cystine accumulation.

Retina/choroid: highly vascularized structures

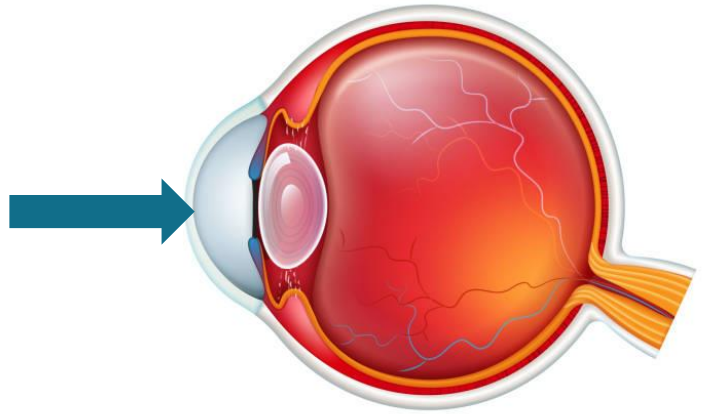
→ rate of maculopathy and retinopathy ⇊



# Effect of oral cysteamine on the eye?

corneal avascular structure:  no effect on corneal cystine crystals

→ need of topical treatment



# Statement 3

Patients with cystinosis  have access to cysteamine eye drops.

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# Perfect drops?

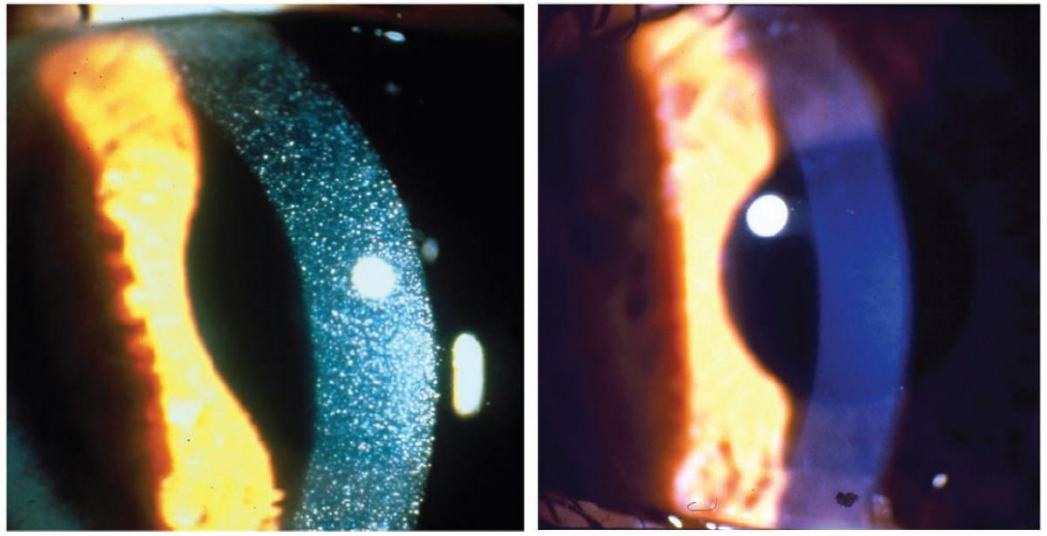


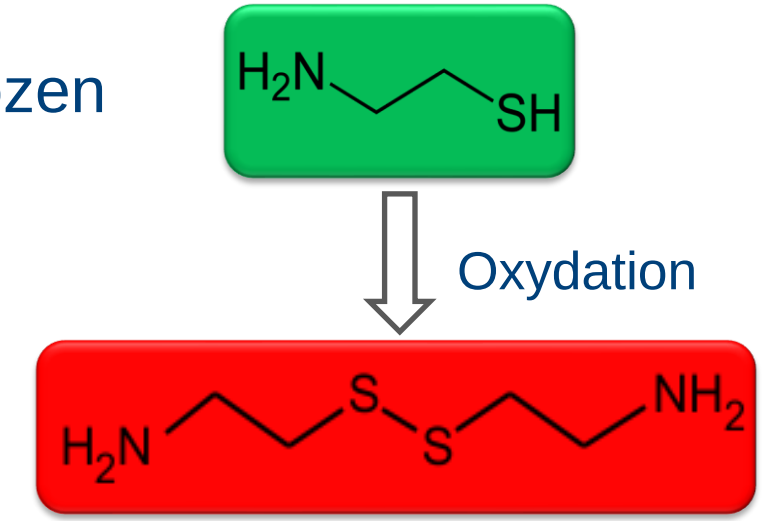
**Figure 1** Slit lamp photographs of 3-year-old patient with nephropathic cystinosis, before (left) and after (right) cysteamine eye drop therapy. Source: NIH Clinical Center, National Institutes of Health, Bethesda, MD.

