CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

200740Orig1s000

MEDICAL REVIEW(S)

Deputy Division Director Review for NDA 200740

Date	September 28, 2012
From	Wiley A. Chambers, M.D.
NDA #	200740
Applicant	Sigma-Tau Pharmaceuticals, Inc.
Date of Original Submission	March 3, 2010
Date of Resubmission	April 2, 2012
Type of Application	505(b)(2)
Name	Cystaran (cysteamine ophthalmic solution) 0.44%
Dosage forms / Strength	Topical ophthalmic solution
Proposed Indication(s)	Treatment of corneal cystine crystal accumulation in patients with cystinosis
Recommended Action:	Approval

1. Introduction

Cystinosis is a rare autosomal recessive metabolic disorder characterized by the intracellular accumulation of cystine, the disulfide of the amino acid cysteine, in many organs and tissues. Cystine accumulation is due to a defective lysosomal cystine transport system and results in tissue-damaging cystine crystal formation within cells of the kidney, bone marrow, pancreas, muscle, brain, and eye. If untreated, leads to renal failure by the age of 10 years. The mainstay of treatment for cystinosis is oral cysteamine. Oral cysteamine was approved in the United States as Cystagon (cysteamine bitartrate) Capsules (NDA 20-392) in 1994 for the management of nephropathic cystinosis in children and adults. If administered chronically and diligently beginning prior to 2 years of age, oral cysteamine retards or prevents glomerular deterioration and enhances growth in children with nephropathic cystinosis.

Corneal cystine crystals are an ocular manifestation of nephropathic cystinosis that progressively worsens with time and does not spontaneously resolve. In the cornea, cystine crystals generally appear by 1 year of age and are pathonemonic of cystinosis. They initially appear in the central cornea and progress to the full thickness of the peripheral cornea and anterior two-thirds of the central cornea with age. These cystine crystals are considered partly responsible for clinical symptoms of photophobia, recurrent corneal erosions, and secondary b
lepharospasm that complicate longstanding cystinosis.

Cysteamine is an aminothiol that converts cystine to cysteine and cysteine-cysteamine mixed disulfide, both of which can pass through the lysosomal membrane of patients with cystinosis without a functional carrier and both of which can then be eliminated from the cell. The lack of effect of oral cysteamine on the ocular effects of cystinosis led to the development of an ophthalmic formulation. Cystaran is a sterile ophthalmic solution containing 6.5 mg of cysteamine hydrochloride, equivalent to 4.4 mg of cysteamine as the active ingredient.

2. Background

This is a 505(b)(2) application. The applicant, Sigma Tau Pharmaceuticals, Inc., lists Cystagon (cysteamine bitartrate) Capsules (Mylan Pharmaceuticals, Inc.) as the reference listed drug product.

The information referenced by Sigma Tau is toxicology information of the drug substance. The drug substance is chemically the same between Cystaran and Cystagon.

There are no approved drug products for the prevention and treatment of corneal cystine crystal accumulation in patients with cystinosis. An orphan designation for cysteamine hydrochloride for the treatment of corneal cystine crystal accumulation in patients with cystinosis was granted in August 1997.

3. CMC

Cysteamine HCl drug substance is a [redacted] (b) (4) It is prone to oxidation and forms the disulfide, cystamine 2HCl, [redacted] (b) (4) The drug substance is manufactured by [redacted] (b) (4)

Formulation:

Cysteamine HCl	6.5 mg/mL
Sodium Chloride	[redacted] (b) (4)
Benzalkonium Chloride	0.1 mg/mL
HCl/NaOH	adjust to pH [redacted] (b) (4)
Water	[redacted] (b) (4)

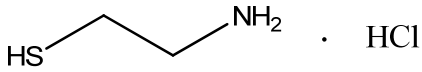
The original commercial formulation proposed in the NDA had [redacted] (b) (4) sodium chloride [redacted] (b) (4) The Division, in a teleconference with Sigma-Tau on April 28, 2010, informed the company that the commercial formulation should be identical to the formulation used in the clinical trials. The company agreed to revise the NDA commercial formulation to match formulation 3, and accordingly sodium chloride was revised [redacted] (b) (4) The revised formulation results in a [redacted] (b) (4)

Stability Specifications

Description	Clear, colorless solution
pH	3.8-4.8
Osmolality	360-420 mOsmol/kg
Particulate matter	NMT [redacted] (b) (4)
[redacted] (b) (4)	NMT [redacted]
Identification	Retention time on UPLC matches standard UV-vis spectrum concordant with sample
Cysteamine HCl	[redacted] (b) (4)
Specified impurities	NMT [redacted] (b) (4)
Individual unspecified impurities	NMT [redacted]
Total specified and unspecified impurities	NMT [redacted]
Benzalkonium chloride	[redacted] (b) (4)
[redacted] (b) (4)	[redacted] (b) (4)
Bacterial endotoxin	NMT [redacted] (b) (4)

Sterility Meets USP

Cysteamine HCl Structural Formula:



Molecular Formula: C_2H_7NS HCl

The drug product will be packaged in 15 mL LDPE round bottles with a white LDPE controlled drop dispenser and a white propylene cap. Container closure parts are (b) (4)

FACILITY INSPECTIONS
Manufacturing facilities for the drug substance and the drug product are in compliance with current good manufacturing practice.

4. Nonclinical Pharmacology/Toxicology

Studies of cysteamine hydrochloride ophthalmic solution 0.1-10% included one GLP study conducted by the Applicant and two studies from the peer-reviewed scientific literature.

In the GLP-compliant study in rabbits, 2 drops of 0.44% cysteamine ophthalmic solution was administered hourly for 8 hours per day for 30 days to the right eye of 12 rabbits/sex. No findings of irritation, corneal disruption, or ocular histopathology were reported. In published studies in rabbits, gross and/or microscopic signs of irritation or inflammation were seen following ocular administration of cysteamine at concentrations of 1% and higher when administered hourly for 8 consecutive hours for 4 weeks, while eyes treated with 0.08% or 0.4% cysteamine for 3 months were reported to be normal.

5. Clinical Pharmacology/Biopharmaceutics

The Applicant did not perform any human pharmacokinetic assessment of cysteamine HCl ophthalmic solution and was granted a waiver based on 21 CFR 320.22 (e) of the *in vivo* bioavailability requirement because of the expected low systemic exposure of cysteamine following ophthalmic administration of cysteamine solution in comparison to exposures observed following orally administered cysteamine bitartrate as described below.

The total daily dose of 0.44% cysteamine HCl ophthalmic solution is estimated to be 7.8 mg/day based on a 100 µL dose per hour × 12 waking hours. The recommended daily maintenance dose approved for orally administered cysteamine ranges from 400 mg/day for an infant with body weight <10 pounds to 2000 mg/day for adults. Therefore, the total daily ophthalmic dose is less than 2% of the recommended oral daily dose of cysteamine. Even assuming complete systemic availability, the peak plasma concentration of cysteamine following ophthalmic administration is expected to be substantially less than the peak plasma concentration following oral administration of cysteamine.

6. Sterility Assurance

There are no microbiology deficiencies identified. Container closure integrity testing was conducted using 20 media filled experimental containers (obtained from three consecutive media fills) plus one positive control (container pierced with a 27 g needle) and one negative control. Experimental vials and the positive control were immersed in a suspension of *B. diminuta* for 18-24 hours then scored for growth. All experimental vials were negative for growth. All positive control vials were positive for growth.

Preservative effectiveness testing was conducted according to USP <51> on lots containing 50, 75, and 100% of the labeled preservative content. The stability protocol states that lots must contain a minimum of 75% % of the preservative content. All of the samples met the acceptance criteria for a category 1 product.

Endotoxin testing will be conducted according to USP <85> using the kinetic turbidimetric method. The applicant has proposed an endotoxin limit of (b) (4) The sensitivity of the lysate to be used for endotoxin testing is (b) (4) The Applicant proposes the use of a (b) (4) for endotoxin testing and provided the results of inhibition/enhancement testing using the (b) (4) No inhibition or enhancement of the test was observed (b) (4) The results of endotoxin testing on three product lots were provided in the 28 July 2010 submission. Each of the product lots contained (b) (4) of drug product.

7. Clinical/Statistical - Efficacy

Three clinical studies, STP869294 (CAPTOC), 98-EI-0109S, and 98-EI-1090E, were submitted to provide efficacy and safety data for cysteamine ophthalmic solution (Formulation 3). In these studies, the applicant defined a response as an eye with a decrease from baseline of at least 1.00 unit in CCCS at some time during the study when baseline CCCS is $\geq$ 1.00 or CCCS does not increase by at least 1.00 unit at some time during the study when baseline CCCS is < 1.00. This implies a reduction in CCCS, in eyes with high CCCS ($\geq$1) at baseline, which need not be sustained, i.e., transient reduction in CCCS. While, in eyes with low CCCS (<1) at baseline, the lack of increase in CCCS has to be sustained.

The CAPTOC Study, a combined study of three historically controlled single center studies, shows that 30% of eyes using cysteamine ophthalmic solution (Formulations 1-4) responded for the mITT population. Cumulative response rates were also calculated for eyes with CCCS $\geq$1 at baseline and results show that about 10% had response in Year 1 and by Year 6 about 30% of the patients had response at some time during the study.

In Study 98-EI-0109S, a double-masked, randomized, within-patient-controlled study, the mean change from baseline CCCS score at month 6 in Formulation 3 is -0.22 and 0.24 for Formulation 5. This means that Formulation 3 reduces CCCS by 0.22 while Formulation 5 has an increase in CCCS by 0.24.

In Study 98-EI-0109E, a double-masked, randomized, within-patient-controlled study, the number of eyes with a reduction of CCCS of 1.00 unit or more was higher in those that received Formulation (67%) compared with Formulation 5 (13%) at some time during the treatment period. The difference in the mean change from baseline CCCS is higher in Formulation 3 than in Formulation 5 at every visit from Month 3, Month 6, Month 9, and Month 12.

The three studies demonstrate that cysteamine ophthalmic solution (Formulation 3) reduces formation of corneal crystals. This reduction however is temporary. Strict adherence to therapy is essential to the efficacy of Formulation 3.

Study STP869294 (CAPTOC)

Timepoint	N	n (%)	(95% confidence interval)
Response at any time during study	321	98 (30%)	(25-36%)
Eyes with CCCS ≥1 at baseline	291	94 (32%)	(27-38%)
Eyes with CCCS<1 at baseline	30	4 (13%)	(4-31%)
Cumulative Response Rates by Year in Eyes with CCCS ≥1			
Year 1		27 (9%)	(6-13%)
Year 2		51 (17%)	(13-22%)
Year 3		72 (25%)	(20-30%)
Year 4		80 (27%)	(22-35%)
Year 5		85 (29%)	(24-35%)
Year 6		87 (30%)	(25-36%)

Study 98 EI0109E

Timepoint	Formulation 5	Formulation 3	p-value
Month 3	2 (13%)	4 (29%)	0.08
Month 6	2 (14%)	7 (50%)	0.025
Month 9	1 (7%)	8 (57%)	0.008
Month 12	1 (7%)	7 (47%)	0.01
Anytime	2 (13%)	10 (67%)	0.005

Study 98 EI0109S

Group	Formulation 5	Formulation 3	p-value
Eyes with CCCS ≥1	8 (44%)	9 (50%)	>0.05
Eyes with CCCS<1	0	3 (33%)	0.08

Summary - There is substantial evidence of effectiveness consisting of adequate and well controlled studies which demonstrate that Cystaran (cysteamine hydrochloride ophthalmic solution) 0.44% reduces the accumulation of cystine corneal crystals considered partly responsible for clinical symptoms of photophobia, recurrent corneal erosions, and secondary blepharospasm that complicate longstanding cystinosis.

8. Safety

Studies STP869294 (CAPTOC), 98 EI0109E, and 98 EI0109S were utilized to evaluate safety.

For the purposes of labeling the adverse event profile of cysteamine hydrochloride ophthalmic solution 0.44%, the data from STP869294 (CAPTOC) was utilized. CAPTOC enrolled 247 subjects; the trial duration was 19 years. The adverse event profiles seen in 98 EI0109E, and 98 EI0109S are consistent with STP869294 (CAPTOC).

	CAPTOC		Safety Update	
Adverse Events	**247 evaluated patients**		**112 evaluated patients**	
Photophobia	157	(64%)	54	(53%)
Conjunctival hyperemia	69	(28%)		
Eye pain	48	(19%)	5	(5%)
Ocular hyperemia	43	(17%)	3	(3%)
Eye irritation	42	(17%)	4	(4%)
Instillation site irritation	30	(12%)		
Lacrimation increased	21	(9%)		
Keratitis	19	(8%)		
Optic disc disorder	18	(7%)		
Vision blurred	17	(7%)		
Instillation site pain	17	(7%)		
Dry Eye	13	(5%)		
Eyelid edema	12	(5%)		
Retinal disorder	11	(5%)		
Conjunctivitis	10	(4%)		
Eye pruritis	10	(4%)		
Blindness	7	(3%)		
Corneal epithelial disorder	6	(2%)		
Blepharitis	5	(2%)		
Erythema of eyelid	5	(2%)		

Deaths
Eighteen deaths were reported in the three studies comprising the CAPTOC analysis. Two of the patient deaths (Patient 374973 and Patient 835249) were reported to FDA in IND Safety Reports. Five patients (Patients 221252, 315632, 352157, 727697, and 883818) died with no cause provided. There were no deaths in 98 EI0109S and 98 EI0109S. One additional death was reported with the safety update. The patient had been on study medication for 20 years having started on the eye drops when she was 2 and a half years of age.

Safety Summary -There is substantial evidence of safety consisting of adequate and well controlled studies which demonstrate that Cystaran (cysteamine hydrochloride ophthalmic solution) 0.44%, dosed every hour while awake, is safe for the treatment of corneal cystine crystal accumulation in patients

with cystinosis. The most common ocular adverse events in CAPTOC occurring in ≥ 10 % of patients were sensitivity to light, redness, and eye pain/irritation.

9. Advisory Committee Meeting

No Advisory Committee Meeting was held. There were no new issues raised in the review of the application which were thought to benefit from an Advisory Committee Meeting.

10. Pediatrics

The safety and effectiveness of Cystaran (cysteamine hydrochloride ophthalmic solution) 0.44% in pediatric patients have been established for the treatment of corneal cystine crystal accumulation in patients with cystinosis.

11. Other Relevant Regulatory Issues

DSI

A Division of Scientific Investigations (DSI) audit was requested; DSI completed their review on August 23, 2010. The protocols inspected were Protocol 98-EI-0109E, Protocol 98-EI-0109S, and Protocol STP869294. Two domestic clinical investigators, Drs. Gahl (Muriel Kaiser) and Monte, and the applicant and CRO were inspected.

The preliminary classification of Clinical Investigator inspections of Dr. William A. Gahl and Dr. Monte A. Del Monte, are Voluntary Action Indicated (VAI). While DSI considers primary safety and efficacy data from these sites to be generally reliable in support of the requested indication, the review division will need to determine the potential impact of the following observations on approvability of the application:

- At Dr. Gahl's site, the potential impact, if any, that missing safety data from study 98-EI-0109S has on safety analyses and conclusions.
- At Dr. Del Monte's site, whether discrepancies in drug bottles issued compared with drug bottles returned accounting for ≤10% of the total number of bottles or doses potentially administered is within acceptable limits for total potential doses administered.

The preliminary classification of the sponsor/applicant, Sigma-Tau Pharmaceuticals, Inc. and the CRO, (b) (4) are No Action Indicated (NAI), based on preliminary communications with the FDA field investigator.

Regarding the Drs. Gahl/Kaiser site, alternate source data (diary entries, drug dispensation records, ophthalmic evaluation records, and subject interview questionnaires) support that study drug, as randomized, was administered to the subjects. The missing study data discussed by DSI are not expected to have any impact on safety analyses and conclusions.

Regarding Dr. Del Monte's site, discrepancies in drug bottles issued compared with drug bottles returned accounting for ≤10% of the total number of bottles or doses potentially administered are well within acceptable limits for total potential doses administered. These four subjects received over 100

bottles of study drug during the course of the efficacy study. The bottle count discrepancy discussed by DSI is not expected to have any impact on efficacy or safety analyses and conclusions.

FINANCIAL DISCLOSURE

The applicant has examined its financial data regarding significant payments of other sorts made to all investigators in the studies and equity information as provided by the investigators, as defined in 21 CFR 54.2. There is no evidence to suggest that the results of the study were impacted by any financial payments.

DPDP

The Division of Professional Drug Promotion (DPDP) performed a Proprietary Name Risk Assessment and evaluated "Cystoran" as the proposed proprietary name for cysteamine hydrochloride ophthalmic solution. DMEPA found the name "Cystoran" unacceptable (b) (4)
During a teleconference with the applicant on May 6, 2010, DMEPA informed Sigma-Tau the name would be unacceptable and requested submission of an alternate proprietary name.

On May 13, 2010, the name "Cystoran" was withdrawn, and on May 14, 2010, the name "Cystaran" was submitted as an alternate proprietary name by the applicant. DPDP approved this alternate proprietary name in a letter dated August, 12, 2010. DPDP completed a second review on 9/13/12, concluding that the name was still acceptable.

DDMAC

The Division of Drug Marketing, Advertising, and Communications (DDMAC) reviewed the draft product labeling, including the package insert (PI), draft carton label, and draft container label for Cystaran (cysteamine hydrochloride ophthalmic solution) 0.44%. DDMAC was invited to the two labeling meetings held on August 4 and 13, 2010, and provided a separate review.

DRISK

The Division of Risk Management (DRISK) reviewed the draft product labeling, including the package insert (PI), draft carton label, and draft container label for Cystaran (cysteamine hydrochloride ophthalmic solution) 0.44%. DRISK was invited to the two labeling meetings held on August 4 and 13, 2010, and provided a separate review. A decision was made at the second labeling meeting not to include a Patient Package Insert with the Cystaran labeling because there was nothing new or novel regarding the administration of this ophthalmic solution to the eyes.

12. Labeling

The labeling submitted by Sigma-Tau Pharmaceuticals, Inc. in September 2012 is acceptable.

9 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

WILEY A CHAMBERS
10/02/2012

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	200740
Priority or Standard	P
Submit Date(s)	March 30, 2012
Received Date(s)	April 2, 2012
PDUFA Goal Date	October 2, 2012
Division / Office	DAIOP
Reviewer Name(s)	Martin P. Nevitt, M.D., M.P.H.
Review Completion Date	September 18, 2012
Established Name	cysteamine ophthalmic solution 0.44%
(Proposed) Trade Name	Cystaran
Therapeutic Class	Cystine-depleting agent
Applicant	Sigma-Tau Pharmaceuticals, Inc.
Formulation(s)	topical ophthalmic solution
Dosing Regimen	Instill one drop in both eyes daily, every waking hour
Indication(s)	treatment of corneal cystine crystal accumulation in patients with cystinosis
Intended Population(s)	children and adults with cystinosis

Template Version: March 6, 2009

Table of Contents

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

NDA 200740, Cystaran (cysteamine ophthalmic solution) 0.44%, is recommended for the approval for the treatment of corneal cystine crystal accumulation in patients with cystinosis.

Refer to medical officer review of NDA 200740 received March 2010 for the complete clinical review.

1.2 Risk Benefit Assessment

The benefits of Cystaran (cysteamine ophthalmic solution) 0.44%, for the recommended indication outweigh the associated risks.

Refer to medical officer review of NDA 200740 received March 2010 for the complete clinical review.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

There are no proposed risk management actions.

1.4 Recommendations for Postmarket Requirements and Commitments

There are no Phase 4 clinical study commitments.

2 Introduction and Regulatory Background

2.1 Product Information

Refer to medical officer review of NDA 200740 received March 2010 for the complete clinical review.

2.2 Tables of Currently Available Treatments for Proposed Indications

Refer to medical officer review of NDA 200740 received March 2010 for the complete clinical review.

2.3 Availability of Proposed Active Ingredient in the United States

Refer to medical officer review of NDA 200740 received March 2010 for the complete clinical review.

2.4 Important Safety Issues With Consideration to Related Drugs

Refer to medical officer review of NDA 200740 received March 2010 for the complete clinical review.

2.5 Summary of Regulatory Activity Related to Submission

This March 30, 2012, submission contains a Safety Update for the period of May 1, 2010 through December 30, 2011 (Section 7.7), and the applicant's response to FDA's Complete Response Letter dated 03 September 2010 identifying the deficiency for not approving the NDA. The Complete Response Letter noted the following deficiency: manufacturing facilities for drug substance (DS) and drug product (DP) were not in compliance with current good manufacturing practices (cGMPs).

2.6 Other Relevant Background Information

Refer to medical officer review of NDA 200740 received March 2010 for the complete clinical review.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Refer to medical officer review of NDA 200740 received March 2010 for the complete clinical review.

3.2 Compliance with Good Clinical Practices

Refer to medical officer review of NDA 200740 received March 2010 for the complete clinical review.

3.3 Financial Disclosures

Refer to medical officer review of NDA 200740 received March 2010 for the complete clinical review.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Refer to medical officer review of NDA 200740 received March 2010 for the complete clinical review.