# What *was* available?

Off-licence formulations

- with various concentrations, composition and buffers
- no viscosity agent
- frequent administration: 6-12 times/day
- progression of the corneal disease

- At room temperature, **cysteamine** oxidizes to **cystamine**
- **Cystamine** is not effective in depleting corneal cystine crystals
- To prevent oxidation, **cysteamine** eyedrops should be frozen or kept from oxygen




*Iwata, F., Kuehl, E. M., Reed, G. F., McCain, L. M., Gahl, W. A., & Kaiser-Kupfer, M. I. (1998). A randomized clinical trial of topical cysteamine disulfide (cystamine) versus free thiol (cysteamine) in the treatment of corneal cystine crystals in cystinosis. Molecular genetics and metabolism, 64(4), 237-242.*

# Alternatives to Hospital preparations

The first pharmaceutical product to be approved by EMA in the European Union in 2017

Table 1. Current ophthalmic formulations available or under development for the treatment of ocular cystinosis

| Name | Manufacturer/ developer | Phase of development | Dosage | Administration | Pharmaceutical form | Storage | Shelf-life |
|---|---|---|---|---|---|---|---|
| Cystaran™ (cysteamine hydrochioride)[6] | Sigma-Tau Pharmaceuticals | Marketed in the US | 0.65% | Every waking hour | Solution | From –25 to –15°C before use; from 2 to 25°C when in use | Seven days |
| Cystadrops (cysteamine hydrochloride)[4,8,10] | Orphan Europe | Marketing authorisation in the EU obtained in January 2017 | 3.8mg/g equivalent to 0.55% | Four times a day | Solution | From 2 to 8°C before use; fbelow 25°C after first opening | Seven days |
| Dropcys (cysteamine hydrochloride)[7] | Lucane Pharma | Marketing authorisation in the EU rejected | 0.1% | Every waking hour | Lyophilised powder for reconstitution | Not reported | Not reported |
| Cysteamine nanowafer | Baylor College of Medicine and University of California | Preclinical evaluation | 10µg | Once a day | Nanowafer | At room temperature | Up to four months |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# Cystadrops® is the only drug approved in EUROPE for the treatment of corneal crystal deposits


**Market authorization : January 27th, 2017**

**Cystadrops® : 3.8 mg/mL cysteamine hydrochloride in a viscous-eye drops solution**

**Indication: treatment of corneal cystine crystal deposits in adults and children from 2 years old with cystinosis**

**Viscous formulation:**

- Allows **a longer contact with ocular surface** (2)
- **Reduces frequency dosing** in comparison with a non-viscous eye drops solution (2)


Cystadrops® Summary of Product Characteristics. Lyseng-Williamson KA. Cystadrops® (cysteamine hydrochloride 0.55% viscous eye-drops solution) in treating corneal cystine crystal deposits in patients with cystinosis: a profile of its use. Drugs & Therapy Perspectives 2017;33(1):1-7.
Liang H *et al*. A New Viscous Cysteamine Eye Drops Treatment for Ophthalmic Cystinosis: An Open-Label Randomized Comparative Phase III Pivotal Study. Invest Opthalmol Vis Sci 2017;58:2275-83.


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# Statement 4

**Treatment of eye problems is available for all cystinosis patients with an off-licence formulation or with vCH 0.55% eye drops.**

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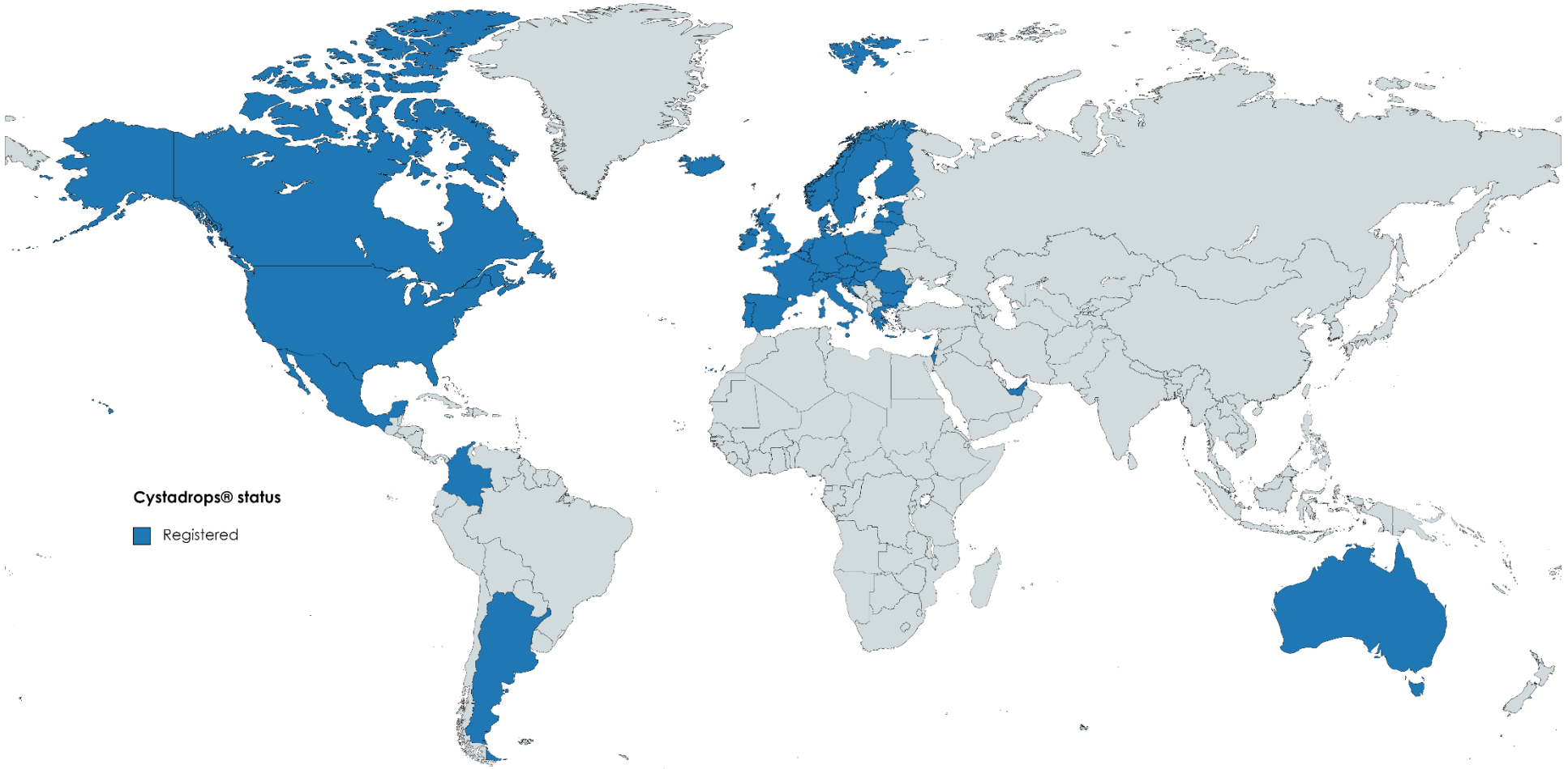
# Cystadrops® registration status