4.2 Clinical Microbiology

Refer to medical officer review of NDA 200740 received March 2010 for the complete clinical review.

4.3 Preclinical Pharmacology/Toxicology

Refer to medical officer review of NDA 200740 received March 2010 for the complete clinical review.

4.4 Clinical Pharmacology

Refer to medical officer review of NDA 200740 received March 2010 for the complete clinical review.

4.4.1 Mechanism of Action

Refer to medical officer review of NDA 200740 received March 2010 for the complete clinical review.

4.4.2 Pharmacodynamics

Refer to medical officer review of NDA 200740 received March 2010 for the complete clinical review.

4.4.3 Pharmacokinetics

Refer to medical officer review of NDA 200740 received March 2010 for the complete clinical review.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Refer to medical officer review of NDA 200740 received March 2010 for the complete clinical review.

5.2 Review Strategy

Refer to medical officer review of NDA 200740 received March 2010 for the complete clinical review.

5.3 Discussion of Individual Studies/Clinical Trials

Refer to medical officer review of NDA 200740 received March 2010 for the complete clinical review.

6 Review of Efficacy

Efficacy Summary

6.1 Indication

Refer to medical officer review of NDA 200740 received March 2010 for the complete clinical review.

6.1.1 Methods

Refer to medical officer review of NDA 200740 received March 2010 for the complete clinical review.

6.1.2 Demographics

Refer to medical officer review of NDA 200740 received March 2010 for the complete clinical review.

6.1.3 Subject Disposition

Refer to medical officer review of NDA 200740 received March 2010 for the complete clinical review.

6.1.4 Analysis of Primary Endpoint(s)

Refer to medical officer review of NDA 200740 received March 2010 for the complete clinical review.

6.1.5 Analysis of Secondary Endpoints(s)

Refer to medical officer review of NDA 200740 received March 2010 for the complete clinical review.

6.1.6 Other Endpoints

Refer to medical officer review of NDA 200740 received March 2010 for the complete clinical review.

6.1.7 Subpopulations

Refer to medical officer review of NDA 200740 received March 2010 for the complete clinical review.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Refer to medical officer review of NDA 200740 received March 2010 for the complete clinical review.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Refer to medical officer review of NDA 200740 received March 2010 for the complete clinical review.

6.1.10 Additional Efficacy Issues/Analyses

Refer to medical officer review of NDA 200740 received March 2010 for the complete clinical review.

7 Review of Safety

Safety Summary

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

As requested in FDA's September 3, 2010 Complete Response Letter the Safety Update has been submitted for the period of May 1, 2010, through December 30, 2011.

During this period a total of 112 cystinosis patients were exposed to cysteamine ophthalmic solution: 102 returning patients and 10 new patients.

7.1.2 Categorization of Adverse Events

The same process that was utilized in previous 120-day safety updates for collecting Terms of Interest applied to the present safety update.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

During this safety update period adverse events (AEs) were reported in 69 of the 112 (62%) participating patients.

Refer to Section 7.3.4 for Table of AEs.

7.2 Adequacy of Safety Assessments

The same process that was utilized in previous 120-day safety updates for collecting Terms of Interest applied to the present safety update.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

During this period of the safety update, a total of 112 cystinosis patients were exposed to cysteamine ophthalmic solution: 102 returning patients, and 10 new patients.

7.2.2 Explorations for Dose Response

Refer to medical officer review of NDA 200740 received March 2010 for the complete clinical review.

7.2.3 Special Animal and/or In Vitro Testing

Refer to medical officer review of NDA 200740 received March 2010 for the complete clinical review.

7.2.4 Routine Clinical Testing

Refer to medical officer review of NDA 200740 received March 2010 for the complete clinical review.

7.2.5 Metabolic, Clearance, and Interaction Workup

Refer to medical officer review of NDA 200740 received March 2010 for the complete clinical review.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Refer to medical officer review of NDA 200740 received March 2010 for the complete clinical review.

7.3 Major Safety Results

7.3.1 Deaths

During the safety update reporting period from May 1, 2010, to December 30, 2011, one patient died. The patient death occurred on (b) (6) in a female 23.7 years of age due to uremia and pericarditis. The patient was in the study for 20 years, with the first assessment on (b) (6) when the patient was 2½ years of age, and the last assessment was on May 27, 2009. The death was considered unrelated to Cystaran.

7.3.2 Nonfatal Serious Adverse Events

During the current safety update one ocular serious adverse event (SAE) of blindness was reported and no non-ocular SAEs were reported. The SAE of blindness was considered by the investigator as not related to cysteamine and due to progressive decline in the cornea that had started before the administration of cysteamine drops.

This patient entered into the cysteamine HCL ophthalmic solution protocol in January 1997, at which time her vision was 20/160 in the right eye and 20/80 in the left, the reduction was resulting from a severe corneal epitheliopathy (filaments and disrupted epithelium) in the setting of a heavy crystal burden in the cornea from cystinosis. The patient was started on cysteamine ophthalmic solution, which over the ensuing years,

caused the corneal crystal density to decline and brought the patient relief from ocular pain. However, her vision continued to deteriorate as her corneal epithelium remained disrupted, eventually leading to corneal neovascularization and calcification.

7.3.3 Dropouts and/or Discontinuations

During this safety update period of May 1, 2010 through December 30, 2011, a total of 112 cystinosis patients were exposed to cysteamine ophthalmic solution: 102 returning patients, and 10 new patients.

7.3.4 Significant Adverse Events

Summary of the Incidence of the Most Common (≥ 2.0%) Adverse Events (n and %) for the Study Update Safety population	
System Organ Class Preferred Term	**May 1, 2010 to December 30, 2011 (N=112)**
Number of patients with at least one AE	69 (62%)
Eye Disorders	59 (53%)
Photophobia	54 (48%)
Eye pain	5 (5%)
Ocular Hyperemia	3 (3%)
Eye Irritation	4 (4%)
Nervous System Disorders	22 (20%)
Headache	19 (17%)
Benign Intracranial Hypertension	5 (5%)
General Disorders and Administration Site Conditions	7 (6%)
Instillation site pain	5 (5%)

Note: A patient experiencing multiple occurrences of an AE is counted only within each system organ class and within each preferred term.

7.3.5 Submission Specific Primary Safety Concerns

No new or unexpected information was found during the reporting period that would require changes to the labeling or overall safety conclusions previously submitted in the NDA.

7.4 Supportive Safety Results

Refer to Section 7.3.4 for Table of AEs.

7.4.1 Common Adverse Events

Refer to Section 7.3.4 for Table of AEs.

7.4.2 Laboratory Findings

Refer to medical officer review of NDA 200740 received March 2010 for the complete clinical review.

7.4.3 Vital Signs

Refer to medical officer review of NDA 200740 received March 2010 for the complete clinical review.

7.4.4 Electrocardiograms (ECGs)

Refer to medical officer review of NDA 200740 received March 2010 for the complete clinical review.

7.4.5 Special Safety Studies/Clinical Trials

Refer to medical officer review of NDA 200740 received March 2010 for the complete clinical review.

7.4.6 Immunogenicity

No studies were performed given the well established profile of FA.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Refer to medical officer review of NDA 200740 received March 2010 for the complete clinical review.

7.5.2 Time Dependency for Adverse Events

Refer to medical officer review of NDA 200740 received March 2010 for the complete clinical review.

7.5.3 Drug-Demographic Interactions

Refer to medical officer review of NDA 200740 received March 2010 for the complete clinical review.

7.5.4 Drug-Disease Interactions

Refer to medical officer review of NDA 200740 received March 2010 for the complete clinical review.

7.5.5 Drug-Drug Interactions

Refer to medical officer review of NDA 200740 received March 2010 for the complete clinical review.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Refer to medical officer review of NDA 200740 received March 2010 for the complete clinical review.

7.6.2 Human Reproduction and Pregnancy Data

Refer to medical officer review of NDA 200740 received March 2010 for the complete clinical review.

7.6.3 Pediatrics and Assessment of Effects on Growth

Refer to medical officer review of NDA 200740 received March 2010 for the complete clinical review.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Refer to medical officer review of NDA 200740 received March 2010 for the complete clinical review.

7.7 Additional Submissions / Safety Issues

On August 24, 2012 the 120 Day Safety Update was submitted. No new or unexpected information was found that would require changes to the label or overall safety conclusions previously submitted in the NDA.

8 Postmarket Experience

Refer to medical officer review of NDA 200740 received March 2010 for the complete clinical review.

Appendices

9.1 Literature Review/References

Refer to medical officer review of NDA 200740 received March 2010 for the complete clinical review.

9.2 Labeling Recommendations

The labeling found in this Appendix (package insert submitted by Sigma-Tau Pharmaceuticals, Inc. on 8/17/12 and carton and container labeling submitted on 9/13/12) is acceptable.

A typographical error in the package insert Table of Contents (misplaced WARNING) should be corrected in the final printed labeling.

9.3 Advisory Committee Meeting

No new issues have been raised in this application which were believed to benefit from an Advisory Committee discussion.

6 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

MARTIN P NEVITT
09/19/2012

WILLIAM M BOYD
09/19/2012

Division Director Review for NDA 200740

Date	September 2, 2010
From	Wiley A. Chambers, M.D.
NDA #	200740
Applicant	Sigma-Tau Pharmaceuticals, Inc.
Date of Submission	March 3, 2010
Type of Application	505(b)(2)
Name	Cystaran (cysteamine hydrochloride ophthalmic solution) 0.44%
Dosage forms / Strength	Topical ophthalmic solution
Proposed Indication(s)	Treatment of corneal cystine crystal accumulation in patients with cystinosis
Action:	Not approved

1. Introduction

Cystinosis is a rare autosomal recessive metabolic disorder characterized by the intracellular accumulation of cystine, the disulfide of the amino acid cysteine, in many organs and tissues. Cystine accumulation is due to a defective lysosomal cystine transport system and results in tissue-damaging cystine crystal formation within cells of the kidney, bone marrow, pancreas, muscle, brain, and eye. If untreated, leads to renal failure by the age of 10 years. The mainstay of treatment for cystinosis is oral cysteamine. Oral cysteamine was approved in the United States as Cystagon (cysteamine bitartrate) Capsules (NDA 20-392) in 1994 for the management of nephropathic cystinosis in children and adults. If administered chronically and diligently beginning prior to 2 years of age, oral cysteamine retards or prevents glomerular deterioration and enhances growth in children with nephropathic cystinosis.

Corneal cystine crystals are an ocular manifestation of nephropathic cystinosis that progressively worsens with time and does not spontaneously resolve. In the cornea, cystine crystals generally appear by 1 year of age and are pathonemonic of cystinosis. They initially appear in the central cornea and progress to the full thickness of the peripheral cornea and anterior two-thirds of the central cornea with age. These cystine crystals are considered partly responsible for clinical symptoms of photophobia, recurrent corneal erosions, and secondary blepharospasm that complicate longstanding cystinosis.

Cysteamine is an aminothiol that converts cystine to cysteine and cysteine-cysteamine mixed disulfide, both of which can pass through the lysosomal membrane of patients with cystinosis without a functional carrier and both of which can then be eliminated from the cell. The lack of effect of oral cysteamine on the ocular effects of cystinosis led to the development of an ophthalmic formulation. Cystaran is a sterile ophthalmic solution containing 6.5 mg of cysteamine hydrochloride, equivalent to 4.4 mg of cysteamine as the active ingredient.

2. Background

This is a 505(b)(2) application. The applicant, Sigma Tau Pharmaceuticals, Inc., lists Cystagon (cysteamine bitartrate) Capsules (Mylan Pharmaceuticals, Inc.) as the reference listed drug product.

The information referenced by Sigma Tau is toxicology information of the drug substance. The drug substance is chemically the same between Cystaran and Cystagon.

There are no approved drug products for the prevention and treatment of corneal cystine crystal accumulation in patients with cystinosis. An orphan designation for cysteamine hydrochloride for the treatment of corneal cystine crystal accumulation in patients with cystinosis was granted in August 1997.

3. CMC

Cysteamine HCl drug substance is a [redacted] It is prone to oxidation and forms the disulfide, cystamine 2HCl, [redacted] The drug substance is manufactured by [redacted]

Formulation:

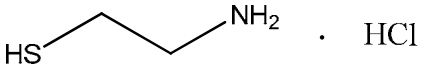
Cysteamine HCl	6.5 mg/mL
Sodium Chloride	[redacted]
Benzalkonium Chloride	0.1 mg/mL
HCl/NaOH	adjust to pH [redacted]
Purified water	[redacted]

The original commercial formulation proposed in the NDA had [redacted] sodium chloride [redacted] The Division, in a teleconference with Sigma-Tau on April 28, 2010, informed the company that the commercial formulation should be identical to the formulation used in the clinical trials. The company agreed to revise the NDA commercial formulation to match formulation 3, and accordingly sodium chloride was revised [redacted] The revised formulation results in a [redacted]

Stability Specifications

Description	Clear, colorless solution
pH	3.8-4.8
Osmolality	360-420 mOsmol/kg
Particulate matter	NMT [redacted]
[redacted]	NMT [redacted]
Identification	Reten s standard UV-vis spectrum concordant with sample
Cysteamine HCl	[redacted]
Specified impurities	NMT [redacted]
Individual unspecified impurities	NMT
Total specified and unspecified impurities	NMT
Benzalkonium chloride	[redacted]
[redacted]	[redacted]
Bacterial endotoxin	NMT [redacted]
Sterility	Meets USP

Cysteamine HCl Structural Formula:



Molecular Formula: C_2H_7NS HCl

The drug product will be packaged in 15 mL LDPE round bottles with a white LDPE controlled drop dispenser and a white propylene cap. Container closure parts are (b) (4)

FACILITY INSPECTIONS

Manufacturing facilities for the drug substance and the drug product are not in compliance with current good manufacturing practice. Satisfactory resolution of this deficiency is required before this application may be approved.

4. Nonclinical Pharmacology/Toxicology

Studies of cysteamine hydrochloride ophthalmic solution 0.1-10% included one GLP study conducted by the Applicant and two studies from the peer-reviewed scientific literature.

In the GLP-compliant study in rabbits, 2 drops of 0.44% cysteamine ophthalmic solution was administered hourly for 8 hours per day for 30 days to the right eye of 12 rabbits/sex. No findings of irritation, corneal disruption, or ocular histopathology were reported. In published studies in rabbits, gross and/or microscopic signs of irritation or inflammation were seen following ocular administration of cysteamine at concentrations of 1% and higher when administered hourly for 8 consecutive hours for 4 weeks, while eyes treated with 0.08% or 0.4% cysteamine for 3 months were reported to be normal.

5. Clinical Pharmacology/Biopharmaceutics

The Applicant did not perform any human pharmacokinetic assessment of cysteamine HCl ophthalmic solution and was granted a waiver based on 21 CFR 320.22 (e) of the *in vivo* bioavailability requirement because of the expected low systemic exposure of cysteamine following ophthalmic administration of cysteamine solution in comparison to exposures observed following orally administered cysteamine bitartrate as described below.

The total daily dose of 0.44% cysteamine HCl ophthalmic solution is estimated to be 7.8 mg/day based on a 100 µL dose per hour × 12 waking hours. The recommended daily maintenance dose approved for orally administered cysteamine ranges from 400 mg/day for an infant with body weight <10 pounds to 2000 mg/day for adults. Therefore, the total daily ophthalmic dose is less than 2% of the recommended oral daily dose of cysteamine. Even assuming complete systemic availability, the peak plasma concentration of cysteamine following ophthalmic administration is expected to be substantially less than the peak plasma concentration following oral administration of cysteamine.

6. Sterility Assurance

There are no microbiology deficiencies identified. Container closure integrity testing was conducted using 20 media filled experimental containers (obtained from three consecutive media fills) plus one positive control (container pierced with a 27 g needle) and one negative control. Experimental vials and the positive control were immersed in a suspension of *B. diminuta* for 18-24 hours then scored for growth. All experimental vials were negative for growth. All positive control vials were positive for growth.

Preservative effectiveness testing was conducted according to USP <51> on lots containing 50, 75, and 100% of the labeled preservative content. The stability protocol states that lots must contain a minimum of 75% % of the preservative content. All of the samples met the acceptance criteria for a category 1 product.

Endotoxin testing will be conducted according to USP <85> using the kinetic turbidimetric method. The applicant has proposed an endotoxin limit of (b) (4) The sensitivity of the lysate to be used for endotoxin testing is (b) (4) The Applicant proposes the use of a (b) (4) for endotoxin testing and provided the results of inhibition/enhancement testing using the (b) (4). No inhibition or enhancement of the test was observed (b) (4) The results of endotoxin testing on three product lots were provided in the 28 July 2010 submission. Each of the product lots contained (b) (4) of drug product.

7. Clinical/Statistical - Efficacy

Three clinical studies, STP869294 (CAPTOC), 98-EI-0109S, and 98-EI-1090E, were submitted to provide efficacy and safety data for cysteamine ophthalmic solution (Formulation 3). In these studies, the applicant defined a response as an eye with a decrease from baseline of at least 1.00 unit in CCCS at some time during the study when baseline CCCS is ≥ 1.00 or CCCS does not increase by at least 1.00 unit at some time during the study when baseline CCCS is < 1.00. This implies a reduction in CCCS, in eyes with high CCCS (≥1) at baseline, which need not be sustained, i.e., transient reduction in CCCS. While, in eyes with low CCCS (<1) at baseline, the lack of increase in CCCS has to be sustained.

The CAPTOC Study, a combined study of three historically controlled single center studies, shows that 30% of eyes using cysteamine ophthalmic solution (Formulations 1-4) responded for the mITT population. Cumulative response rates were also calculated for eyes with CCCS ≥1 at baseline and results show that about 10% had response in Year 1 and by Year 6 about 30% of the patients had response at some time during the study.

In Study 98-EI-0109S, a double-masked, randomized, within-patient-controlled study, the mean change from baseline CCCS score at month 6 in Formulation 3 is -0.22 and 0.24 for Formulation 5. This means that Formulation 3 reduces CCCS by 0.22 while Formulation 5 has an increase in CCCS by 0.24.

In Study 98-EI-0109E, a double-masked, randomized, within-patient-controlled study, the number of eyes with a reduction of CCCS of 1.00 unit or more was higher in those that received Formulation (67%) compared with Formulation 5 (13%) at some time during the treatment period. The difference in the mean change from baseline CCCS is higher in Formulation 3 than in Formulation 5 at every visit from Month 3, Month 6, Month 9, and Month 12.

The three studies demonstrate that cysteamine ophthalmic solution (Formulation 3) reduces formation of corneal crystals. This reduction however is temporary. Strict adherence to therapy is essential to the efficacy of Formulation 3.

Study STP869294 (CAPTOC)

Timepoint	N	n (%)	(95% confidence interval)
Response at any time during study	321	98 (30%)	(25-36%)
Eyes with CCCS ≥1 at baseline	291	94 (32%)	(27-38%)
Eyes with CCCS<1 at baseline	30	4 (13%)	(4-31%)
Cumulative Response Rates by Year in Eyes with CCCS ≥1			
Year 1		27 (9%)	(6-13%)
Year 2		51 (17%)	(13-22%)
Year 3		72 (25%)	(20-30%)
Year 4		80 (27%)	(22-35%)
Year 5		85 (29%)	(24-35%)
Year 6		87 (30%)	(25-36%)

Study 98 EI0109E

Timepoint	Formulation 5	Formulation 3	p-value
Month 3	2 (13%)	4 (29%)	0.08
Month 6	2 (14%)	7 (50%)	0.025
Month 9	1 (7%)	8 (57%)	0.008
Month 12	1 (7%)	7 (47%)	0.01
Anytime	2 (13%)	10 (67%)	0.005

Study 98 EI0109S

Group	Formulation 5	Formulation 3	p-value
Eyes with CCCS ≥1	8 (44%)	9 (50%)	>0.05
Eyes with CCCS<1	0	3 (33%)	0.08

Summary - There is substantial evidence of effectiveness consisting of adequate and well controlled studies which demonstrate that Cystaran (cysteamine hydrochloride ophthalmic solution) 0.44% reduces the accumulation of cystine corneal crystals considered partly responsible for clinical symptoms of photophobia, recurrent corneal erosions, and secondary blepharospasm that complicate longstanding cystinosis.

8. Safety

Studies STP869294 (CAPTOC), 98 EI0109E, and 98 EI0109S were utilized to evaluate safety.

For the purposes of labeling the adverse event profile of cysteamine hydrochloride ophthalmic solution 0.44%, the data from STP869294 (CAPTOC) was utilized. CAPTOC enrolled 247 subjects; the trial duration was 19 years. The adverse event profiles seen in 98 EI0109E, and 98 EI0109S are consistent with STP869294 (CAPTOC).

Adverse Events for 247 evaluated patients

Photophobia	157	(64%)
Conjunctival hyperemia	69	(28%)
Eye pain	48	(19%)
Ocular hyperemia	43	(17%)
Eye irritation	42	(17%)
Instillation site irritation	30	(12%)
Lacrimation increased	21	(9%)
Keratitis	19	(8%)
Optic disc disorder	18	(7%)
Vision blurred	17	(7%)
Instillation site pain	17	(7%)
Dry Eye	13	(5%)
Eyelid edema	12	(5%)
Retinal disorder	11	(5%)
Conjunctivitis	10	(4%)
Eye pruritis	10	(4%)
Blindness	7	(3%)
Corneal epithelial disorder	6	(2%)
Blepharitis	5	(2%)
Erythema of eyelid	5	(2%)

Deaths
Eighteen deaths were reported in the three studies comprising the CAPTOC analysis. Two of the patient deaths (Patient 374973 and Patient 835249) were reported to FDA in IND Safety Reports. Five patients (Patients 221252, 315632, 352157, 727697, and 883818) died with no cause provided. There were no deaths in 98 EI0109S and 98 EI0109S.

Safety Summary -There is substantial evidence of safety consisting of adequate and well controlled studies which demonstrate that Cystaran (cysteamine hydrochloride ophthalmic solution) 0.44%, dosed every hour while awake, is safe for the treatment of corneal cystine crystal accumulation in patients with cystinosis. The most common ocular adverse events in CAPTOC occurring in ≥ 10 % of patients were sensitivity to light, redness, and eye pain/irritation.

9. Advisory Committee Meeting

No Advisory Committee Meeting was held. There were no new issues raised in the review of the application which were thought to benefit from an Advisory Committee Meeting.

10. Pediatrics

The safety and effectiveness of Cystaran (cysteamine hydrochloride ophthalmic solution) 0.44% in pediatric patients have been established for the treatment of corneal cystine crystal accumulation in patients with cystinosis.

11. Other Relevant Regulatory Issues

DSI

A Division of Scientific Investigations (DSI) audit was requested; DSI completed their review on August 23, 2010. The protocols inspected were Protocol 98-EI-0109E, Protocol 98-EI-0109S, and Protocol STP869294. Two domestic clinical investigators, Drs. Gahl (Muriel Kaiser) and Monte, and the applicant and CRO were inspected.

The preliminary classification of Clinical Investigator inspections of Dr. William A. Gahl and Dr. Monte A. Del Monte, are Voluntary Action Indicated (VAI). While DSI considers primary safety and efficacy data from these sites to be generally reliable in support of the requested indication, the review division will need to determine the potential impact of the following observations on approvability of the application:

- At Dr. Gahl's site, the potential impact, if any, that missing safety data from study 98-EI-0109S has on safety analyses and conclusions.
- At Dr. Del Monte's site, whether discrepancies in drug bottles issued compared with drug bottles returned accounting for ≤10% of the total number of bottles or doses potentially administered is within acceptable limits for total potential doses administered.

The preliminary classification of the sponsor/applicant, Sigma-Tau Pharmaceuticals, Inc. and the CRO, (b) (4) are No Action Indicated (NAI), based on preliminary communications with the FDA field investigator.

Regarding the Drs. Gahl/Kaiser site, alternate source data (diary entries, drug dispensation records, ophthalmic evaluation records, and subject interview questionnaires) support that study drug, as randomized, was administered to the subjects. The missing study data discussed by DSI are not expected to have any impact on safety analyses and conclusions.

Regarding Dr. Del Monte's site, discrepancies in drug bottles issued compared with drug bottles returned accounting for ≤10% of the total number of bottles or doses potentially administered are well within acceptable limits for total potential doses administered. These four subjects received over 100 bottles of study drug during the course of the efficacy study. The bottle count discrepancy discussed by DSI is not expected to have any impact on efficacy or safety analyses and conclusions.

FINANCIAL DISCLOSURE

The applicant has examined its financial data regarding significant payments of other sorts made to all investigators in the studies and equity information as provided by the investigators, as defined in 21 CFR 54.2. There is no evidence to suggest that the results of the study were impacted by any financial payments.

DMEPA

The Division of Medication Error Prevention and Analysis (DMEPA) Proprietary Name Risk Assessment evaluated "Cystoran" as the proposed proprietary name for cysteamine hydrochloride ophthalmic solution. DMEPA found the name "Cystoran" unacceptable (b) (4) During a teleconference with the applicant on May 6, 2010, DMEPA informed Sigma-Tau the name would be unacceptable and requested submission of an alternate proprietary name.

On May 13, 2010, the name "Cystoran" was withdrawn, and on May 14, 2010, the name "Cystaran" was submitted as an alternate proprietary name by the applicant. DMEPA approved this alternate proprietary name in a letter dated August, 12, 2010.

DDMAC

The Division of Drug Marketing, Advertising, and Communications (DDMAC) reviewed the draft product labeling, including the package insert (PI), draft carton label, and draft container label for Cystaran (cysteamine hydrochloride ophthalmic solution) 0.44%. DDMAC was invited to the two labeling meetings held on August 4 and 13, 2010, and provided a separate review.

DRISK

The Division of Risk Management (DRISK) reviewed the draft product labeling, including the package insert (PI), draft carton label, and draft container label for Cystaran (cysteamine hydrochloride ophthalmic solution) 0.44%. DRISK was invited to the two labeling meetings held on August 4 and 13, 2010, and provided a separate review. A decision was made at the second labeling meeting not to include a Patient Package Insert with the Cystaran labeling because there was nothing new or novel regarding the administration of this ophthalmic solution to the eyes.

12. Labeling

The labeling submitted by Sigma-Tau Pharmaceuticals, Inc. on August 30, 2010 is acceptable.

(b) (4)

6 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/ TS) immediately following this page

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200740	ORIG-1	SIGMA TAU PHARMACEUTICALS INC	(Cysteamine hydrochloride ophthalmic solution) 0.65% Sterile

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/s/

WILEY A CHAMBERS
09/03/2010

Cross-Discipline Team Leader Review for NDA 200740

Date	August 31, 2010
From	William M. Boyd, M.D.
Subject	Cross-Discipline Team Leader Review
NDA #	200740
Applicant	Sigma-Tau Pharmaceuticals, Inc.
Date of Submission	March 3, 2010
PDUFA Goal Date	September 4, 2010
Type of Application	505(b)(2)
Name	Cystaran (cysteamine hydrochloride ophthalmic solution) 0.44%
Dosage forms / Strength	Topical ophthalmic solution
Proposed Indication(s)	treatment of corneal cystine crystal accumulation in patients with cystinosis
Recommended:	Not recommended for Approval

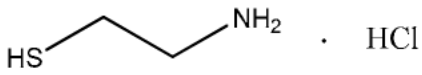
1. Introduction

Cystinosis is a rare autosomal recessive metabolic disorder characterized by the intracellular accumulation of cystine, the disulfide of the amino acid cysteine, in many organs and tissues. Cystine accumulation is due to a defective lysosomal cystine transport system and results in tissue-damaging cystine crystal formation within cells of the kidney, bone marrow, pancreas, muscle, brain, and eye. The disease often presents with growth retardation and renal tubular Fanconi syndrome in the first year of life and, if untreated, leads to renal failure by the age of 10 years.

The mainstay of treatment for cystinosis is oral cysteamine. If administered chronically and diligently beginning prior to 2 years of age, oral cysteamine retards or prevents glomerular deterioration and enhances growth in children with nephropathic cystinosis.

Corneal cystine crystals are an ocular manifestation of nephropathic cystinosis that progressively worsens with time and does not spontaneously resolve. In the cornea, cystine crystals generally appear by 1 year of age and are pathognomonic of cystinosis. They initially appear in the central cornea and progress to the full thickness of the peripheral cornea and anterior two-thirds of the central cornea with age. These cystine crystals are considered partly responsible for clinical symptoms of photophobia, recurrent corneal erosions, and secondary blepharospasm that complicate longstanding cystinosis.

Cysteamine HCl Structural Formula:



Molecular Formula: C_2H_7NS HCl

Cysteamine is an aminothiol that converts cystine to cysteine and cysteine-cysteamine mixed disulfide, both of which can pass through the lysosomal membrane of patients with cystinosis without a functional carrier and both of which can then be eliminated from the cell. Oral cysteamine was approved in the United States as Cystagon (cysteamine bitartrate) Capsules in 1994 for the management of nephropathic cystinosis in children and adults. Originally, it was thought that oral cysteamine therapy would prevent the ophthalmic complications of cystinosis, including corneal crystals, photophobia, blepharospasm, and eye pain; however, this did not occur. The absence of a vascular supply to the cornea limits cystine depletion in the eye following oral cysteamine administration.

The lack of effect of oral cysteamine on the ocular effects of cystinosis led to the development of an ophthalmic formulation. Cystaran is a sterile ophthalmic solution containing 6.5 mg of cysteamine hydrochloride, equivalent to 4.4 mg of cysteamine as the active ingredient.

2. Background

This is a 505(b)(2) application. The Form 356h submitted by Sigma Tau Pharmaceuticals, Inc., lists Cystagon (cysteamine bitartrate) Capsules (Mylan Pharmaceuticals, Inc.) as the reference listed drug Product.

The information being used by Sigma Tau as the 505(b)(2) information is toxicology information using an overexposure to the drug substance. This overexposure to the drug substance cannot be achieved with the drug product Cystaran for either a 505(b)(1) or a (b)(2) application; overexposure to drug substance is instead done with a different dosing regimen and formulation of the active ingredient. The bridge between Cystaran and Cystagon is that the drug substance is chemically the same (cysteamine) determined chemically.

There are no approved drug products for the prevention and treatment of corneal cystine crystal accumulation in patients with cystinosis. An orphan designation for cysteamine hydrochloride for the treatment of corneal cystine crystal accumulation in patients with cystinosis was granted in August 1997.

NDA 20-392 for Cystagon (cysteamine bitartrate) Capsules was approved in 1994 for the management of nephropathic cystinosis in children and adults.

3. CMC

From the CMC Review finalized 8/2/2010:

Cysteamine HCl drug substance is a [redacted] (b) (4) (b) (4) It is prone to oxidation and forms the disulfide, cystamine 2HCl, [redacted] (b) (4)

The drug substance is manufactured by (b) (4)

The drug substance is freely soluble in water. (b) (4) Cysteamine degrades to a dimer, cystamine 2 HCl, and for this reason the DP is stored frozen until use.

DESCRIPTION AND COMPOSITION OF THE DRUG PRODUCT:

The original commercial formulation proposed in the NDA had (b) (4) sodium chloride (b) (4) (b) (4) The Division, in a teleconference with Sigma-Tau on April 28, 2010, informed the company that the commercial formulation should be identical to the formulation used in the clinical trials. The company agreed to revise the NDA commercial formulation to match formulation 3, and accordingly sodium chloride was revised (b) (4) The revised formulation results in a (b) (4)

Component	Clinical NIH Formulation 2	Clinical NIH Formulation 3	NDA Commercial Formulation 2
Cysteamine HCl	6.5 mg[a]	6.5 mg[a]	6.5 mg
Sodium Chloride	(b) (4)	(b) (4)	
Benzalkonium Chloride		0.1 mg	(b) (4)
Hydrochloric acid			(b) (4)
Sodium Hydroxide			
(b) (4)			
Purified Water			
			(b) (4)

The drug product will be packaged in 15 mL LDPE round bottles with a white LDPE controlled drop dispenser and a white propylene cap. Container closure parts are (b) (4)

FACILITY INSPECTIONS

Manufacturing facilities for the drug substance and the drug product are not in compliance with current good manufacturing practice. Satisfactory resolution of this deficiency is required before this application may be approved.

The CMC Reviewer has not recommended approval for this application based on these outstanding cGMP issues.

PROPOSED SPECIFICATIONS:

Table 3.2.P.5.1-1. Release and Stability Specifications for Cysteamine HCl Ophthalmic Solution

Test	Release Acceptance Criteria	Stability Acceptance Criteria	Analytical Procedures
Description	Clear, colorless solution	Clear, colorless solution	Visual
pH	4.00–4.60	3.80–4.80	USP <791>
Osmolality	360-420 mOsmol/kg[a]	360-420 mOsmol/kg[a]	*M-239*
Deliverable Volume	Meets requirements	NA	USP <698>
Particulate Matter	(b) (4)		USP <789> Microscopic
(b) (			*M-737*
Identification UPLC	The retention time of the cysteamine HCl peak in the chromatogram of the test sample preparation corresponds to the cysteamine HCl peak in the chromatogram of the standard preparation.	NA	*M-1017*
UV-Vis	The UV-vis spectrum (between (b) (4) for the cysteamine HCl in the product sample preparation concordant with the UV-vis spectrum of cysteamine HCl in the cysteamine HCl standard preparation.	NA	
Cysteamine HCl	(b) (4)		
Specified Impurities/Degradation Product (b) (4)	NMT (b) (4)	NMT (b) (4)	
Individual Unspecified Impurities/Degradation Products	NMT (b) (4)	NMT (b) (4)	

Table 3.2.P.5.1-1. Release and Stability Specifications for Cysteamine HCl Ophthalmic Solution			
Test	**Release Acceptance Criteria**	**Stability Acceptance Criteria**	**Analytical Procedures**
Total Specified and Unspecified Impurities/Degradation Products of Cysteamine HCl	(b) (4)	(b) (4)	(b) (4)
Benzalkonium Chloride	(b) (4)	(b) (4)	*M-1015*
(b) (4)			
Sterility	Meets requirements	Meets requirements	*M-226*, USP <71>
Preservative Challenge[b]	Meets requirements	Meets requirements	*M-03* USP <51>
Bacterial Endotoxin	(b) (4)	NA	USP <85>

[a] = Specification for previously proposed commercial formulation (supporting stability studies) was 260-330 mOsmol/kg.
[b] = Preservative challenge testing will only be conducted on the development and validation batches.
NA = Not applicable.

Source: July 30, 2010 submission, 3.2.P.5.1 Specifications

4. Nonclinical Pharmacology/Toxicology

From the original Pharmacology/Toxicology Review finalized 7/7/2010:

Studies of cysteamine hydrochloride ophthalmic solution 0.1-10% included one GLP study conducted by the Applicant and two studies from the peer-reviewed scientific literature.

In the GLP-compliant study in rabbits, 2 drops of 0.55% cysteamine ophthalmic solution was administered hourly for 8 hours per day for 30 days to the right eye of 12 rabbits/sex. No findings of irritation, corneal disruption, or ocular histopathology were reported. In published studies in rabbits, gross and/or microscopic signs of irritation or inflammation were seen following ocular administration of cysteamine at concentrations of 1% and higher when administered hourly for 8 consecutive hours for 4 weeks, while eyes treated with 0.1% or 0.5% cysteamine for 3 months were reported to be normal.

5. Clinical Pharmacology/Biopharmaceutics

From the original Clinical Pharmacology Review finalized 8/4/2010:

Cysteamine acts as a cystine-depleting agent by converting cystine to cysteine and cysteine-cysteamine mixed disulfides and thus reduces corneal cystine crystal accumulation

The Applicant did not perform any human pharmacokinetic assessment of cysteamine HCl ophthalmic solution and did not specifically request a waiver of the *in vivo* bioavailability requirement. Based on 21 CFR 320.22 (e), the Applicant was granted a waiver of the *in vivo* bioavailability requirement because of the expected low systemic exposure of cysteamine following ophthalmic administration of cysteamine solution in comparison to exposures observed following orally administered cysteamine bitartrate as described below.

The total daily dose of 0.65%[1] cysteamine HCl ophthalmic solution is estimated to be 7.8 mg/day based on a 100 µL dose per hour × 12 waking hours. The recommended daily maintenance dose approved for orally administered cysteamine ranges from 400 mg/day for an infant with body weight <10 pounds to 2000 mg/day for adults. Therefore, the total daily ophthalmic dose is less than 2% of the recommended oral daily dose of cysteamine. Even assuming complete systemic availability, the peak plasma concentration of cysteamine following ophthalmic administration is expected to be substantially less than the peak plasma concentration following oral administration of cysteamine.

6. Sterility Assurance

From the original Product Quality Microbiology Review finalized 8/3/2010:

There are no microbiology deficiencies identified.

Container closure integrity testing was conducted using 20 media filled experimental containers (obtained from three consecutive media fills) plus one positive control (container pierced with a 27 g needle) and one negative control. Experimental vials and the positive control were immersed in a suspension of *B. diminuta* for 18-24 hours then scored for growth. All experimental vials were negative for growth. All positive control vials were positive for growth.

Preservative effectiveness testing was conducted according to USP <51> on lots containing 50, 75, and 100% of the labeled preservative content. The stability protocol states that lots must contain a minimum of 75% % of the preservative content. All of the samples met the acceptance criteria for a category 1 product.

Endotoxin testing will be conducted according to USP <85> using the kinetic turbidimetric method. The applicant has proposed an endotoxin limit of (b) (4). The sensitivity of the lysate to be used for endotoxin testing is (b) (4) The Applicant proposes the use of a (b) (4) for endotoxin testing and provided the results of inhibition/enhancement testing using the (b) (4). No inhibition or enhancement of the test was observed (b) (4). The results of endotoxin testing on

1 Cystaran is a sterile ophthalmic solution containing 6.5 mg of cysteamine hydrochloride, equivalent to 4.4 mg of cysteamine as the active ingredient.

three roduct lots were provided in the 28 July 2010 submission. Each of the roduct lots contained (b) (4) (b) (4) of drug product.

7. Clinical/Statistical - Efficacy

From the original Medical Officer Review dated 8/31/2010:

Analyses of Primary Endpoints

STP869294 (CAPTOC)

Table 12. Proportion of Eyes with Corneal Cystine Crystal Score (CCCS) Response (mITT Population)

Time Point	N[b]	Total Eyes (N = 322)	
		n (%)	95% CI[c]
Response at Any Time During Study[a]	321	98 (30.5%)	[25.5, 35.9%]
Eyes with CCCS ≥1.00 at Baseline	291	94 (32.3%)	[27.0, 38.0%]
Eyes with CCCS <1.00 at Baseline	30	4 (13.3%)	[3.8, 30.7%]
Cumulative Response Rates by Year (Eyes with CCCS ≥1.00 at Baseline)[a]	291		
Year 1		27 (9.3%)	[6.2, 13.2%]
Year 2		51 (17.5%)	[13.3, 22.4%]
Year 3		72 (24.7%)	[19.9, 30.1%]
Year 4		80 (27.5%)	[22.4, 33.0%]
Year 5		85 (29.2%)	[24.0, 34.8%]
Year 6[d]		87 (29.9%)	[24.7, 35.5%]

[a] = A response was defined as a decrease from baseline of at least 1.00 unit in CCCS at any time on study when baseline was ≥1.00, or CCCS did not increase at least 1.00 unit at any time on study when baseline CCCS was <1.00.
[b] = Percentages were based on the number of total eyes evaluated.
[c] = Clopper and Pearson 95% CI for percentage.
[d] = Cumulative response rates for Year 7 through Year 19 may be found in *Table 14.2.1.1*.
Source: *Table 14.2.1.1*.

Source: May 6, 2010, Clinical Study Report Amendment, CAPTOC, 11.4.1.1 Primary End Point

For eyes with a lower baseline CCCS of <1, the response rate in the mITT population was 13% (4/30) [95% CI: (4, 31)]. For eyes with a higher baseline CCCS of ≥1, the response rate was 32% (94/291) [95% CI: (27, 38)].

Values highlighted in yellow in this table and subsequent tables were revised in the May 20, 2010, submission.[2]

Table 13. Proportion of Eyes with Corneal Cystine Crystal Score (CCCS) Response (mITT-1 Population)			
		Total Eyes (N = 184)	
Time Point	**N[b]**	***n* (%)**	**95% CI[c]**
Response at Any Time During Study[a]	183	53 (29.0%)	[22.5, 36.1%]
Eyes with CCCS ≥1.00 at Baseline	156	49 (31.4%)	[24.2, 39.3%]
Eyes with CCCS <1.00 at Baseline	27	4 (14.8%)	[4.2, 33.7%]
Cumulative Response Rates by Year (Eyes with CCCS ≥1.00 at Baseline)[a]	156		
Year 1		11 (7.1%)	[3.6, 12.3%]
Year 2		22 (14.1%)	[9.1, 20.6%]
Year 3		33 (21.2%)	[15.0, 28.4%]
Year 4		40 (25.6%)	[19.0, 33.2%]
Year 5		43 (27.6%)	[20.7, 35.3%]
Year 6[d]		45 (28.8%)	[21.9, 36.6%]

[a] = A response was defined as a decrease from baseline of at least 1.00 unit in CCCS at any time on study when baseline was ≥1.00, or CCCS did not increase at least 1.00 unit at any time on study when baseline CCCS was <1.00.
[b] = Percentages were based on the number of total eyes evaluated.
[c] = Clopper and Pearson 95% CI for percentage.
[d] = Cumulative response rates for Year 7 through Year 19 may be found in *Table 14.2.1.2*.
Source: *Table 14.2.1.2*.

Source: May 6, 2010, Clinical Study Report Amendment, CAPTOC, 11.4.1.1 Primary End Point

For eyes with a lower baseline CCCS of <1, the response rate in the mITT-1 population was 15% (4/27) [95% CI: (4, 34)]. For eyes with a higher baseline CCCS of ≥1, the response rate was 32% (49/156) [95% CI: (24, 39)]. This is consistent with the mITT population results.