Cystadrops® is registered in 40 countries

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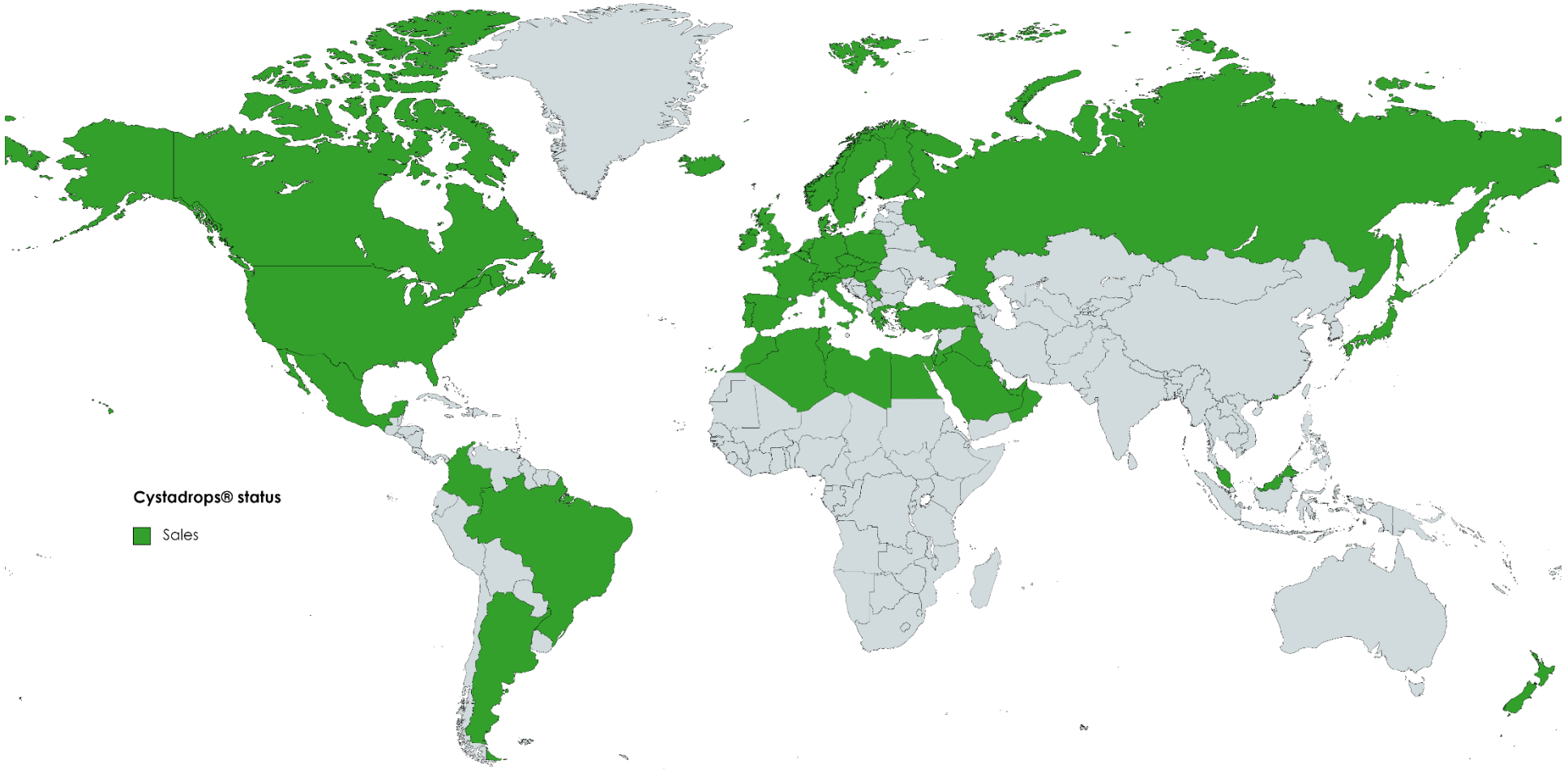
# Cystadrops® marketing status




Cystadrops® is sold in more than 47 countries

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# no registration of cystadrops?

Contact:

Giordano.v@recordati.com Vincenzo Giordano ( International Medical Advisor)

or

www.recordatirarediseases.com

# vCH 0.55% clinical trials

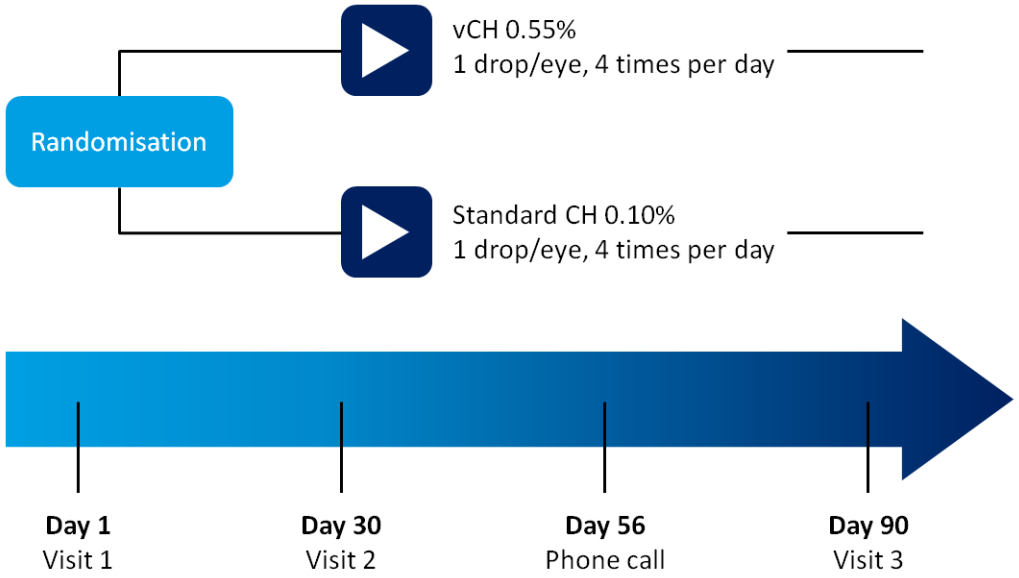
- SHORT-term efficacy
  - **CHOC** study 3 months
  - **SCOB2** trial 3 months
- LONG-term efficacy
  - **OCT-1** study 48 months
  - **French ATU** 45 months
  - **PASS** study 60 months