2 Per the May 20, 2010, submission: Upon review of the study data and the SAS program coding used to generate the initial analysis outcomes, Sigma-Tau confirmed the discrepancy between the CCCS response rates observed by FDA and those reported by Sigma-Tau. These differences were attributed to the manner in which missing values were handled in the response rate calculations. The Sigma-Tau analysis provided that patient eyes with one or more missing change-from-baseline CCCS values, due to missing post-baseline CCCS's, would be assigned as a response to treatment. This resulted in some patient eyes being regarded as responders when in fact there were no data to support that outcome. Sigma-Tau confirmed that when excluding any missing eye-year assessments of change-from-baseline CCCS values from the response rate calculations, the response outcome as observed by FDA was verified. In an effort to facilitate the review process, Sigma-Tau performed a new analysis based on FDA's method. The revised efficacy datasets and analyses have been amended in the STP869294 CSR and replace the original analyses.

98 EI0109E

Table 7. Proportion of Eyes with Reduction in CCCS of 1 Unit or More (Per-Protocol Population)

	Formulation 5		Formulation 3		
Time Point	***n* (%)[a]**	**95% CI[b]**	***n* (%)[a]**	**95% CI[b]**	***p*-Value[c]**
Any Time During Study	2 (13.3%)	1.7-40.5	10 (66.7%)	38.4-88.2	0.0047[d]
Month 3	2 (13.3%)	1.7-40.5	4 (28.6%)[e]	8.4-58.1	0.0833[f]
Month 6	2 (14.3%)[e]	1.8-42.8	7 (50.0%)[e]	23.0-77.0	0.0253[d]
Month 9	1 (7.1%)[e]	0.2-33.9	8 (57.1%)[e]	28.9-82.3	0.0082[d]
Month 12	1 (6.7%)	0.2-31.9	7 (46.7%)	21.3-73.4	0.0143[d]

[a] = Percentages are based on the number of eyes with non-missing values at the corresponding time point.
[b] = Clopper and Pearson 95% CI for percentage.
[c] = Results from McNemar's Test.
[d] = Statistically significant (p <0.05).
[e] = The number of eyes evaluated at this time point was only 14 as opposed to 15.
[f] = Note: At Month 3, Patient 3003 is excluded from the McNemar Test due to the fact that a valid assessment was not available for both eyes.
Source: *Table 14.2.1.1.1*.

Source: December 17, 2009, Clinical Study Report, 98 EI0109E, 11.4.1 Analysis of Efficacy

This study evaluated ocular cystinosis patients who had a baseline CCCS ≥1. The response rate in the Per Protocol population was 67% (10/15) [95% CI: (38, 88)] with Formulation 3. The response rate was 13% (2/15) [95% CI: (2, 41)] with Formulation 5.

98 EI0109S

Table 11.	**Proportion of Eyes with Reduction in CCCS of 1 Unit or More at Month 6 (Per-Protocol Population and Subset of Patients 2–12 Years of Age)**				
	Formulation 5		**Formulation 3**		
	***n* (%)**	**95% CI[b]**	***n* (%)**	**95% CI[b]**	***p*-Value[c]**
Per-Protocol Population (*n* = 18)					
Eyes With a CCCS ≥1 Unit at Baseline	8 (44.4%)	N/A	9 (50.0%)	N/A	N/A
Eyes With a Reduction in CCCS ≥1 Unit[a]	0 (0.0%)	0.0-36.9	3 (33.3%)	7.5-70.1	0.0833
Patients 2–12 years of Age (*n* = 8)					
Eyes With a CCCS ≥1 Unit at Baseline	3 (37.5%)	N/A	4 (50.0%)	N/A	N/A
Eyes With a Reduction in CCCS ≥1 Unit[a]	0 (0.0%)	0.0-70.8	0 (0.0%)	0.0-60.2	N/A

[a] = Percentages are based on the number of eyes with a CCCS of ≥1 at baseline.
[b] = Clopper and Pearson 95% CI for percentage.
[c] = Results from McNemar's Test.
N/A = Not applicable.
Source: *Table 14.2.1.1.1* and *Table 14.2.1.1.1a*.

Source: December 17, 2009, Clinical Study Report, 98 EI0109S, 11.4.1 Analysis of Efficacy

The majority of these patients in this study (12/20) had a baseline CCCS ≤1. The response rate in the Per Protocol Population with Formulation 3 was 33% (3/9) [95% CI: (8, 70)].

Although the focus of this study was on safety as defined by SAEs in eyes treated with Formulation 5, an increase in CCCS and/or a worsening of the ocular signs and symptoms of cystinosis could also be a safety concern. Although no decision on how to analyze these data was made a priori, the efficacy assessments were collected as per protocol.

Efficacy Summary Statement

There is substantial evidence of effectiveness consisting of adequate and well controlled studies which demonstrate that Cystaran (cysteamine hydrochloride ophthalmic solution) 0.44% reduces the accumulation of cystine corneal crystals considered partly responsible for clinical symptoms of photophobia, recurrent corneal erosions, and secondary blepharospasm that complicate longstanding cystinosis.

8. Safety

From the original Medical Officer Review dated 8/31/2010:

Studies STP869294 (CAPTOC), 98 EI0109E, and 98 EI0109S were utilized to evaluate safety.

Pooled adverse event data was not submitted in the new drug application.

For the purposes of labeling the adverse event profile of cysteamine hydrochloride ophthalmic solution 0.44%, the data from STP869294 (CAPTOC) was utilized. CAPTOC enrolled 247 subjects; the trial duration was 19 years.

The adverse event profiles seen in 98 EI0109E, and 98 EI0109S are consistent with STP869294 (CAPTOC).

Overall Exposure at Appropriate Doses/Durations

STP869294 (CAPTOC)

Because compliance was not analyzable in CAPTOC, the safety analyses were based on the assumption that all patients were on active treatment with ophthalmic cysteamine. As a conservative effort, these analyses actually encompassed times where patients may have been treated with cysteamine, placebo, or cystamine. The Table below provides the summary of study duration that details average treatment duration, minimum and maximum treatment duration, and how many patients were receiving treatment every year. For the Safety Population, the mean (±SD) treatment duration for the 247 patients was 5.8 ± 5.54 years. There were 4 patients that had been receiving treatment for the maximum duration of 19 years.

Table 14.1.5.1

Summary of Study Duration
ITT Population

	Total (N=247)
Duration on study (years)	
n	247
Mean	5.8
S.D.	5.54
Median	4.5
Min, Max	0.0, 19.0
Patients on study by year	
Baseline	247 (100.0)
1	180 (72.9)
2	176 (71.3)
3	153 (61.9)
4	137 (55.5)
5	128 (51.8)
6	113 (45.7)
7	102 (41.3)
8	94 (38.1)
9	85 (34.4)
10	74 (30.0)
11	63 (25.5)
12	55 (22.3)
13	47 (19.0)
14	34 (13.8)
15	25 (10.1)
16	15 (6.1)
17	10 (4.0)
18	7 (2.8)
19	4 (1.6)

Source: May 6, 2010, Clinical Study Report Amendment, CAPTOC, 12.1 Extent of Exposure

Subject Disposition

STP869294 (CAPTOC)

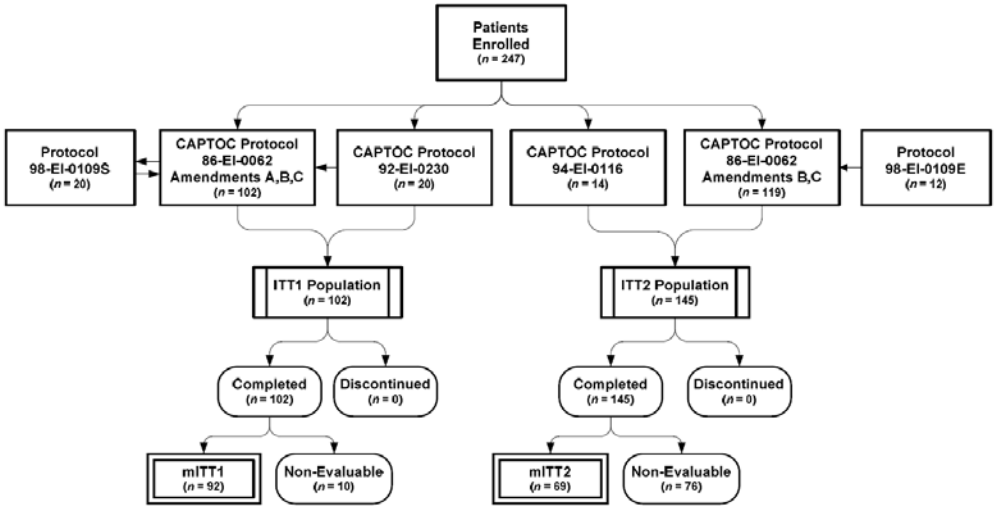


Figure 2. Patient disposition overview.

ITT-1 and ITT-2 populations labeled in this figure are for descriptive purposes only to delineate the discontinuation of placebo treatment. No efficacy analyses were performed on ITT-1 and ITT-2 populations.

Adverse Events

CAPTOC

Table 23. Summary of the Incidence of the Most Common (≥2.0%) Ocular Adverse Events (*n* and %) for the Treatment Period: Safety Population	
System Organ Class Preferred Term[a]	**Total (N = 247) *n* (%)**
Number of Patients With at Least One AE	**169 (68.4)**
Eye Disorders	**166 (67.2)**
Photophobia	157 (63.6)
Conjunctival Hyperaemia	69 (27.9)
Eye Pain	48 (19.4)
Ocular Hyperaemia	43 (17.4)
Eye Irritation	42 (17.0)
Lacrimation Increased	21 (8.5)
Keratitis	19 (7.7)
Optic Disc Disorder	18 (7.3)
Vision Blurred	17 (6.9)
Dry Eye	13 (5.3)
Eyelid Oedema	12 (4.9)
Retinal Disorder	11 (4.5)
Conjunctivitis	10 (4.0)
Eye Pruritus	10 (4.0)
Blindness	7 (2.8)
Corneal Epithelium Disorder	6 (2.4)
Blepharitis	5 (2.0)
Erythema of Eyelid	5 (2.0)
General Disorders and Administration Site Conditions	**40 (16.2)**
Instillation Site Irritation	30 (12.1)
Instillation Site Pain	17 (6.9)
Adverse Drug Reaction	2 (0.8)[b]
Instillation Site Erythema	5 (2.0)

Table 23.	**Summary of the Incidence of the Most Common (≥2.0%) Ocular Adverse Events (*n* and %) for the Treatment Period: Safety Population**
System Organ Class Preferred Term[a]	**Total (N = 247) *n* (%)**
Infections and Infestations	**11 (4.5)**
Eye Infection	5 (2.0)

[a] = All AE terms were coded using MedDRA Dictionary Version 9.0.
[b] = There were a total of 7 patients experiencing adverse drug reactions; 2 ocular and 5 non-ocular. Although when separated out, ocular adverse drug reactions occurred in less than 2.0% of the population (0.8%), it continues to be included in this table because of its relevancy to the drug and indication. Please see below and *Table 24* for additional details.
Note: A patient experiencing multiple occurrences of an AE is counted only once within each system organ class and within each preferred term.
Source: *Table 14.3.1.2*.

Source: May 6, 2010, Clinical Study Report Amendment, CAPTOC, 12.2.2.3 Non-Ocular Adverse Events

The most common ocular adverse events in CAPTOC occurring in ≥ 10 % of patients were sensitivity to light, redness, and eye pain/irritation.

Deaths

Eighteen deaths were reported in the three studies comprising the CAPTOC analysis. Two of the patient deaths (Patient 374973 and Patient 835249) were reported to FDA in IND Safety Reports.

Five patients (Patients 221252, 315632, 352157, 727697, and 883818) died with no cause provided.

Table 28. Cause of Death in Patients by Preferred Term: Safety Population	
Patient Number (*n* = 18)	**Cause of Death[a]**
221252	No cause given
221478	Central nervous system lymphoma
268427	Therapeutic response unexpected (complications due to dialysis); Azotaemia
288466	Neuropathy; Azotaemia
292824	Pneumonia
315632	No cause given
352157	No cause given
374973	Renal failure
419131	Cardiac arrest; Peritonitis
665494	Congenital neurological disorder; Sudden infant death syndrome; Aspiration
717581	Respiratory failure
724841	Sepsis; Pneumonia aspiration
727697	No cause given
736117	Endocarditis; Sepsis
835249	Intestinal obstruction; Gastrointestinal infection; Renal failure
883818	No cause given
893478	Colon injury
997414	Myopathy; Depression
[a] = All AE terms were coded using MedDRA Dictionary Version 9.0. Source: *Appendix 16.2.7.1.5*	

Source: May 6, 2010, Clinical Study Report Amendment, CAPTOC, 12.3.2.1 Deaths

The Case Report Forms (CRFs) for all 18 patients were reviewed. For the five patients where no cause was provided, there was additional information in the CRFs for two.

Patient 21252 apparently rejected her renal allograft and refused dialysis. Patient 352157 was found unresponsive and died despite vigorous resuscitation attempts.

There were no deaths in 98 EI0109S and 98 EI0109S.

Safety Summary Statement

There is substantial evidence of safety consisting of adequate and well controlled studies which demonstrate that Cystaran (cysteamine hydrochloride ophthalmic solution) 0.44%, dosed every hour while awake, is safe for the treatment of corneal cystine crystal accumulation in patients with cystinosis.

The most common ocular adverse events in CAPTOC occurring in ≥ 10 % of patients were sensitivity to light, redness, and eye pain/irritation.

9. Advisory Committee Meeting

No Advisory Committee Meeting was held. There were no new issues raised in the review of the application which were thought to benefit from an Advisory Committee Meeting.

10. Pediatrics

The safety and effectiveness of Cystaran (cysteamine hydrochloride ophthalmic solution) 0.44% in pediatric patients have been established for the treatment of corneal cystine crystal accumulation in patients with cystinosis.

Cystinosis often presents with growth retardation and renal tubular Fanconi syndrome in the first year of life and, if untreated, leads to renal failure by the age of 10 years.

11. Other Relevant Regulatory Issues

DSI
A Division of Scientific Investigations (DSI) audit was requested; DSI completed their review on August 23, 2010. The protocols inspected were Protocol 98-EI-0109E, Protocol 98-EI-0109S, and Protocol STP869294. Two domestic clinical investigators, Drs. Gahl (Muriel Kaiser) and Monte, and the applicant and CRO were inspected.

Per the DSI Summary:

> The preliminary classification of Clinical Investigator inspections of Dr. William A. Gahl and Dr. Monte A. Del Monte, are Voluntary Action Indicated (VAI). While DSI considers primary safety and efficacy data from these sites to be generally reliable in support of the requested indication, the review division will need to determine the potential impact of the following observations on approvability of the application:
>
> - At Dr. Gahl's site, the potential impact, if any, that missing safety data from study 98-EI-0109S has on safety analyses and conclusions.
> - At Dr. Del Monte's site, whether discrepancies in drug bottles issued compared with drug bottles returned accounting for ≤10% of the total number of bottles or doses potentially administered is within acceptable limits for total potential doses administered.

The preliminary classification of the sponsor/applicant, Sigma-Tau Pharmaceuticals, Inc. and the CRO, (b) (4) are No Action Indicated (NAI), based on preliminary communications with the FDA field investigator.

Regarding the Drs. Gahl/Kaiser site, alternate source data (diary entries, drug dispensation records, ophthalmic evaluation records, and subject interview questionnaires) support that study drug, as randomized, was administered to the subjects. The missing study data discussed by DSI are not expected to have any impact on safety analyses and conclusions.

Regarding Dr. Del Monte's site, discrepancies in drug bottles issued compared with drug bottles returned accounting for ≤10% of the total number of bottles or doses potentially administered are well within acceptable limits for total potential doses administered. These four subjects received over 100 bottles of study drug during the course of the efficacy study. The bottle count discrepancy discussed by DSI is not expected to have any impact on efficacy or safety analyses and conclusions.

FINANCIAL DISCLOSURE

The applicant has examined its financial data regarding significant payments of other sorts made to all investigators in the studies and equity information as provided by the investigators, as defined in 21 CFR 54.2. There is no evidence to suggest that the results of the study were impacted by any financial payments.

DMEPA

The Division of Medication Error Prevention and Analysis (DMEPA) Proprietary Name Risk Assessment evaluated "Cystoran" as the proposed proprietary name for cysteamine hydrochloride ophthalmic solution. DMEPA found the name "Cystoran" unacceptable (b) (4) . During a teleconference with the applicant on May 6, 2010, DMEPA informed Sigma-Tau the name would be unacceptable and requested submission of an alternate proprietary name.

On May 13, 2010, the name "Cystoran" was withdrawn, and on May 14, 2010, the name "Cystaran" was submitted as an alternate proprietary name by the applicant. DMEPA approved this alternate proprietary name in a letter dated August, 12, 2010.

DMEPA provided recommendations on the packaging configuration and the package insert labeling in a separate review and during labeling meetings held on August 4 and 13, 2010.

DDMAC

The Division of Drug Marketing, Advertising, and Communications (DDMAC) reviewed the draft product labeling, including the package insert (PI), draft carton label, and draft container label for Cystaran (cysteamine hydrochloride ophthalmic solution) 0.44%. DDMAC was invited to the two labeling meetings held on August 4 and 13, 2010, and provided a separate review.

DRISK

The Division of Risk Management (DRISK) reviewed the draft product labeling, including the package insert (PI), draft carton label, and draft container label for Cystaran (cysteamine hydrochloride ophthalmic solution) 0.44%. DRISK was invited to the two labeling meetings held on August 4 and

13, 2010, and provided a separate review. A decision was made at the second labeling meeting not to include a Patient Package Insert with the Cystaran labeling because there was nothing new or novel regarding the administration of this ophthalmic solution to the eyes.

BIOSTATISTICS
Per the Biostatistics consultative review finalized 8/9/2010:

Three clinical studies, STP869294 (CAPTOC), 98-EI-0109S, and 98-EI-1090E, were submitted to provide efficacy and safety data for cysteamine ophthalmic solution (Formulation 3). In these studies, the Applicant defined a response as an eye with a decrease from baseline of at least 1.00 unit in CCCS at some time during the study when baseline CCCS is ≥ 1.00 or CCCS does not increase by at least 1.00 unit at some time during the study when baseline CCCS is < 1.00. This implies a reduction in CCCS, in eyes with high CCCS (≥1) at baseline, which need not be sustained, i.e., transient reduction in CCCS. While, in eyes with low CCCS (<1) at baseline, the lack of increase in CCCS has to be sustained.

The CAPTOC Study, a combined study of three historically controlled single center studies, shows that 30.5% of eyes using cysteamine ophthalmic solution (Formulations 1-4) responded for the mITT population. Cumulative response rates were also calculated for eyes with CCCS ≥1 at baseline and results show that about 10% had response in Year 1 and by Year 6 about 30% of the patients had response at some time during the study.

In Study 98-EI-0109S, a double-masked, randomized, within-patient-controlled study, the mean change from baseline CCCS score at month 6 in Formulation 3 is -0.2222 and 0.2361for Formulation 5. This means that Formulation 3 reduces CCCS by 0.2222 while Formulation 5 has an increase in CCCS by 0.2361.

In Study 98-EI-0109E, a double-masked, randomized, within-patient-controlled study, the number of eyes with a reduction of CCCS of 1.00 unit or more was higher in those that received Formulation (66.7%) compared with Formulation 5 (13.3%) at some time during the treatment period. The difference in the mean change from baseline CCCS is higher in Formulation 3 than in Formulation 5 at every visit from Month 3, Month 6, Month 9, and Month 12.

The three studies demonstrate that cysteamine ophthalmic solution (Formulation 3) reduces formation of corneal crystals. This reduction however is temporary. Strict adherence to therapy is essential to the efficacy of Formulation 3.

Pharmacology/Toxicology, Clinical Pharmacology, Product Quality Microbiology, Clinical, and Biostatistics recommended approval of this new drug application. CMC does not recommend approval based on the outstanding cGMP issues.

12. Labeling

NDA 200740, Cystaran (cysteamine hydrochloride ophthalmic solution) 0.44% is not currently recommended for approval for the treatment of corneal cystine crystal accumulation in patients with cystinosis based on the outstanding cGMP issues.

The labeling found in the Appendix at the end of this CDTL review (submitted by Sigma-Tau Pharmaceuticals, Inc. on 8/30/10) is acceptable.

13. Recommendations/Risk Benefit Assessment

RECOMMENDED REGULATORY ACTION:
NDA 200740, Cystaran (cysteamine hydrochloride ophthalmic solution) 0.44% is not currently recommended for approval for the treatment of corneal cystine crystal accumulation in patients with cystinosis based on the outstanding cGMP issues.

Manufacturing facilities for the drug substance and the drug product are not in compliance with current good manufacturing practice. Satisfactory resolution of this deficiency is required before this application may be approved.

RISK BENEFIT ASSESSMENT:
There is substantial evidence of effectiveness consisting of adequate and well controlled studies which demonstrate that Cystaran (cysteamine hydrochloride ophthalmic solution) 0.44% reduces the accumulation of cystine corneal crystals considered partly responsible for clinical symptoms of photophobia, recurrent corneal erosions, and secondary blepharospasm that complicate longstanding cystinosis.

The most common ocular adverse events in CAPTOC occurring in ≥ 10 % of patients were sensitivity to light, redness, and eye pain/irritation.

The benefits of using this drug product outweigh the risks for the above indication.

Pharmacology/Toxicology, Biostatistics, Clinical, Clinical Pharmacology, and Product Quality Microbiology have recommended approval for this application. CMC does not recommend approval based on the outstanding cGMP issues.

RECOMMENDATION FOR POSTMARKETING RISK MANAGEMENT ACTIVITIES:
There are no risk management activities recommended beyond the routine monitoring and reporting of all adverse events.

There are no recommended Postmarketing Requirements or Phase 4 Commitments.

7 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200740	ORIG-1	SIGMA TAU PHARMACEUTICALS INC	(Cysteamine hydrochloride ophthalmic solution) 0.65% Sterile

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/s/

WILLIAM M BOYD
09/02/2010

WILEY A CHAMBERS
09/03/2010

CLINICAL REVIEW NDA 200740

Application Type	NDA
Application Number(s)	200740
Priority or Standard	Priority
Submit Date(s)	March 3, 2010
Received Date(s)	March 4, 2010
PDUFA Goal Date	September 4, 2010
Division / Office	DAIOP/OAP
Reviewer Name(s)	William M. Boyd, M.D.
Review Completion Date	August 31, 2010
Established Name	cysteamine hydrochloride ophthalmic solution 0.44%
(Proposed) Trade Name	Cystaran
Therapeutic Class	cystine-depleting agent
Applicant	Sigma-Tau Pharmaceuticals, Inc.
Formulation(s)	topical ophthalmic solution
Dosing Regimen	Instill one drop in both eyes daily, every waking hour
Indication(s)	treatment of corneal cystine crystal accumulation in patients with cystinosis
Intended Population(s)	children and adults with cystinosis

Table of Contents

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

NDA 200740, Cystaran (cysteamine hydrochloride ophthalmic solution) 0.44%, is recommended for approval for treatment of corneal cystine crystal accumulation in patients with cystinosis.

1.2 Risk Benefit Assessment

The benefits of Cystaran (cysteamine hydrochloride ophthalmic solution) 0.44%, for the recommended indication outweigh the associated risks.

This is a 505(b)(2) application. See Section 2.6.

Cystinosis is a rare autosomal recessive metabolic disorder characterized by the intracellular accumulation of cystine, the disulfide of the amino acid cysteine, in many organs and tissues. The absence of a vascular supply to the cornea limits cystine depletion in the eye following oral cysteamine administration. There are no approved drug products for the prevention and treatment of corneal cystine crystal accumulation in patients with cystinosis.

Cystaran (cysteamine hydrochloride ophthalmic solution) 0.44% reduces the accumulation of cystine corneal crystals considered partly responsible for clinical symptoms of photophobia, recurrent corneal erosions, and secondary blepharospasm that complicate longstanding cystinosis.

Cystaran is a sterile ophthalmic solution containing 6.5 mg of cysteamine hydrochloride, equivalent to 4.4 mg of cysteamine as the active ingredient.

All patients with cystinosis expected to receive Cystaran will also be receiving the oral Cystagon (cysteamine bitartrate) Capsules. The adverse event profile of Cystagon Capsules is well-documented. See Section 2.4.

In controlled clinical trials of six months to 19 years duration with cysteamine hydrochloride ophthalmic solution in approximately 300 patients, the most frequently reported ocular adverse reactions occurring in ≥ 10 % of patients were sensitivity to light, redness, and eye pain/irritation, headache and visual field defects.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

There are no postmarket risk management activities recommended beyond the routine monitoring and reporting of all adverse events.

1.4 Recommendations for Postmarket Requirements and Commitments

There are no recommended Postmarket Requirements or Phase 4 Commitments.

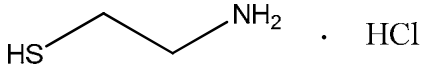
2 Introduction and Regulatory Background

2.1 Product Information

Cystinosis is a rare autosomal recessive metabolic disorder characterized by the intracellular accumulation of cystine, the disulfide of the amino acid cysteine, in many organs and tissues. Cystine accumulation is due to a defective lysosomal cystine transport system and results in tissue-damaging cystine crystal formation within cells of the kidney, bone marrow, pancreas, muscle, brain, and eye. The disease often presents with growth retardation and renal tubular Fanconi syndrome in the first year of life and, if untreated, leads to renal failure by the age of 10 years.

The mainstay of treatment for cystinosis is oral cysteamine. If administered chronically and diligently beginning prior to 2 years of age, oral cysteamine retards or prevents glomerular deterioration and enhances growth in children with nephropathic cystinosis. Corneal cystine crystals are an ocular manifestation of nephropathic cystinosis that progressively worsens with time and does not spontaneously resolve. In the cornea, cystine crystals generally appear by 1 year of age and are pathognomonic of cystinosis. They initially appear in the central cornea and progress to the full thickness of the peripheral cornea and anterior two-thirds of the central cornea with age. These cystine crystals are considered partly responsible for clinical symptoms of photophobia, recurrent corneal erosions, and secondary blepharospasm that complicate longstanding cystinosis.

Cysteamine HCl Structural Formula:



Molecular Formula: C_2H_7NS HCl

Cysteamine is an aminothiol that converts cystine to cysteine and cysteine-cysteamine mixed disulfide, both of which can pass through the lysosomal membrane of patients with cystinosis without a functional carrier and both of which can then be eliminated from the cell. Oral cysteamine was approved in the United States as Cystagon (cysteamine bitartrate) Capsules in 1994 for the management of nephropathic cystinosis in children and adults. Originally, it was thought that oral cysteamine therapy would prevent the ophthalmic complications of cystinosis, including corneal crystals, photophobia, blepharospasm, and eye pain; however, this did not occur. The absence of a vascular supply to the cornea limits cystine depletion in the eye following oral cysteamine administration.

The lack of effect of oral cysteamine on the ocular effects of cystinosis led to the development of an ophthalmic formulation.

2.2 Tables of Currently Available Treatments for Proposed Indications

There are no approved drug products for the prevention and treatment of corneal cystine crystal accumulation in patients with cystinosis.

2.3 Availability of Proposed Active Ingredient in the United States

NDA 20-392 for Cystagon (cysteamine bitartrate) Capsules was approved in 1994 for the management of nephropathic cystinosis in children and adults.

2.4 Important Safety Issues With Consideration to Related Drugs

Because adverse effects may result from the underlying disease, the causality of side effects from use of oral Cystagon (cysteamine bitartrate) Capsules is sometimes difficult to determine. The most common events seen clinical trials with Cystagon (> 5%) were: vomiting 35%, anorexia 31%, fever 22%, diarrhea 16%, lethargy 11%, and rash 7%.

CNS symptoms such as seizures, lethargy, somnolence, depression, and encephalopathy have been associated with oral cysteamine, but neurological complications have been described in some cystinotic patients not on cysteamine treatment.

There have been reports of benign intracranial hypertension (or pseudotumor cerebri) associated with oral cysteamine treatment that has resolved with the addition of diuretic therapy.

Gastrointestinal ulceration and bleeding have been reported in patients receiving oral cysteamine bitartrate.

Cysteamine has occasionally been associated with reversible leukopenia and abnormal liver function studies.

There have been reports of serious skin lesions in patients treated with high doses of Cystagon or other cysteamine salts that have responded to cysteamine dose reduction. These skin lesions are purplish hemorrhagic lesions over the elbow area on both arms and have been described as molluscoid pseudotumors. Skin striae, bone lesions (that have been described as osteopenia, compression fractures, scoliosis and genu valgum) along with leg pain and joint hyperextension have been described.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

IND 40,593 was originally held and opened by Dr. William Gahl in 1992.

An orphan designation for cysteamine hydrochloride for the treatment of corneal cystine crystal accumulation in patients with cystinosis was granted in August 1997.

An October 19, 2001, Pre-NDA Meeting was held with what was then the Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products.

2.6 Other Relevant Background Information

This is a 505(b)(2) application. The Form 356h submitted by Sigma Tau Pharmaceuticals, Inc., lists Cystagon (cysteamine bitartrate) Capsules (Mylan Pharmaceuticals, Inc.) as the reference listed drug Product.

The information being used by Sigma Tau as the 505(b)(2) information is toxicology information using an overexposure to the drug substance. This overexposure to the drug substance cannot be achieved with the drug product Cystaran for either a 505(b)(1) or a (b)(2) application; overexposure to drug substance is instead done with a different dosing regimen and formulation of the active ingredient. The bridge between Cystaran and Cystagon is that the drug substance is chemically the same (cysteamine) determined chemically.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The Division of Scientific Investigations completed their review on August 23, 2010. The protocols inspected were Protocol 98-EI-0109E, Protocol 98-EI-0109S, and Protocol STP869294. Two domestic clinical investigators, Drs. Gahl (Muriel Kaiser) and Monte, and the applicant and CRO were inspected.

Name of CI, IRB, or Sponsor Location	Protocol # and # of Subjects:	Inspection Date	Final Classification
William A. Gahl, M.D., Ph. D./ Muriel Kaiser, M.D. National Institutes of Health National Eye Institute Building 10, Clinical Center 10 Center Drive Bethesda, MD 20892	98-EI-0109E / Site #1, Site # (n=5) 98-EI-0109S/site # 9/20 STP869294 (86-EI-0062 , 94-EI-0116, 92-EI-0230) / NEI Clinical Center /247	6/3/2010-7/8/2010	Pending (Interim classification: VAI)
Monte A. Del Monte, M.D University of Michigan Medical School M7301 Medical Sciences Building I Box 0624 Ann Arbor, MI 48109-0624	98-EI-0109E / site 02 /6	6/ 10/ 2010 - 7/13/2010	Pending (Interim classification: VAI)
Sponsor: **Sigma-Tau Pharmaceuticals, Inc.** 9841 Washingtonian Blvd. Suite 500, Gaithersburg, MD 20878 Contact Person: Gianfranco Fornasini, Ph.D. Senior Vice President, Scientific Affairs Phone # (301) 670-2192	98-EI-0109E / Site #1, Site # (n=5) 98-EI-0109S/site # 9/20 STP869294 (86-EI-0062 ,94-EI-0116,92-EI-0230) / NEI Clinical Center /247 98-EI-0109E / site 02 /6	August 17, 2010	*Pending (Interim classification: NAI)
(b) (4)			

Key to Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.
Pending = Preliminary, letter has not yet issued to the CI.
* Observations noted above are based on communications with the field investigator; an inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

Source: August 23, 2010, DSI Clinical Inspection Summary

Per the DSI Summary:

> The preliminary classification of Clinical Investigator inspections of Dr. William A. Gahl and Dr. Monte A. Del Monte, are Voluntary Action Indicated (VAI). While DSI considers primary safety and efficacy data from these sites to be generally reliable in support of the requested indication, the review division will need to determine the potential impact of the following observations on approvability of the application:
>
> - At Dr. Gahl's site, the potential impact, if any, that missing safety data from study 98-EI-0109S has on safety analyses and conclusions.
> - At Dr. Del Monte's site, whether discrepancies in drug bottles issued compared with drug bottles returned accounting for ≤10% of the total number of bottles or doses potentially administered is within acceptable limits for total potential doses administered.
>
> The preliminary classification of the sponsor/applicant, Sigma-Tau Pharmaceuticals, Inc. and the CRO, (b) (4) are No Action Indicated (NAI), based on preliminary communications with the FDA field investigator.

Regarding the Drs. Gahl/Kaiser site, alternate source data (diary entries, drug dispensation records, ophthalmic evaluation records, and subject interview questionnaires) support that study drug, as randomized, was administered to the subjects. The missing study data discussed by DSI are not expected to have any impact on safety analyses and conclusions.

Regarding Dr. Del Monte's site, discrepancies in drug bottles issued compared with drug bottles returned accounting for ≤10% of the total number of bottles or doses potentially administered are well within acceptable limits for total potential doses administered. These four subjects received over 100 bottles of study drug during the course of the efficacy study. The bottle count discrepancy discussed by DSI is not expected to have any impact on efficacy or safety analyses and conclusions.

No other issues related to data quality or data integrity have been identified.

3.2 Compliance with Good Clinical Practices

With the exception of the DSI findings noted above in Section 3.1, the clinical trials reviewed in this application were conducted in accordance with good clinical trial practices.

3.3 Financial Disclosures

Gianfranco Fornasini, PH.D., Senior Vice President, Scientific Affairs, Sigma-Tau Pharmaceuticals, Inc, signed a Form 3454 certifying that the listed clinical investigators did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)): had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

See Section 2.1 of this review.

See Appendices for Release and Stability Specification.

4.2 Clinical Microbiology

There is no clinical microbiology review for this product. It is not an anti-infective.

4.3 Preclinical Pharmacology/Toxicology

Studies of cysteamine hydrochloride ophthalmic solution 0.1-10% included one GLP study conducted by the Applicant and two studies from the peer-reviewed scientific literature.

In the GLP-compliant study in rabbits, 2 drops of 0.55% cysteamine ophthalmic solution was administered hourly for 8 hours per day for 30 days to the right eye of 12 rabbits/sex. No findings of irritation, corneal disruption, or ocular histopathology were reported. In published studies in rabbits, gross and/or microscopic signs of irritation or inflammation were seen following ocular administration of cysteamine at concentrations of 1% and higher when administered hourly for 8 consecutive hours for 4 weeks, while eyes treated with 0.1% or 0.5% cysteamine for 3 months were reported to be normal.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Cysteamine acts as a cystine-depleting agent by converting cystine to cysteine and cysteine-cysteamine mixed disulfides and thus reduces corneal cystine crystal accumulation

4.4.2 Pharmacodynamics/Pharmacokinetics

Per the Clinical Pharmacology Review dated 8/4/2010:

The Applicant did not perform any human pharmacokinetic assessment of cysteamine HCl ophthalmic solution and did not specifically request a waiver of the *in vivo* bioavailability requirement. Based on 21 CFR 320.22 (e), the Applicant was granted a waiver of the *in vivo* bioavailability requirement because of the expected low systemic exposure of cysteamine following ophthalmic administration of cysteamine solution in comparison to exposures observed following orally administered cysteamine bitartrate as described below.

The total daily dose of 0.65%[1] cysteamine HCl ophthalmic solution is estimated to be 7.8 mg/day based on a 100 µL dose per hour × 12 waking hours. The recommended daily maintenance dose approved for orally administered cysteamine ranges from 400 mg/day for an infant with body weight <10 pounds to 2000 mg/day for adults. Therefore, the total daily ophthalmic dose is less than 2% of the recommended oral daily dose of cysteamine. Even assuming complete systemic availability, the peak plasma concentration of cysteamine following ophthalmic administration is expected to be substantially less than the peak plasma concentration following oral administration of cysteamine.

5 Sources of Clinical Data

1 Cystaran is a sterile ophthalmic solution containing 6.5 mg of cysteamine hydrochloride, equivalent to 4.4 mg of cysteamine as the active ingredient.

5.1 Tables of Studies/Clinical Trials

Clinical Trials

Table 2.7.6-1. Listing of Clinical Studies

Type of Study	Study Identifier Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration; Duration of Treatment	Healthy Subjects or Diagnosis of Patients Number of Subjects	Study Status Type of Report
Efficacy and Safety	*Study 98-EI-0109E* 5.3.5.1	To evaluate the efficacy and safety of two formulations of ophthalmic cysteamine solution in the treatment of corneal cystine crystal accumulation in naïve ocular cystinosis patients.	A Multicenter, Randomized, Double-Masked, Comparative Efficacy Trial	Formulation 3: 0.65% cysteamine hydrochloride with BAK, 0.01% Formulation 5: 0.55% cysteamine hydrochloride (b) (4) (b) (4) 1 drop administered to each eye hourly during waking hours 1 year	Naïve ocular cystinosis patients 16 enrolled	Complete Full
Safety and Efficacy	*Study 98-EI-0109S* 5.3.5.1	To estimate the proportion of cystinosis patients experiencing an SAE in the eye treated with the formulation of ophthalmic cysteamine solution (Formulation 5) that had been developed with longer room temperature stability.	A Single-Center, Randomized, Double-Masked, Comparative Safety and Efficacy Trial	Formulation 3: 0.65% cysteamine hydrochloride with BAK, 0.01%. Formulation 5: 0.55% cysteamine hydrochloride (b) (4) (b) (4) 1 drop administered to each eye hourly during waking hours 6 months	Ocular cystinosis patients 20 enrolled	Complete Full
Efficacy and Safety	*Study STP869294* 5.3.5.1	To collectively demonstrate the safety and efficacy of cysteamine ophthalmic solution in the treatment of corneal cystine crystals in cystinosis patients.	Randomized, Double-Masked	Formulation 1: 0.11% cysteamine hydrochloride. Formulation 2: 0.65% cysteamine hydrochloride. Formulation 3: 0.65% cysteamine hydrochloride with BAK, 0.01%. Formulation 4: 0.55% cystamine hydrochloride (b) (4) (b) (4) Initially, cysteamine ophthalmic solution (1 drop) was administered to 1 eye and placebo solution (1 drop saline) to the companion eye, once each waking hour. During the course of the study, the treatment design was amended to provide active treatment for both eyes. 19 years[a]	Ocular cystinosis patients 247 enrolled	Ongoing Full

[a] = CAPTOC analysis comprised 19 years of treatment; Study 86-EI-0062 still ongoing.
BAK = Benzalkonium chloride.

5.2 Review Strategy

The March 3, 2010, submission was submitted electronically. Subsequent amendments were also submitted in electronically. All study reports were reviewed. The included clinical study reports, literature review, and package insert formed the basis for the review of efficacy and safety for the proposed indication.

A literature search conducted by this reviewer failed to identify any literature references which were contrary to the information provided or referenced by Sigma Tau in this application for this indication.

5.3 Discussion of Individual Studies/Clinical Trials

STP869294 (CAPTOC)

Title: Combined Analysis of Patients Treated with Ophthalmic Cysteamine (CAPTOC)

The CAPTOC report provides a combined analysis of three protocols (Protocol 86-EI-0062, Protocol 92-EI-0230, and Protocol 94-EI-0116) collectively evaluating the safety and efficacy of cysteamine ophthalmic solution in the treatment of corneal cystine crystals in cystinosis patients.

All three protocols were single center studies conducted at NEI from April 1986 through July 13, 2005. Formulations 1, 2, 3, 4 and/or placebo were evaluated in cystinosis patients who were currently receiving oral cysteamine.

BRIEF HISTORY OF 86-EI-0062, 92-EI-0230, AND 94-EI-0116

Note: these formulations below describe the concentration of the cysteamine hydrochloride, not cysteamine alone as in the final Cystaran (cysteamine hydrochloride ophthalmic solution) 0.44% name. Cystaran is a sterile ophthalmic solution containing 6.5 mg of cysteamine hydrochloride, equivalent to 4.4 mg of cysteamine as the active ingredient.

Formulation 1 contained 0.11% cysteamine HCl and was tested in the original **Protocol 86-EI-0062** (March 20, 1986). Patients were randomly assigned to receive Formulation 1 of the ophthalmic cysteamine solution in one eye and placebo in the companion eye.

Formulation 2 contained 0.65% cysteamine HCl and was tested in the amended Protocol 86-EI-0062 (Amendment 1, April 15, 1988; and Amendment 2, February 24, 1992); patients were randomly assigned to receive Formulation 2 in one eye and placebo in the companion eye.

Formulation 3 contained 0.65% cysteamine HCl plus 0.01% BAK was tested in a pilot clinical toxicity study as an amendment to Protocol 86-EI-0062 (Amendment A; May 20, 1992). In this study, patients were randomized to receive Formulation 2 in one eye and Formulation 3 in the companion eye. Formulation 3 was further tested in a new protocol, **Protocol 92-EI-0230** (July 13, 1992). Again, in this study, patients were randomized to receive Formulation 2 in one eye and Formulation 3 in the companion eye.