# vCH 0.55% clinical trials

- SHORT-term efficacy
  - **CHOC** study 3 months
  - **SCOB2** trial 3 months
- LONG-term efficacy
  - **OCT-1** study 48 months
  - **French ATU** 45 months
  - **PASS** study 60 months

# CHOC study

Open-label, phase III, randomized, two-arm, multicenter trial to evaluate the efficacy of vCH 0.55% compared with standard CH 0.10% eye drops treatment in patients with nephropathic cystinosis (N = 31; ≥2 years old)




- **Primary efficacy endpoint:** Total corneal cystine crystal density score by IVCM across 7 layers
- **Secondary efficacy endpoints:** Photophobia, CCCS, crystal thickness on OCT
- **Safety:** Monitoring for AEs, SAEs, laboratory evaluations and concomitant medications

AE, adverse event; CH, cysteamine hydrochloride; SAE, serious adverse event.

Liang H, et al. Invest Opthalmol Vis Sci 2017;58:2275–83.

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# CHOC study

- vCH 0.55% significantly decreased
  - crystal thickness on OCT
  - CCCS and photophobia
  - crystal deposits on IVCM

- Adverse effects were:
  - Transient
  - Mild or moderate in severity (burning, stinging)

# vCH 0.55% clinical trials

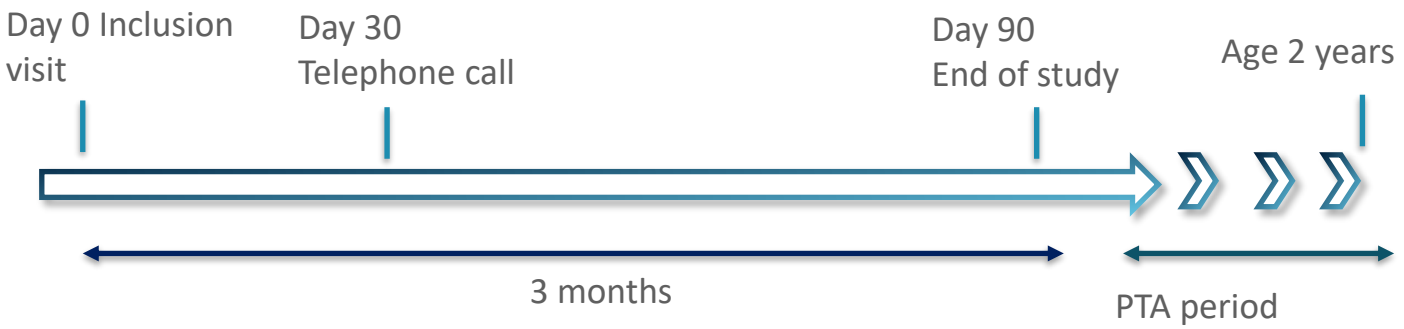
- SHORT-term efficacy
  - **CHOC** study 3 months
  - **SCOB2** trial > 3 months
- LONG-term efficacy
  - **OCT-1** study 48 months
  - **French ATU** 45 months
  - **PASS** study 60 months

# SCOB2

Study Cystadrops® Ophthalmic Below 2 years

- Part of the Pediatric Investigational Plan

- **Objective**: To evaluate the safety profile of vCH 0.55% in a pediatric population with cystinosis **from 6 months to 2 years of age**




PTA, Product Trial Access.

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# Statement 5

**Treatment with cysteamine eye drops should be started before 2 years of age.**

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# vCH 0.55% clinical trials

- SHORT-term efficacy
  - **CHOC** study 3 months
  - **SCOB2** trial
- LONG-term efficacy
  - **OCT-1** study 48 months N = 8
  - **French ATU** 45 months N = 130
  - **PASS** study 60 months

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# OCT-1 study

- Cystadrops® gel had a good safety profile over a long follow-up period

- Cystadrops® gel was superior to CH 0.1% AGEPS formulation in terms of efficacy

AGEPS: Agence Générale des Equipements et Produits de Santé

# vCH 0.55% clinical trials

- SHORT-term efficacy
  - **CHOC** study 3 months
  - **SCOB2** trial 3 months
- LONG-term efficacy
  - **OCT-1** study 48 months
  - **French ATU** 45 months
  - **PASS** study 60 months

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# French ATU

- Adverse events: Mild/moderate
- Good compliance:
  - Treatment discontinuation in 8/130 patients
    - Average dose = 3.3 ± 0.94 drops/day
    - (Recommended dose = 4 drops/day)

Temporary authorization for use of vCH 0.55% in France

4-year follow-up
(Sept 2013 – June 2017)

N=130

ATU: Autorisation Temporaire d'Utilisation.

French ATU 2017. Recordati Rare Diseases. Data on file.

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# French ATU

3 parameters of ophthalmic evaluation

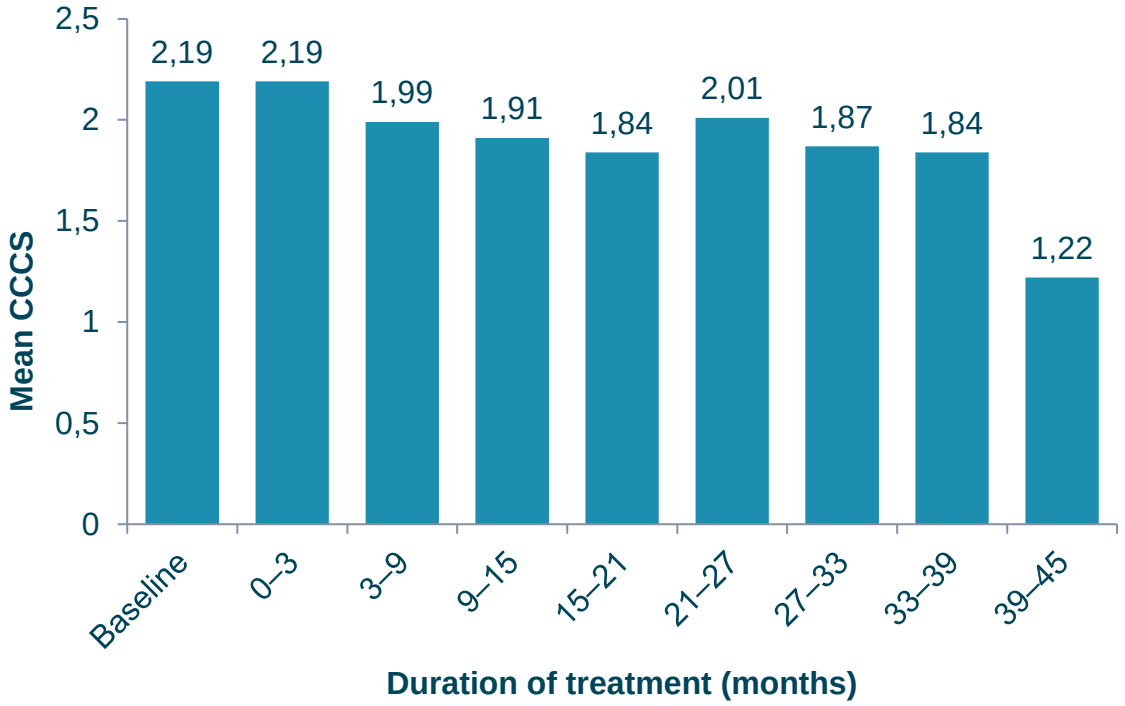
- Stabilization of visual acuity
- Stabilization of CCCS
- Improvement of photophobia within 3 months

ATU: Autorisation Temporaire d'Utilisation.