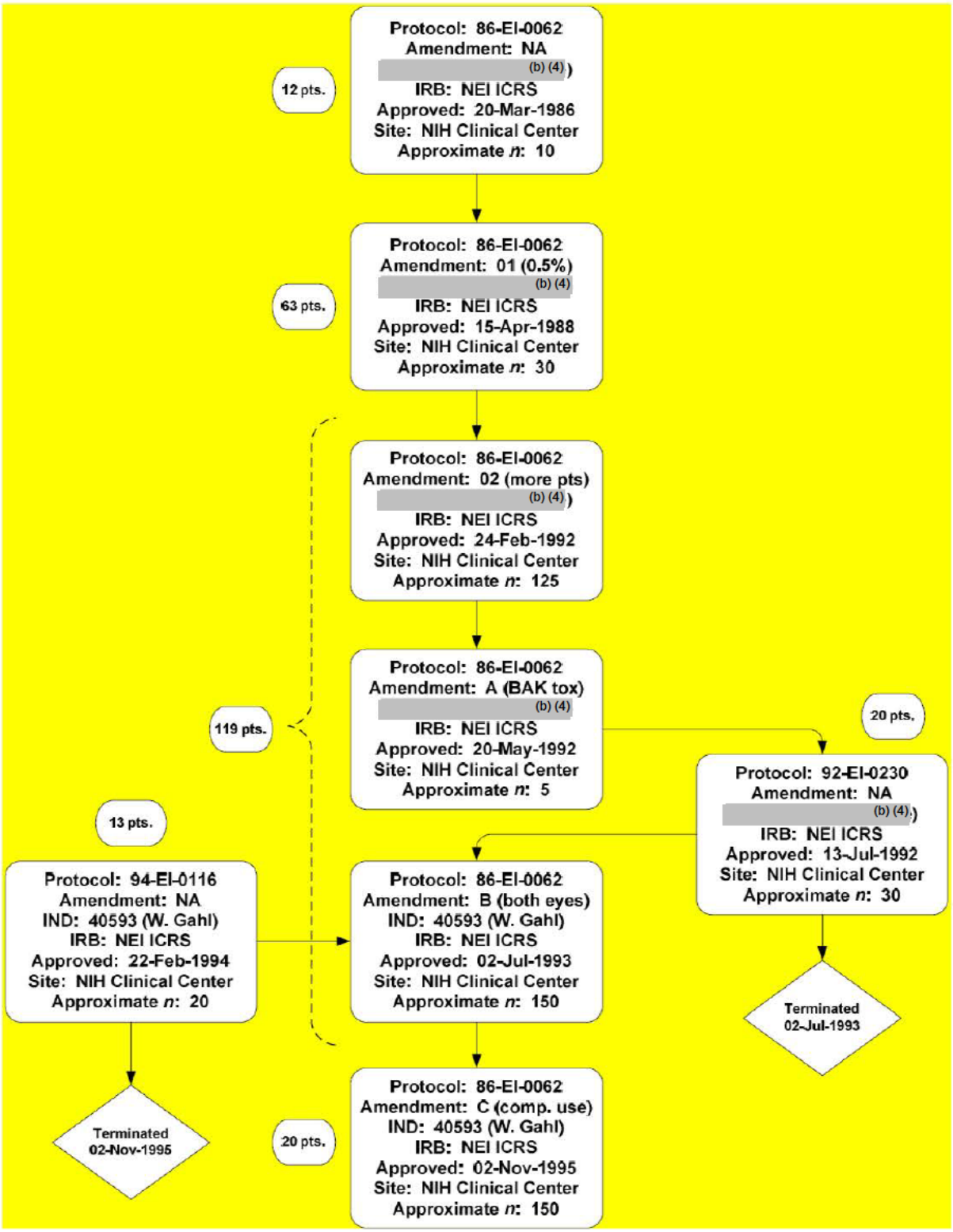
Based on the results seen with Formulation 3, the Protocol 92-EI-0230 (July 13, 1992) study was terminated, Protocol 86-EI-0062 was amended (Amendment B; July 2, 1993), and all patients in the Protocol 92-EI-0230 study were enrolled into the Protocol 86-EI-0062 study. All patients received Formulation 3 in both eyes.

In 1994, in an attempt to develop a more stable formulation, Formulation 4, which consisted of 0.55% cystamine (b) (4) was developed. **Protocol 94-EI-0116** (February 22, 1994; and Amendment 1, May 17, 1994) tested the efficacy of cystamine versus cysteamine, as well as to show any potential toxicities from cystamine. Patients were randomized to receive Formulation 3 in one eye and Formulation 4 in the companion eye. This study was terminated when NEI determined that Formulation 4 was not as effective as Formulation 3. All patients who had been randomized into Protocol 94-EI-0116 were eligible for transfer to Protocol 86-EI-0062 and to receive Formulation 3 in both eyes.

Due to the progressive nature of formulation and clinical development of the ophthalmic cysteamine studies at NEI, it was determined by NEI that a conventional approach of independent analyses of the individual protocols (86-EI-0062, 92-EI-0230, and 94-EI-0116) would not portray an accurate reflection of the clinical exposure regarding safety and efficacy. An approach to combine all available exposure data from NEI studies was undertaken; for administrative purposes, this analysis is identified as CAPTOC (Study **STP869294**).

Prior to April 1993, NEI did not use Case Report Forms (CRFs) to collect study data. NEI retrospective generated CRFs based on medial records for all prior patient visits. 247 patients were enrolled.

Figure 1 - Overview of protocols and amendments analyzed in CAPTOC



INCLUSION/EXCLUSION CRITERIA CAPTOC
Across all three protocols, patients were eligible for inclusion in the studies if all of the following criteria were met:

- Patient has a clinical history consistent with cystinosis and may presently be undergoing treatment with Cystagon (oral cysteamine bitartrate) Capsules.
- Patient is willing and able to tolerate photographs.
- Patient is within the age range of birth-60 years (inclusive).
- Patient is willing and able to comply with treatment and follow-up procedures.
- Patient or the patient's parent/guardian is able to understand and sign an ICF.

A patient was not eligible for inclusion in the studies if any of the following criteria applied:

- Patient is unable or unwilling to consent to participate in the study.
- Patient is likely unable or unwilling to comply with treatment and/or follow-up procedures.
- Patient is >60 years of age.

PRIMARY EFFICACY VARIABLE CAPTOC
The primary end point in these studies was a reduction in Corneal Cystine Crystal Score (CCCS) in eyes with high CCCS at baseline, and a lack of increase in CCCS in eyes with low CCCS at baseline. A response was defined as a decrease from baseline of at least 1.00 unit in CCCS at any time during the study when baseline CCCS is ≥ 1.00 or CCCS does not increase by at least 1.00 unit at any time during the study when baseline CCCS is < 1.00.

This endpoint was based on the premise that a spontaneous reduction of CCS (a maximum 1.00 unit decrease without treatment in 12 months) may occur in only 7% of follow-up examinations of patients, and these spontaneous reductions are not sustained.[2]

The primary and secondary end points were based on photo-rated CCCS. The use of photo-rated CCCS (slit-lamp photography in conjunction with a photography-based scoring system) had been with success to quantify and document the accumulation of corneal cystine crystal accumulation in cystinosis patients over time.

Per the original photography instructions:

2 Gahl WA, Kuehl EM, Iwata F, Lindblad A, Kaiser-Kupfer MI. Corneal crystals in nephropathic cystinosis: natural history and treatment with cysteamine eyedrops. *Mol Genet Metab*, 2000;71(1-2):100-120.

> After positioning the patient at the chin rest of the Zeiss photo slit lamp, a narrow (0.5 mm) slit beam is focused on the camera so that the cornea can be visualized in the zone of specular reflection just adjacent to the beam. Using the Zeiss Nikon camera with high speed Ektachrome daylight film (ASA 160), and magnification on the slit lamp of 16xd-40x, the cornea is photographed with lens setting *f*22-*f*32. The photograph will then be compared to a standard library developed at the NEI.

An example of the standard library is submitted in Gahl, et al 2000:

SECONDARY EFFICACY MEASUREMENTS CAPTOC
Secondary end points included the following:

• Mean change from baseline in CCCS
• Shift from baseline to lowest post-baseline CCCS category
• Shift from baseline to post-baseline time points (years) in CCCS categories
• Improvement in corneal haziness
• Improvement in photophobia
• Improvement in foreign body sensation
• Correlation between CCCS and photophobia.

ANALYSIS POPULATIONS CAPTOC
The following populations were analyzed:

- Safety/ITT: included all patients enrolled in the study to which one or more doses of study medication was administered.
- mITT: included all ITT patients for whom a baseline CCCS assessment and at least one post-baseline CCCS assessment was available.
- mITT-1: included all mITT patients who started study medication before July 2, 1993 (the study period that included the use of placebo).
- mITT-2: included all mITT patients who started study medication on or after July 2, 1993 (the study period that discontinued the use of placebo).

LIST OF INVESTIGATORS/SUBINVESTIGATORS CAPTOC

Protocol Number	Investigator Name	Facility Name and Address
86-EI-0062	Muriel Kaiser, M.D. National Institutes of Health National Eye Institute	National Eye Institute Building 10, Clinical Center 10 Center Drive Bethesda, MD 20892
92-EI-0230	Muriel Kaiser, M.D. National Institutes of Health National Eye Institute	National Eye Institute Review Board 10 Center Drive MSC 1858 Building 10, Room 10N226 Bethesda, MD 20892
94-EI-0116	Muriel Kaiser, M.D. National Institutes of Health National Eye Institute	National Eye Institute Review Board 10 Center Drive MSC 1858 Building 10, Room 10N226 Bethesda, MD 20892

STUDY PLAN CAPTOC

Table 7. Study Time and Events Schedule						
	Time Point					
	Planned				Actual	
Assessment	Baseline[a]	Week 1	Follow-up Telephone Interviews	Follow-Up Visits[c,e,f,g,h]	Baseline	Follow-up
Medical History	X			X	X[i]	
Physical Examination	X			X		
Ophthalmic Examination						
Observation for Presence of Crystals in Cornea; on Surface of Lens, Iris, and Retina; and Presence of Posterior Synechiae	X			X	X[j]	X[j]
Fluorescein Angiography	X			X		
Visual Acuity	X			X	X	X
Slit-Lamp Photographs	X			X	X	X
Clinical Assessment of Photophobia	X			X	X	X
Patient Assessment of Photophobia					X	X
Clinical Assessment of Blepharospasm	X			X		
Clinical Assessment of Haziness					X	X
Assessment of Foreign Body Sensation					X	X
Psychophysical Testing of Dark Adaption and Color Perception	X			X		

Table 7. Study Time and Events Schedule

Assessment	Time Point					
	Planned				Actual	
	Baseline[a]	Week 1	Follow-up Telephone Interviews	Follow-Up Visits[c,e,f,g,h]	Baseline	Follow-up
Electroretinography	X			X		
In-Patient Treatment and Observation[b,d,f,g]		X				
Assessment of Dosing Compliance					X	X
AEs (Ocular)			X[f,g,h]	X		X
Routine Blood Tests	X			X		
Urinalysis	X			X		
Leukocyte Cystine Value	X			X		
Fibroblast Cystine Content	X			X		
Oral Cysteamine					X	X
Eye Medications					X	X

[a] = Baseline evaluations for patients in Protocol 86-EI-0062 (versions dated March 20, 1986; April 15, 1988; February 24, 1992; and May 20, 1992), Protocol 92-EI-0230 (version dated July 13, 1992), and Protocol 94-EI-0116 (versions dated February 22, 1994, and May 17, 1994) were to be performed during the 4-5 day in-patient admission or follow-up examinations required by the oral cysteamine study, Protocol 78-CH-0093. The records showing that patients came out of Protocol 78-CH-0093 and were enrolled into these subsequent ocular studies are part of the oral cysteamine (Cystagon) study files and are not available to STP. Patients going into the CAPTOC studies were clinically diagnosed with cystinosis.

[b] = Patients in Protocol 86-EI-0062 (versions dated March 20, 1986, and April 15, 1988) were to be treated and observed daily during the first week of medication. This regimen was to be continued on an outpatient basis in a double-masked fashion. If, after 1 year of therapy, no benefit attributable to topical cysteamine therapy was noted, the treatment was to be terminated. If benefit was apparent by noting a decrease in corneal crystals, the therapy was to continue for the full 3 years.

[c] = Patients in Protocol 86-EI-0062 (versions dated March 20, 1986, and April 15, 1988) were to be re-admitted to the NIH Clinical Center for examination every 3 months for 2-3 years for an evaluation identical to the initial evaluation. The interval history (based on the patient's daily calendar) for older patients was to be assessed for each eye with special regard to the number of episodes of corneal erosions, degree of photophobia, and presence of irritation or other side effects.

[d] = Patients in Protocol 86-EI-0062 (versions dated February 24, 1992; July 2, 1993; and November 2, 1995) and Protocol 94-EI-0116 (versions dated February 22, 1999, and May 17, 1994) were to be treated and observed daily during the first week of medication. This regimen was to be continued on an outpatient basis in a double-masked fashion. If, after 2 years of therapy, no benefit attributable to topical cysteamine therapy was noted, the treatment was to be terminated. If benefit was apparent by noting a decrease in corneal crystals, the therapy was to continue for as long as the accumulation of crystals remained stable. For Protocol 94-EI-116 (version dated May 17, 1994), no statement was made about treatment being terminated; only that eyes would be assessed at 6 months and 1 year (study duration).

Table 7. Study Time and Events Schedule

Assessment	Time Point					
	Planned				Actual	
	Baseline[a]	Week 1	Follow-up Telephone Interviews	Follow-Up Visits[c,e,f,g,h]	Baseline	Follow-up

[e] = Patients in Protocol 86-EI-0062 and Protocol 94-EI-0116 were to be re-admitted to the NIH Clinical Center for examination every 6-8 months (Protocol 86-EI-0062, February 24, 1992, and July 2, 1993; and Protocol 94-EI-0116, February 22, 1994) or 8-12 months (Protocol 86-EI-0062, November 2, 1995) for 3 years for an evaluation identical to the initial evaluation except for the psychophysical and electrodiagnostic testing, which was to be performed yearly. The interval history (based on the patient's daily calendar) for older patients was assessed for each eye with special regard to the number of episodes of corneal erosions, degree of photophobia, and presence of irritation or other side effects.

[f] = Patients in Protocol 86-EI-0062 (version dated May 20, 1992) were to receive a telephone call once weekly for 1 month to check for any symptoms of irritation, redness, or discomfort. If there was evidence of any of these symptoms, the use of benzalkonium was to be discontinued and the patient was to resume using the medication originally prescribed (0.5% cysteamine) in both eyes. Patients were to be re-admitted to the NIH Clinical Center for examination at the end of 6 months, which was the duration of the study.

[g] = Patients in Protocol 92-EI-0230 (version dated July 13, 1992) were to receive a telephone call once weekly for 1 month and then monthly for the duration of the study (3 years). If there was evidence of any of these symptoms, the use of BAK was to be discontinued for 1 week. After 1 week, the patient was to resume the trial using fresh medication. If patients were unable to maintain the frequency of the schedule of eye drops, they would decide if they wished to continue with the study. Patients were to be re-admitted to the NIH Clinical Center for examination every 4 months for 3 years for an evaluation identical to the initial evaluation.

[h] = Patients in Protocol 94-EI-0116 (version dated May 17, 1994) were to receive a telephone call at the end of the first week and the first month to check for any symptoms of irritation, redness, or discomfort. Patients were to be re-admitted to the NIH Clinical Center for examination at the end of 6 months and 1 year, which was the duration of the study.

[i] = Retrospectively collected by STP from medical records.

[j] = Observation for presence of crystals in cornea, lens, iris, and conjunctiva only.

98 EI0109E

Title: A Multicenter, Randomized, Double-Masked, Comparative Efficacy Trial of Two Formulations of Ophthalmic Cysteamine Solution in the Treatment of Corneal Cystine Crystal Accumulation in Naïve Ocular Cystinosis Patients

This study was a 1 year, multicenter, double-masked, randomized trial designed to evaluate the efficacy and safety of Formulation 3 (formulation in use at NEI at the time of this trial) in one eye and Formulation 5 in the companion eye in naïve ocular cystinosis patients.

INCLUSION/EXCLUSION CRITERIA 98 EI0109E
Patients were eligible for inclusion in this study if all of the following criteria were met:

- Patient is diagnosed with cystinosis (either >2 nmole half-cystine/mg protein in leukocytes or presence of corneal crystals consistent with cystinosis and distributed in corneal stroma observed by slit-lamp biomicroscopy). (The definition of cystinosis was modified by Protocol Amendment 1 and again by Protocol Amendment 2).
- Patient has a clinical history consistent with cystinosis.
- Patient is willing and able to tolerate photographs.
- Patient is 2-12 years of age (inclusive). (Age range was modified by Protocol Amendment 1).
- Patient is willing and able to comply with treatment and follow-up procedures.
- Patient or patient's parent/guardian is able to understand and sign an ICF.
- Patient has a crystal density score of ≥1.00 on photographs. Photographs were to be submitted to the NEI Clinical Center for quality and eligibility verification prior to enrollment.
- Patient is currently on Cystagon (oral cysteamine bitartrate) Capsules and has been taking it for the last 6 months (this criterion was added by Protocol Amendment 1).

A patient was not eligible for inclusion in the study if any of the following criteria applied:

- Prior use of cysteamine drops
- Patient is <2 years or >12 years of age.

PRIMARY EFFICACY VARIABLE 98 EI0109E
The primary analysis compared disease status pre- and post-treatment using a binary outcome that summarized the pre- to post-change in each eye.

The estimated proportion of eyes with a reduction of 1.00 unit or more in CCCS relative to baseline (where CCCS baseline value was ≥1) any time during the treatment period with its exact 95% Clopper-Pearson CI was estimated by treatment.

In addition, the estimated proportion of eyes with a reduction of 1.00 unit or more in CCCS relative to baseline (where CCCS baseline value was ≥1) with its exact 95% CI using the method by Clopper and Pearson was analyzed by time point (Month 3, Month 6, Month 9, and Month 12).

SECONDARY EFFICACY MEASUREMENTS 98 EI0109E

The estimated proportion of eyes with a reduction of <1.00 unit in CCCS relative to baseline during the study with its exact 95% CI using the method by Clopper and Pearson was analyzed by time point and treatment group.

ANALYSIS POPULATIONS 98 EI0109E

Of the 16 patients enrolled, 16 (100%) comprised the Safety Population (patients received at least one dose of study drug) and 15 (93.8%) comprised the Per-Protocol Population (patients with at least one post-baseline CCCS for at least one eye). One (6.3%) patient prematurely discontinued study after 6 weeks of therapy due to patient resistance and parental unwillingness to continue frequent administration of eye drops and was omitted from the efficacy analysis.

LIST OF INVESTIGATORS/SUBINVESTIGATORS 98 EI0109E

Site Number	Investigator Name	Facility Name and Address
01	Muriel Kaiser, M.D.	National Eye Institute Building 10, Clinical Center 10 Center Drive Bethesda, MD 20892
02	Jess G. Thoene, M.D. Monte A. Del Monte, M.D.[a]	University of Michigan Medical School M7301 Medical Sciences Building I Box 0624 Ann Arbor, MI 48109-0624 University of Michigan Mott Children's Hospital 1505 Simpson Ann Arbor, MI 48109
03	Jerry Schneider, M.D.	Abraham Ratner Children's Eye Center University of California, San Diego Shiley Eye Complex La Jolla, CA 92093-0946 Clinical Research Facility University of California, San Diego 9500 Gilman Drive, 0620 La Jolla, CA 92093-0620
[a] = Dr. Del Monte replaced Dr. Thoene at Site 02.		

STUDY PLAN 98 EI0109E

Table 1. Study Time and Events Schedule

Assessment	Time Point							
	Baseline	**Week 1**	**Week 2**	**Month 1**	**Month 3**	**Month 6**	**Month 9**	**Month 12**
Medical History	X[e]	NA	NA	NA	NA	NA	NA	NA
Physical Examination, Weight, Vital Signs	X[e]	NA	NA	NA	NA	NA	NA	NA
Ophthalmic Examination, Corneal Slit-Lamp Examination	X[e]	NA	NA	NA	X	X	X	X
Manifest Refraction	X	NA	NA	NA	NA	X	NA	X
Visual Acuity	X[e]	NA	NA	NA	X	X	X	X
Slit-Lamp Photographs	X[e]	NA	NA	NA	X	X	X	X
Photophobia Clinical Assessment	X[e]	NA	NA	NA	X	X	X	X
Blepharospasm Clinical Assessment	X[e]	NA	NA	NA	X	X	X	X
Psychophysical Testing of Dark Adaptation and Color Perception[a]	X	NA	NA	NA	NA	NA	NA	X
Electroretinography[a]	X	NA	NA	NA	NA	NA	NA	X
Assessment of Dosing Compliance	NA	X[b]	X[b]	X[b]	X	X	X	X
AEs (Ocular and Systemic)	NA	X[b]	X[b]	X[b]	X	X	X	X
CBC/Diff, Acute Care, Hep/Min[c]	X[d,e]	NA	NA	NA	NA	NA	NA	NA
Urinalysis[c]	X[d,e]	NA	NA	NA	NA	NA	NA	NA
Leukocyte Cystine Value	X	NA	NA	NA	NA	X	NA	X

[a] = Only when indicated by clinical signs or symptoms.
[b] = Telephone interview.
[c] = Specific chemistry, hematology, and urinalysis laboratory tests to be performed were not specified in the protocol; however, they were listed in the CRF.
[d] = These time points were not specified in the study schedule contained in the protocol; however, Section 4.2 of the protocol indicated that these tests were to be performed (*Appendix 16.1.1*).
[e] = Performed during the Screening visit which may have occurred on the same day as the Baseline visit.
NA = Not applicable.

98 EI0109S

Title: A Single-Center, Randomized, Double-Masked, Comparative Safety and Efficacy Trial of Two Formulations of Ophthalmic Cysteamine Solution in the Treatment of Corneal Cystine Crystal Accumulation in Ocular Cystinosis Patients

The primary objective of this study was to evaluate the safety of a Formulation 5 of ophthalmic cysteamine in the treatment of cystinosis patients who are already receiving the Formulation 3 of eye drops under follow-up at the NEI Clinical Center. The treatment period was 6 months.