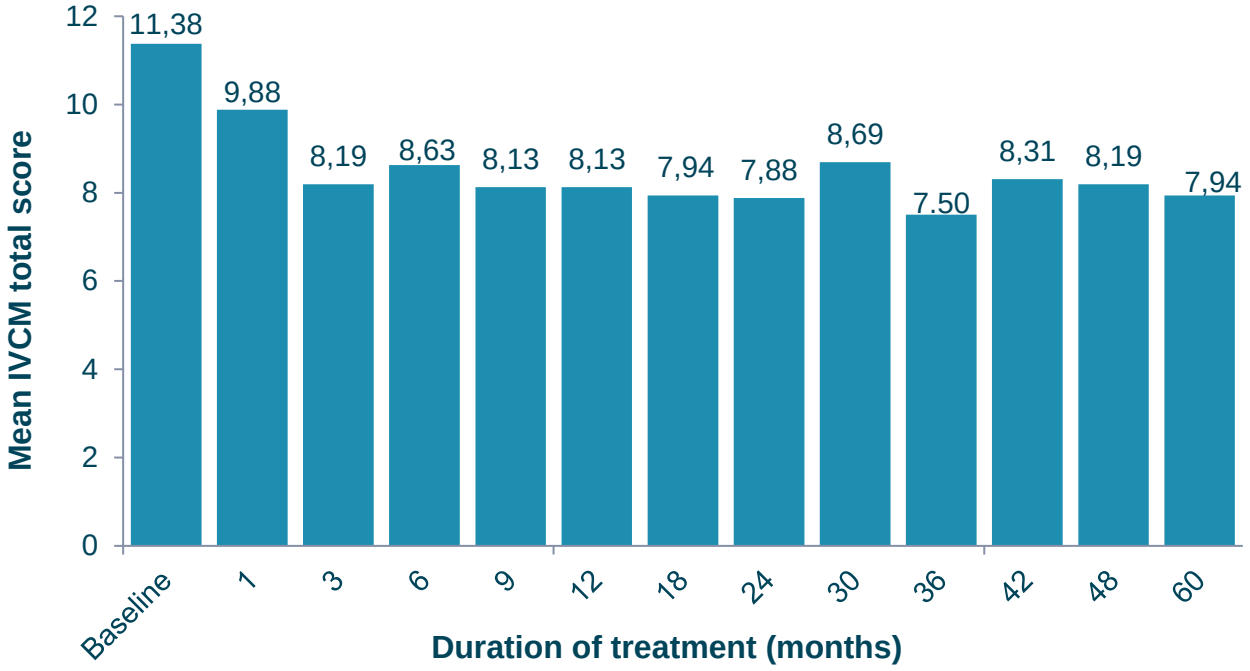
French ATU 2017. Recordati Rare Diseases. Data on file.

# vCH 0.55% clinical trials

**French NPU data[1]**




**OCT-1 study data[2]**




**CCCS and IVCM crystal density scores showed similar patterns, decreasing after three months of treatment and subsequently stabilizing**


1. French ATU 2017. Recordati Rare Diseases. Data on file.
2. Labbé A, et al. Mol Genet Metab 2014;111(3):314–20.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# vCH 0.55% clinical trials

- SHORT-term efficacy
  - **CHOC** study 3 months
  - **SCOB2** trial 3 months
  - LONG-term efficacy
  - **OCT-1** study 48 months
  - **French ATU** 45 months
  - **PASS** study 60 months

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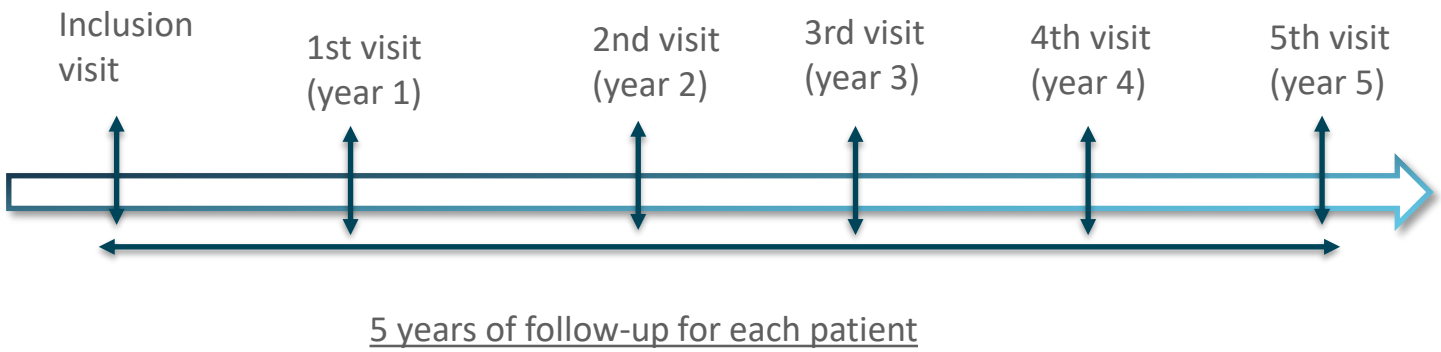
# PASS study