INCLUSION/EXCLUSION CRITERIA 98 EI0109S
Patients were eligible for inclusion in this study if all of the following criteria were met at the time of screening:

- Patient diagnosed with cystinosis (either >2 nmole half-cystine/mg protein in leukocytes or presence of corneal crystals consistent with cystinosis and distributed in corneal stroma observed by slit-lamp biomicroscopy). (The definition of cystinosis was modified by Protocol Amendment 1 and again by Protocol Amendment 2).
- Patient has a clinical history consistent with cystinosis.
- Patient is willing and able to tolerate photographs.
- Patient is ≥1 year of age.
- Patient has the willingness and ability to comply with treatment and follow-up procedures as demonstrated by a history of adherence with their current eye drop and patient follow-up schedule under Protocol 86 EI-0062.
- Patient or the patient's parent/guardian has the ability to understand and sign the ICF.
- Patient has any crystal density score, including zero, on photographs that has been stable or improved over the past year.

A patient was not eligible for inclusion in the study if any of the following criteria applied:

- Patient has a history of noncompliance with eye drops for cystinosis or failure to comply with a follow-up schedule.
- Patient is <1 year of age.

PRIMARY EFFICACY VARIABLE 98 EI0109S
Although the focus of this study was on safety as defined by SAEs in eyes treated with Formulation 5, an increase in CCCS and/or a worsening of the ocular signs and symptoms of cystinosis could also be a safety concern. Although no decision on how to analyze these data was made a priori, the efficacy assessments were collected as per protocol.

ANALYSIS POPULATIONS 98 EI0109S

Eighteen of the 20 eyes per formulation group randomized in this study received at least one post-baseline CCCS assessment for the primary and secondary end point analyses and were, therefore, included in the Per-Protocol Population. All 20 eyes per formulation group randomized received at least one treatment dose; therefore, the safety analysis population was comprised of the same 18 eyes per formulation group included in the Per-Protocol Population in addition to two eyes per formulation group (Patient 9010 and Patient 9011). For the subset of patients 2-12 years of age, 10 eyes per formulation group comprised the safety population and eight eyes per formulation group comprised the Per-Protocol Population.

LIST OF INVESTIGATORS/SUBINVESTIGATORS 98 EI0109S

Site Number	Investigator Name	Facility Name and Address
09	Muriel Kaiser, M.D.	National Eye Institute Building 10, Clinical Center 10 Center Drive Bethesda, MD 20892

STUDY PLAN 98 EI0109S

Table 1. Study Time and Events Schedule

Assessment	Time Point				
	Baseline	Week 1	Week 2	Month 1	Month 6
Medical History	X	NA	NA	NA	NA
Physical Examination, Vital Signs	X	NA	NA	NA	NA
VFQ-25[a]	X	NA	NA	NA	X
Ophthalmic Examination, Corneal Slit-lamp Examination, Fluorescein Angiography	X	NA	NA	NA	X
Manifest Refraction	X	NA	NA	NA	X
Visual Acuity	X	NA	NA	NA	X
Slit-Lamp Photographs	X	NA	NA	NA	X
Photophobia Clinical Assessment	X	NA	NA	NA	X
Blepharospasm Clinical Assessment	X	NA	NA	NA	X
Assessment of Dosing Compliance	NA	X[b]	X[b]	X[b]	X
AEs (Ocular and Systemic)	NA	X[b]	X[b]	X[b]	X
Leukocyte Cystine Value	X	NA	NA	NA	X

[a] = Administered to patients ≥18 years of age.
[b] = Telephone interview.
NA = Not applicable.

Literature Review

Kaiser-Kupfer, et al 1987[3], studied the effects of ophthalmic cysteamine eye drops versus placebo on corneal crystal formulation in two young children (less than 2 years of age) with nephropathic cystinosis in a double-masked, placebo-controlled clinical trial. Two patients received cysteamine 0.11% in one eye and placebo in the companion eye. Cysteamine eye drops appeared to be safe and efficacious in the short-term treatment of patients with cystinosis who were under 2 years of age.

Dufier, et al 1987[4], discussed results of the systematic ocular examinations of 25 cases of cystinosis, 51 cases of nephronophthisis, and 28 cases of Alport's syndrome in order to record the incidence of ocular symptoms and their long-term evolution. Two patients were treated with ophthalmic cysteamine (3 drops/day in each eye, formulation not described), whereupon photophobia decreased, but storage and superficial punctate keratopathy remained the same. The use of ophthalmic cysteamine appeared to be promising, but its production raised many questions, so no definitive conclusions were made.

Dufier , et al 1987[5],discussed results of the ocular changes in long-term evolution of infantile cystinosis. Since 1959, 25 cystinotic patients were followed. Follow-up of these 25 patients demonstrated that infantile cystinosis affects mainly corneal and retinal epithelia just as it affects the kidney epithelium.

MacDonald, et al 1990[6], assessed whether or not ophthalmic cysteamine at a concentration of 0.3% applied 4 times/day would be as effective in reducing crystal formation within the cornea of patients affected by nephropathic cystinosis as cysteamine at a concentration of 0.11% applied hourly. Patients received cysteamine 0.3% in one eye and placebo (normal saline) in the companion eye 4 times/day. After 7 months of therapy, there was no difference in the visual acuity of the treated and untreated eyes. The three observers could not clinically detect any appreciable

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3 Kaiser-Kupfer MI, Fujikawa L, Kuwabara T, Jain S, Gahl WA. Removal of corneal crystals by topical cysteamine in nephropathic cystinosis. *N Engl J Med*, 1987;316(13):775-779.

4 Dufier JL, Orssaud D, Dhermy P, Gubler MC, Gagnadoux MF, et al. Ocular changes in some progressive hereditary nephropathies. *Pediatr Nephrol*, 1987;1(3):525-530.

5 Dufier JL, Dhermy P, Gubler MC, Gagnadoux MF, Broyer M. Ocular changes in long-term evolution of infantile cystinosis. *Ophthalmic Paediatr Genet,* 1987;8(2):131-137.

6 MacDonald IM, Noel LP, Mintsioulis G, Clarke WN. The effect of topical cysteamine drops on reducing crystal formation within the cornea of patients affected by nephropathic cystinosis. *J Pediatr Ophthalmol Strabismus,* 1990;27(5):272-274.

difference in the number of crystals seen in the corneas of the treated and untreated eyes.

Bradbury, et al 1991[7], assessed the ability of cysteamine eye drops to deplete the cornea of cystine crystals and document any improvement in visual function in 5 children with proven cystinosis in a randomized, double-masked, placebo-controlled trial. Patients received cysteamine 0.2% in one eye and placebo (normal saline) in the other eye 6 times/day. All patients showed subjective improvement in visual symptoms such as photophobia, blepharospasm, and visual acuity in the eye receiving ophthalmic cysteamine. There was also a small improvement in visual symptoms in the eye receiving placebo in four out of five cases.

Graf, et al 1992[8], discussed the case of a 2 year old male patient with infantile cystinosis in which cysteamine solutions in various concentrations were administered as eye drops. At the age of 18 months, a local cysteamine therapy was begun in the right eye at a dose of 0.1% cysteamine HCl. The application took place every 2 hours while the patient was awake (6 drops to a maximum of 8 drops daily). After 4 weeks, in a comparison of the treated and untreated eyes that involved the slit-lamp microscope, a decrease of the corneal crystals could be seen in the treated eye. After 26 weeks, the crystals were nearly completely dissolved, and they had increased in the untreated eye. Because no side effects had been reported/observed, the left eye was subsequently treated with 0.5% cysteamine HCl solution with the same frequency of drops. A regression of the crystals was noted after 2 weeks. After a treatment period of 12 weeks, few corneal deposits were visible.

Blanksma, et al 19969, assessed whether ophthalmic P04-cysteamine therapy relieved complaints of photophobia and glare in patients with nephropathic cystinosis. Patients received P04-cysteamine 5 mMol/mL in 0.5% hydroxypropyl methylcellulose with BAK 0.01% in both eyes 5 times/day. The visual acuity, normal in a semidark room at the beginning of the therapy, did not change. At 6 months follow-up, the corneal punctate erosions disappeared in all three patients. All three patients experienced improvement in photophobia. Two out of three patients experienced a significant improvement to their glare disability, and this improvement continued for the following 6 months.

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7 Bradbury JA, Danjoux JP, Voller J, Spencer M, Brocklebank T. A randomised placebo-controlled trial of topical cysteamine therapy in patients with nephropathic cystinosis. *Eye (Lond),* 1991;5:755-760.

8 Graf M, Grote A, Wagner F. Cysteamine Eye Drops for the Treatment of Corneal Cystine Deposits in Nephropathic Cystinosis. *Klin Mbl Augenheik (Clinical Bulletin of Ophthalmology)*, 1992;201:48-50.

9 Blanksma LJ, Jansonius NM, Reitsma-Bierens WC. Cysteamin eyedrops in three patients with nephropathic cystinosis. *Doc Ophthalmol,* 1996-1997;92(1):51-53.

Soliman, et al 2009[10], assessed the use of slit-lamp examination for corneal cystine deposits in suspected cases for the diagnosis of nephropathic cystinosis and the progress of such deposits with treatment. In addition to oral cysteamine, cysteamine eye drops were provided to all diagnosed patients and CCCS was followed-up on a quarterly basis. After 6 months of treatment, the mean CCCS did not increase from the initial value of 1.81; this was associated with a decrease of 0.5 in two cases and a similar increase in two others. Scores decreased in two other patients after 12 months. Compliance was generally inadequate due to the high frequency of administration and the need for a multidrug regimen.

6 Review of Efficacy

Efficacy Summary

6.1 Indication

Treatment of corneal cystine crystal accumulation in patients with cystinosis

6.1.1 Methods

See Section 5.3 for specific trial study designs.

10 Soliman NA, El-Baroudy R, Rizk A, Bazaraa H, Younan A. Nephropathic cystinosis in children: An overlooked disease. *Saudi J Kidney Dis Transpl*, 2009;20(3):436-442.

6.1.2 Demographics

STP869294 (CAPTOC)

Table 9. Patient Demographics				
Demographics	**ITT (N = 247)**	**mITT (N = 161)**	**mITT-1 (N = 92)**	**mITT-2 (N = 69)**
Age (Years)[a]				
Mean ± SD	13.8 ± 9.94	12.1 ± 9.13	11.0 ± 8.02	13.5 ± 10.30
Median	12.8	10.9	11.8	9.3
Minimum, Maximum	0.2, 49.6	0.2, 47.9	0.2, 30.6	1.3, 47.9
Gender (*n*%)				
Male	130 (52.6%)	83 (51.6%)	48 (52.2%)	35 (50.7%)
Female	117 (47.4%)	78 (48.4%)	44 (47.8%)	34 (49.3%)
[a] = Day portion of birthdate was set to 01 because it was not collected in the database. Source: *Table 14.1.2.1*, *Table 14.1.2.2*, *Table 14.1.2.3*, *Table 14.1.2.4*.				

Source: May 6, 2010, Clinical Study Report Amendment, CAPTOC, 11.2.1 Demographic Characteristics

Mean (±SD) age of the ITT Population was 14 ± 9.94 years, with 130 (53%) patients being male and 117 (47%) patients being female. Of the 161 patients in the mITT Population, 83 (52%) were male and 78 (48%) were female. The youngest patient on study was <1 year and the oldest patient was approximately 48 years.

98 EI0109E

Table 3. Patient Demographics	
Demographics	**Overall (n = 16)**
Age (Years)[a]	
Mean ± SD	6.49 ± 2.949
Minimum, Maximum	2.7, 12.0
Median	6.65
Gender (n%)[b]	
Male	8 (50%)
Female	8 (50%)
Race (n%)[b,c]	
White	16 (100%)
Ethnicity (n%)[b]	
Non-Hispanic Origin	16 (100%)
Hispanic Origin	0 (0%)

[a] = Before calculating age, patient data were de-identified by replacing the day portion of date of birth with '01'.
[b] = Percentages are based on the number of patients with non-missing values.
[c] = No other race was enrolled in the study (Black, Asian, Pacific Islander, Native American, Alaskan Native, or Other).
Source: *Table 14.1.2*.

Source: December 17, 2009, Clinical Study Report, 98 EI0109E, 11.2.1 Demographic Characteristics

Of the 16 patients enrolled, 8 (50%) were male and 8 (50%) were female. All 16 patients were of white, non-Hispanic origin and the mean age was approximately 7 years (range 3-12 years).

98 EI0109S

Table 3. Patient Demographics		
Demographics	**Overall (*n* = 20)**	**Patients 2–12 Years of Age (*n* = 10)**
Age (Years)[a]		
Mean ± SD	13.38 ± 5.484	9.83 ± 1.878
Min, Max	5.9, 27.8	5.9, 12.0
Median	12.30	10.25
Gender (*n*%)[b]		
Male	13 (65.0%)	8 (80.0%)
Female	7 (35.0%)	2 (20.0%)
Race (*n*%)[b,c]		
White	20 (100%)	10 (100%)
Ethnicity (*n*%)[b]		
Not Hispanic Origin	20 (100%)	10 (100%)
Hispanic Origin	0 (0%)	0 (0%)

[a] = Before calculating age, patient data were de-identified by replacing the day portion of date of birth with '01'.
[b] = Percentages are based on the number of patients with non-missing values.
[c] = No other races were enrolled in the study (Black, Asian, Pacific Islander, Native American, Alaskan Native, or Other).
Source: *Table 14.1.2* and *Table 14.1.2a*.

Source: December 17, 2009, Clinical Study Report, 98 EI0109S, 11.2.1 Demographic Characteristics

Of the 20 patients enrolled, 13 (65%) were male and seven (35%) were female. All 20 patients were of white non-Hispanic origin and the mean age was approximately 13 years (range 6 to 29 years of age).

6.1.3 Subject Disposition

STP869294 (CAPTOC)

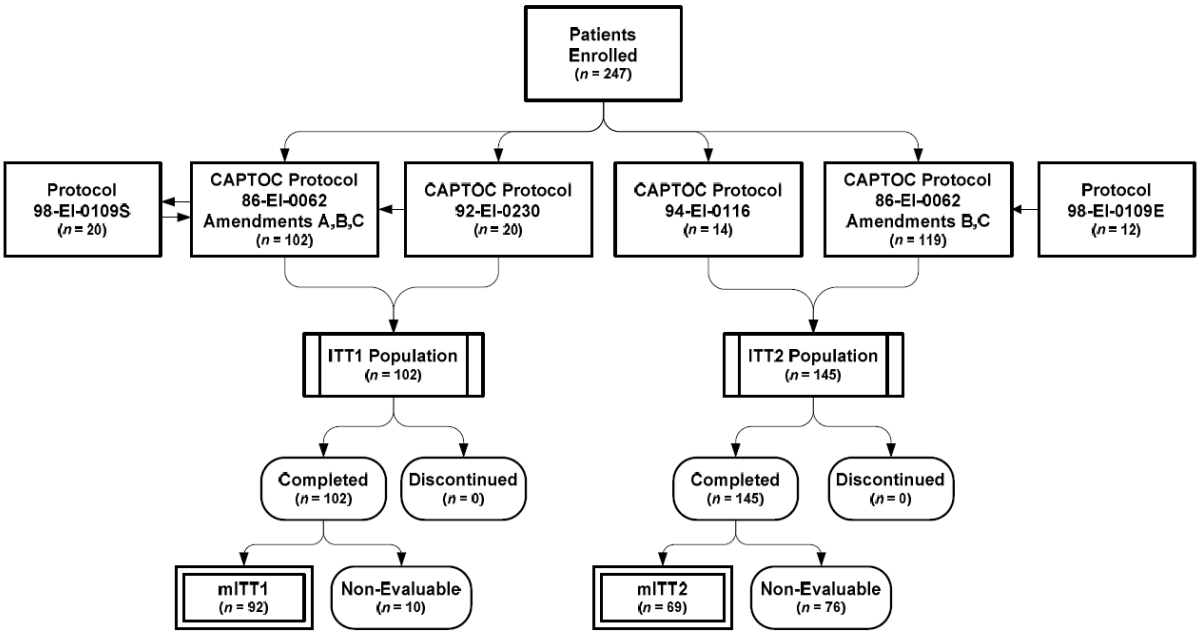

Figure 2. Patient disposition overview.

ITT-1 and ITT-2 populations labeled in this figure are for descriptive purposes only to delineate the discontinuation of placebo treatment. No efficacy analyses were performed on ITT-1 and ITT-2 populations.

Source: May 6, 2010, Clinical Study Report Amendment, CAPTOC, 10.1 Disposition of Patients

A total of 247 patients were enrolled into the study through the three protocols. The mITT populations comprised all patients for whom a baseline CCCS score and a minimum of one post-baseline CCCS score exist. All patients completed the study.

98 EI0109E

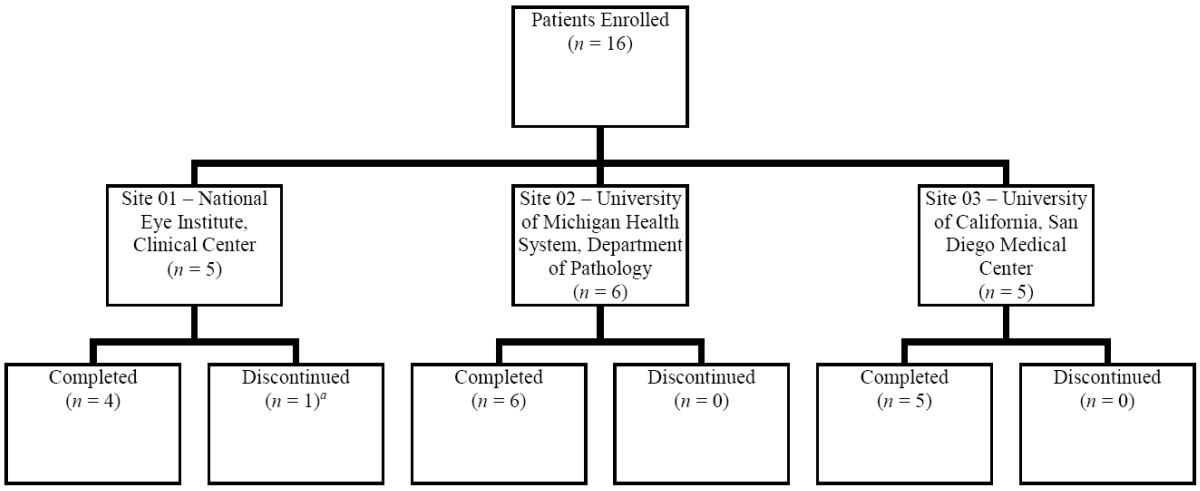

Figure 1. Patient disposition.

[a] = Discontinued due to administrative reason.

Source: *Table 14.1.1.1* and *Table 14.1.1.2*.

Source: December 17, 2009, Clinical Study Report, 98 EI0109S, 10.1 Disposition of Patients

A total of 16 patients were enrolled into the study at three sites. Only one patient discontinued prematurely (from Site 01-NEI) and 15 completed the study.

(Patient 01002) from the NEI site prematurely discontinued study after 6 weeks of therapy due to “patient resistance and parental unwillingness to continue frequent administration of eye drops.” This patient was omitted from the efficacy analysis; this patient should more accurately have been counted as a treatment failure.

98 EI0109S

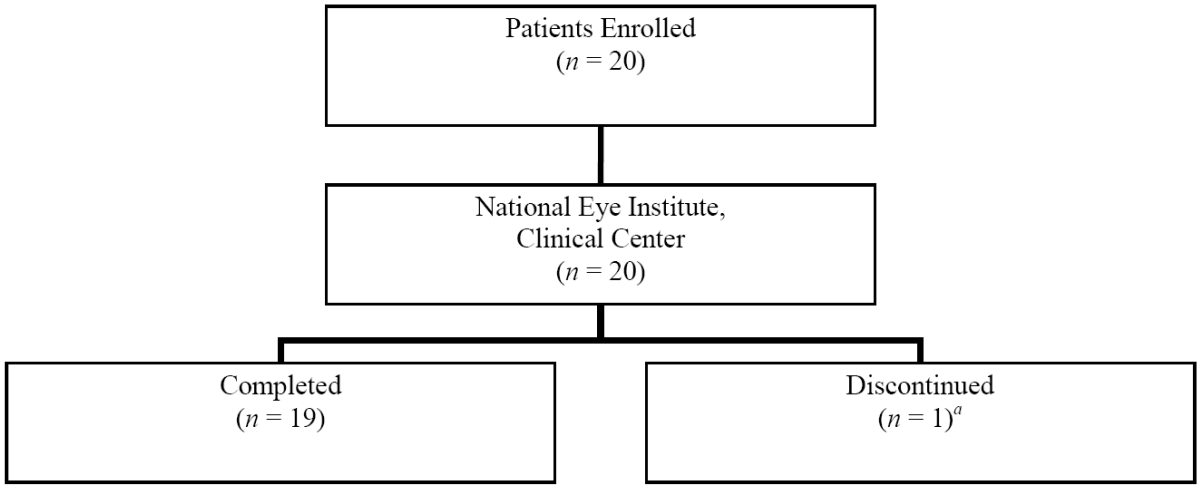

Figure 1. Patient disposition.