- Post-Authorization Safety Study
- **Design:** Observational, non-interventional
- **Primary objective**: To assess the safety profile of vCH 0.55% in long-term use
- **Study Population**: Estimated enrollment approximately 70 patients



# Your experience with cystadrops?

# Statement 6

The package and storage of cystadrops are easy to handle.

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# Cystadrops® storage conditions:

- **Before opening**
  - Store in a refrigerator (2°C - 8°C)
  - Keep the vial in the outer carton in order to protect from light
  - Shelf life: 6 months in the fridge

- **After first opening**
  - Store below 25°C. Do not refrigerate
  - Keep the dropper **bottle tightly closed in the outer carton** in order to protect from light
  - Cystadrops® can be used up to **7 days** from the time of opening


**1 open vial = 7 days then discard**

Cystadrops® Summary of Product Characteristics.

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# Cystadrops® Mode of administration

**1 open vial = 7 days then discard**

Link to video: www.cystadrops.net

In order to facilitate the administration, the patient  brings the new bottle of Cystadrops at room temperature. The recommended dose of Cystadrops is one drop in each eye, 4 times a day during waking hours (3-5).

After using Cystadrops®, press a finger into the corner of your eye by the nose, then gently massage your upper eyelid to spread the eye drops over the eye. Remove excess medicine around the eye with a moist tissue.

The dropper bottle should be discarded after 7 days of use

# Statement 7 a and b

The administration of cystadrops in your eyes is easy.

Patients do not have problems putting in the drops 4 times/day.

# Statement 8

Patients experience only mild and short stinging - burning when putting in the drops.

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# Burning eyes

- CHOC study:
  - Stinging (80% in the Cystadrops® group and 50% in the CH 0.10% group)
  - Burning, redness and blurred vision in ≥ 60% of Cystadrops® group
  - > 98% LADRs lasted less than 1 hour.
  - no safety issues in either group

- OCT-1 study: Mean duration of burning and stinging: 17.5 s. All patients continued the treatment for 5 years.

# BAK?

- BAK may cause eye irritation.
- In Cystadrops®: the concentration of BAK has lowest concentration of 0, 01% to minimise its potential to promote eye irritation.
- BAK:  preservative agent and a permeability enhancer improving corneal uptake
- BAK is known to discolour soft contact lenses

# Burning eyes?

Burning can be related

- to the disease (depending on how much the disease has affected the eye) and
- to some characteristics of Cystadrops®.

In case of severe burning sensation upon instillation of Cystadrops®: ophthalmological examination should be performed.

# Burning eyes: artificial tears?

- It is not recommended to apply artificial tears just after Cystadrops® instillation as it can wash out the medication.
- Wait for at least 10 minutes in order to allow the product to penetrate in the deepest layers of the cornea.
- Exceptionally, in case of dry eyes syndrome, artificial tears could be administered 30 min before Cystadrops.

# Statement 9

You should not spill drops when putting them in.

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- The bottle contains about 100 drops.
- The recommended dosage is 4 drops / day and per eye.
- The bottle can therefore deliver drops for more than 10 days…
- …but because of the stability after opening, the product can only be used for 7 days.

# Statement 10

**The commercially available viscous cysteamine eye drops are an improvement compared to the pharmacy prepared eye drops.**

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# Future treatment option?

- Novel eyedrop formulations?
- Contactlenses for drug-less ocular cystinosis treatment?

# Conclusions

- Cystinosis can lead to severe ocular complications
- Oral cysteamine does not prevent corneal complications
- Hospital preparations of cysteamine drops typically do not provide an effective treatment to prevent and/or reverse ocular cystine crystal deposition
- **vCH 0.55%** demonstrates:
  - Significant **reduction in crystal deposition**
    - As soon as 0–3 months (slit lamp/OCT/IVCM)
    - Effect maintained for >4 years
  - Stabilization of **visual acuity**
  - Improvement of **photophobia**
- New treatment options?

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# THANKS TO

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