[a] = Discontinued due to an administrative reason.

Source: Appendix *Table 14.1.1.1* and *Table 14.1.1.2*.

Source: December 17, 2009, Clinical Study Report, 98 EI0109S, 10.1 Disposition of Patients

A total of 20 patients were enrolled in the study at the NEI. Only one patient discontinued prematurely (due to an administrative reason) and 19 completed the study.

Of the 20 patients enrolled, 20 (100%) eyes comprised the Safety Population (eyes that received at least one dose of study drug) and 18 (90%) eyes comprised the Per-Protocol Population (eyes with at least one post-baseline CCCS). Only one (5%) patient (Patient 9010) discontinued participating in the study after 2 months of therapy due to parental unwillingness to continue frequent administration of the eye drops. Another patient (Patient 9011) was unable to return for the Month 6 visit until 385 days after initiating study therapy. These two patients were omitted from the efficacy analysis: these patients should more accurately have been counted as treatment failures.

6.1.4 Analysis of Primary Endpoint(s)

STP869294 (CAPTOC)

Table 12. Proportion of Eyes with Corneal Cystine Crystal Score (CCCS) Response (mITT Population)			
		Total Eyes (N = 322)	
Time Point	**N[b]**	***n* (%)**	**95% CI[c]**
Response at Any Time During Study[a]	321	98 (30.5%)	[25.5, 35.9%]
Eyes with CCCS ≥1.00 at Baseline	291	94 (32.3%)	[27.0, 38.0%]
Eyes with CCCS <1.00 at Baseline	30	4 (13.3%)	[3.8, 30.7%]
Cumulative Response Rates by Year (Eyes with CCCS ≥1.00 at Baseline)[a]	291		
Year 1		27 (9.3%)	[6.2, 13.2%]
Year 2		51 (17.5%)	[13.3, 22.4%]
Year 3		72 (24.7%)	[19.9, 30.1%]
Year 4		80 (27.5%)	[22.4, 33.0%]
Year 5		85 (29.2%)	[24.0, 34.8%]
Year 6[d]		87 (29.9%)	[24.7, 35.5%]

[a] = A response was defined as a decrease from baseline of at least 1.00 unit in CCCS at any time on study when baseline was ≥1.00, or CCCS did not increase at least 1.00 unit at any time on study when baseline CCCS was <1.00.
[b] = Percentages were based on the number of total eyes evaluated.
[c] = Clopper and Pearson 95% CI for percentage.
[d] = Cumulative response rates for Year 7 through Year 19 may be found in *Table 14.2.1.1*.
Source: *Table 14.2.1.1*.

Source: May 6, 2010, Clinical Study Report Amendment, CAPTOC, 11.4.1.1 Primary End Point

For eyes with a lower baseline CCCS of <1, the response rate in the mITT population was 13% (4/30) [95% CI: (4, 31)]. For eyes with a higher baseline CCCS of ≥1, the response rate was 32% (94/291) [95% CI: (27, 38)].

Values highlighted in yellow in this table and subsequent tables were revised in the May 20, 2010, submission.[11]

11 Per the May 20, 2010, submission: Upon review of the study data and the SAS program coding used to generate the initial analysis outcomes, Sigma-Tau confirmed the discrepancy between the CCCS response rates observed by FDA and those reported by Sigma-Tau. These differences were attributed to the manner in which missing values were handled in the response rate calculations. The Sigma-Tau analysis

Table 13. Proportion of Eyes with Corneal Cystine Crystal Score (CCCS) Response (mITT-1 Population)			
		Total Eyes (N = 184)	
Time Point	**N[b]**	***n* (%)**	**95% CI[c]**
Response at Any Time During Study[a]	183	53 (29.0%)	[22.5, 36.1%]
Eyes with CCCS ≥1.00 at Baseline	156	49 (31.4%)	[24.2, 39.3%]
Eyes with CCCS <1.00 at Baseline	27	4 (14.8%)	[4.2, 33.7%]
Cumulative Response Rates by Year (Eyes with CCCS ≥1.00 at Baseline)[a]	156		
Year 1		11 (7.1%)	[3.6, 12.3%]
Year 2		22 (14.1%)	[9.1, 20.6%]
Year 3		33 (21.2%)	[15.0, 28.4%]
Year 4		40 (25.6%)	[19.0, 33.2%]
Year 5		43 (27.6%)	[20.7, 35.3%]
Year 6[d]		45 (28.8%)	[21.9, 36.6%]

[a] = A response was defined as a decrease from baseline of at least 1.00 unit in CCCS at any time on study when baseline was ≥1.00, or CCCS did not increase at least 1.00 unit at any time on study when baseline CCCS was <1.00.
[b] = Percentages were based on the number of total eyes evaluated.
[c] = Clopper and Pearson 95% CI for percentage.
[d] = Cumulative response rates for Year 7 through Year 19 may be found in *Table 14.2.1.2*.
Source: *Table 14.2.1.2*.

Source: May 6, 2010, Clinical Study Report Amendment, CAPTOC, 11.4.1.1 Primary End Point

For eyes with a lower baseline CCCS of <1, the response rate in the mITT-1 population was 15% (4/27) [95% CI: (4, 34)]. For eyes with a higher baseline CCCS of ≥1, the response rate was 32% (49/156) [95% CI: (24, 39)]. This is consistent with the mITT population results.

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provided that patient eyes with one or more missing change-from-baseline CCCS values, due to missing post-baseline CCCS's, would be assigned as a response to treatment. This resulted in some patient eyes being regarded as responders when in fact there were no data to support that outcome. Sigma-Tau confirmed that when excluding any missing eye-year assessments of change-from-baseline CCCS values from the response rate calculations, the response outcome as observed by FDA was verified. In an effort to facilitate the review process, Sigma-Tau performed a new analysis based on FDA's method. The revised efficacy datasets and analyses have been amended in the STP869294 CSR and replace the original analyses.

Table 14. Proportion of Eyes with Corneal Cystine Crystal Score (CCCS) Response (mITT-2 Population)			
		Total Eyes (N = 138)	
Time Point	**N[b]**	***n* (%)**	**95% CI[c]**
Response at Any Time During Study[a]	138	45 (32.6%)	[24.9, 41.1%]
Eyes with CCCS ≥1.00 at Baseline	135	45 (33.3%)	[25.5, 42.0%]
Eyes with CCCS <1.00 at Baseline	3	0 (0.0%)	[0.0, 70.8%]
Cumulative Response Rates by Year (Eyes with CCCS ≥1.00 at Baseline)[a]	135		
Year 1		16 (11.9%)	[6.9, 18.5%]
Year 2		29 (21.5%)	[14.9, 29.4%]
Year 3		39 (28.9%)	[21.4, 37.3%]
Year 4		40 (29.6%)	[22.1, 38.1%]
Year 5		42 (31.1%)	[23.4, 39.6%]
Year 6[d]		42 (31.1%)	[23.4, 39.6%]

[a] = A response was defined as a decrease from baseline of at least 1.00 unit in CCCS at any time on study when baseline was ≥1.00, or CCCS did not increase at least 1.00 unit at any time on study when baseline CCCS was <1.00.
[b] = Percentages were based on the number of total eyes evaluated.
[c] = Clopper and Pearson 95% CI for percentage.
[d] = Cumulative response rates for Year 7 through Year 11 may be found in *Table 14.2.1.3*.
Source: *Table 14.2.1.3*.

Source: May 6, 2010, Clinical Study Report Amendment, CAPTOC, 11.4.1.1 Primary End Point

For eyes with a lower baseline CCCS of <1, there were no subjects in the mITT-2 population. For eyes with a higher baseline CCCS of ≥1, the response rate was 33% (49/156) [95% CI: (26, 42)]. This is consistent with the mITT and mITT-1 population results.

98 EI0109E

Table 7. Proportion of Eyes with Reduction in CCCS of 1 Unit or More (Per-Protocol Population)

	Formulation 5		Formulation 3		
Time Point	***n* (%)[a]**	**95% CI[b]**	***n* (%)[a]**	**95% CI[b]**	***p*-Value[c]**
Any Time During Study	2 (13.3%)	1.7-40.5	10 (66.7%)	38.4-88.2	0.0047[d]
Month 3	2 (13.3%)	1.7-40.5	4 (28.6%)[e]	8.4-58.1	0.0833[f]
Month 6	2 (14.3%)[e]	1.8-42.8	7 (50.0%)[e]	23.0-77.0	0.0253[d]
Month 9	1 (7.1%)[e]	0.2-33.9	8 (57.1%)[e]	28.9-82.3	0.0082[d]
Month 12	1 (6.7%)	0.2-31.9	7 (46.7%)	21.3-73.4	0.0143[d]

[a] = Percentages are based on the number of eyes with non-missing values at the corresponding time point.
[b] = Clopper and Pearson 95% CI for percentage.
[c] = Results from McNemar's Test.
[d] = Statistically significant (p <0.05).
[e] = The number of eyes evaluated at this time point was only 14 as opposed to 15.
[f] = Note: At Month 3, Patient 3003 is excluded from the McNemar Test due to the fact that a valid assessment was not available for both eyes.
Source: *Table 14.2.1.1.1*.

Source: December 17, 2009, Clinical Study Report, 98 EI0109E, 11.4.1 Analysis of Efficacy

This study evaluated ocular cystinosis patients who had a baseline CCCS ≥1. The response rate in the Per Protocol population was 67% (10/15) [95% CI: (38, 88)] with Formulation 3. The response rate was 13% (2/15) [95% CI: (2, 41)] with Formulation 5.

98 EI0109S

Table 11. Proportion of Eyes with Reduction in CCCS of 1 Unit or More at Month 6 (Per-Protocol Population and Subset of Patients 2–12 Years of Age)					
	Formulation 5		Formulation 3		
	n (%)	95% CI[b]	*n* (%)	95% CI[b]	*p*-Value[c]
Per-Protocol Population (*n* = 18)					
Eyes With a CCCS ≥1 Unit at Baseline	8 (44.4%)	N/A	9 (50.0%)	N/A	N/A
Eyes With a Reduction in CCCS ≥1 Unit[a]	0 (0.0%)	0.0-36.9	3 (33.3%)	7.5-70.1	0.0833
Patients 2–12 years of Age (*n* = 8)					
Eyes With a CCCS ≥1 Unit at Baseline	3 (37.5%)	N/A	4 (50.0%)	N/A	N/A
Eyes With a Reduction in CCCS ≥1 Unit[a]	0 (0.0%)	0.0-70.8	0 (0.0%)	0.0-60.2	N/A

[a] = Percentages are based on the number of eyes with a CCCS of ≥1 at baseline.
[b] = Clopper and Pearson 95% CI for percentage.
[c] = Results from McNemar's Test.
N/A = Not applicable.
Source: *Table 14.2.1.1.1* and *Table 14.2.1.1.1a*.

Source: December 17, 2009, Clinical Study Report, 98 EI0109S, 11.4.1 Analysis of Efficacy

The majority of these patients in this study (12/20) had a baseline CCCS ≤1. The response rate in the Per Protocol Population with Formulation 3 was 33% (3/9) [95% CI: (8, 70)].

Although the focus of this study was on safety as defined by SAEs in eyes treated with Formulation 5, an increase in CCCS and/or a worsening of the ocular signs and symptoms of cystinosis could also be a safety concern. Although no decision on how to analyze these data was made a priori, the efficacy assessments were collected as per protocol.

Analysis of Secondary Endpoints(s)

Analyses for several of the proposed secondary endpoints for CAPTOC are presented. The clinical significance of these secondary endpoints is unclear. There is no correction for multiple endpoints in the analyses provided.

STP869294 (CAPTOC)

Mean Change from Baseline in CCCS

Table 15. Mean Change from Baseline in CCCS by Year on Study (mITT Population)			
	Total Eyes (N = 322)		
Time Point Statistic	Baseline	Time Point	Change
Year 1			
n	218	218	218
Mean ± SD	2.4 ± 0.96	2.2 ± 1.05	-0.2 ± 0.81
Median	3.0	3.0	0.0
Minimum, Maximum	0.0, 3.0	0.0, 3.0	-3.0, 1.5
95% CI	[2.3, 2.6]	[2.1, 2.4]	[-0.3, -0.1]
Year 2			
n	243	243	243
Mean ± SD	2.5 ± 0.90	2.2 ± 1.09	-0.3 ± 0.95
Median	3.0	3.0	0.0
Minimum, Maximum	0.0, 3.0	0.0, 3.0	-3.0, 2.8
95% CI	[2.3, 2.6]	[2.1, 2.3]	[-0.4, -0.1]
Year 3			
n	196	196	196
Mean ± SD	2.3 ± 0.96	1.9 ± 1.18	-0.4 ± 1.14
Median	3.0	2.5	0.0
Minimum, Maximum	0.0, 3.0	0.0, 3.0	-3.0, 2.0
95% CI	[2.2, 2.5]	[1.8, 2.1]	[-0.6, -0.2]
Year 4			
n	167	167	167
Mean ± SD	2.3 ± 0.97	1.9 ± 1.18	-0.4 ± 1.18
Median	3.0	2.4	0.0
Minimum, Maximum	0.0, 3.0	0.0, 3.0	-3.0, 2.8
95% CI	[2.2, 2.5]	[1.7, 2.1]	[-0.6, -0.2]
Year 5			
n	164	164	164
Mean ± SD	2.3 ± 0.98	2.0 ± 1.20	-0.4 ± 1.17
Median	3.0	2.6	0.0
Minimum, Maximum	0.0, 3.0	0.0, 3.0	-3.0, 2.8
95% CI	[2.2, 2.5]	[1.8, 2.1]	[-0.5, -0.2]
Year 6			
n	140	140	140
Mean ± SD	2.2 ± 1.04	2.0 ± 1.19	-0.2 ± 1.16
Median	3.0	2.7	0.0
Minimum, Maximum	0.0, 3.0	0.0, 3.0	-3.0, 2.8
95% CI	[2.0, 2.4]	[1.8, 2.2]	[-0.4, 0.0]
Source: *Table 14.2.2.1*.			

Source: May 6, 2010, Clinical Study Report Amendment, CAPTOC, 11.4.1.2 Secondary End Points

For the first 6 years, the mean change from baseline in the mITT Population showed a decrease in CCCS ranging from approximately -0.2 to -0.4 among the available eyes assessed in each year.

Shift from Baseline to Post-Baseline Time Points (Years) in CCCS Categories

Figure 14.2.1.1
Corneal Cystine Crystal Score (CCCS) by Category and Year
mITT−1 Population

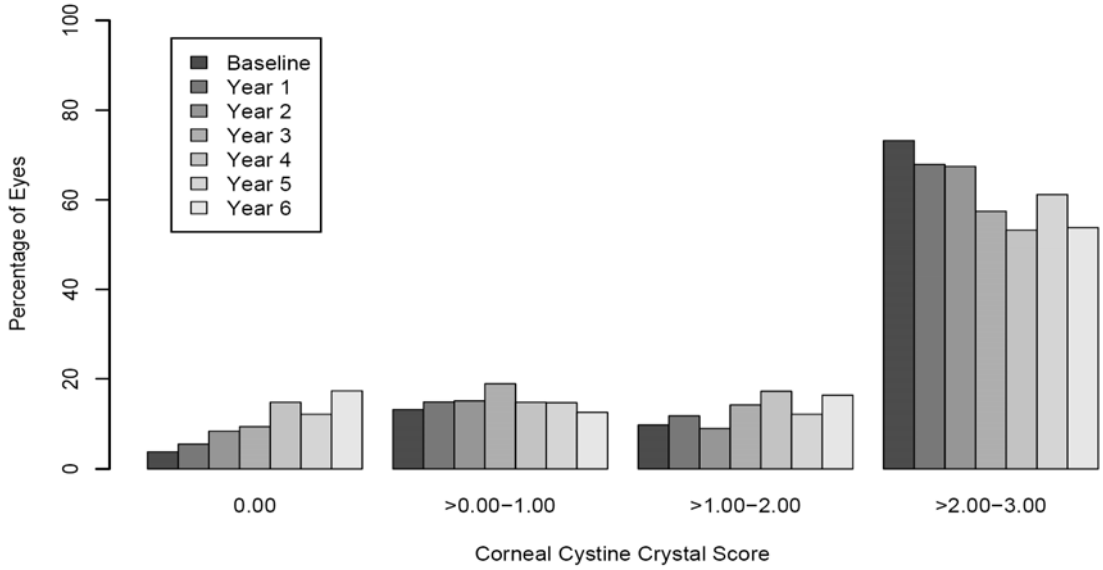
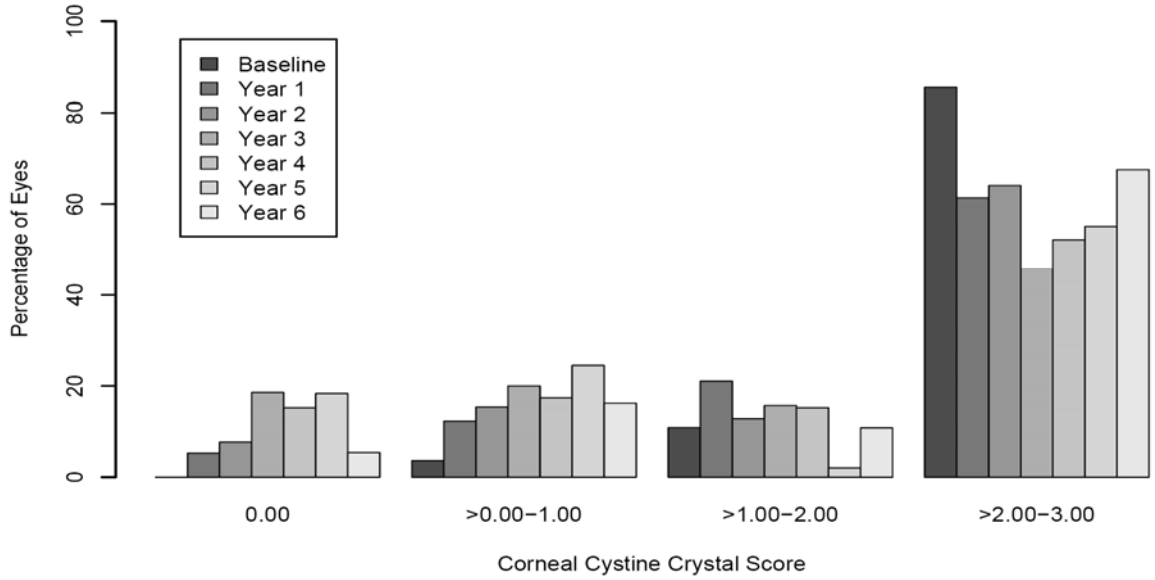


Figure 14.2.1.2
Corneal Cystine Crystal Score (CCCS) by Category and Year
mITT−2 Population



Source: May 6, 2010, Clinical Study Report Amendment, CAPTOC, 11.4.1.2 Secondary End Points

In the mITT-1 Population, there was an increase in the percentage of eyes in the "0.00" category from baseline to Year 6. A steady decrease was observed in the percentage of eyes in the highest category (">2.00-3.00") from baseline to Year 6.

In the mITT-2 Population, no eyes had a CCCS category of "0.00" at baseline. The percentage of eyes in this category had an increasing trend from Year 1 to Year 5, and although it decreased at Year 6, it still remained above baseline.

Improvement in Corneal Haziness, Photophobia, and in Foreign Body Sensation

Table 18. Summary of Corneal Haziness, Photophobia, and Foreign Body Sensation by Year on Study (mITT Population)

	Total Eyes (N = 322)						
Parameter	**Baseline**	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Year 6**
Corneal Haziness (*n*%)[a]							
Severity (*n*%)[a]							
None	62 (19.3%)	42 (18.8%)	78 (31.0%)	66 (31.4%)	60 (34.1%)	67 (38.5%)	46 (31.5%)
Mild	24 (7.5%)	9 (4.0%)	14 (5.6%)	14 (6.7%)	4 (2.3%)	15 (8.6%)	18 (12.3%)
Moderate	31 (9.6%)	13 (5.8%)	12 (4.8%)	6 (2.9%)	16 (9.1%)	8 (4.6%)	8 (5.5%)
Severe	15 (4.7%)	4 (1.8%)	10 (4.0%)	10 (4.8%)	6 (3.4%)	17 (9.8%)	11 (7.5%)
Not Evaluable[b]	172 (53.4%)	132 (58.9%)	125 (49.6%)	100 (47.6%)	78 (44.3%)	54 (31.0%)	51 (34.9%)
Missing	18 (5.6%)	24 (10.7%)	13 (5.2%)	14 (6.7%)	12 (6.8%)	13 (7.5%)	12 (8.2%)
Photophobia (Physician Assessment)[a]							
Severity (*n*%)[a]							
None	42 (13.0%)	50 (22.3%)	66 (26.2%)	62 (29.5%)	60 (34.1%)	60 (34.5%)	45 (30.8%)
Mild	78 (24.2%)	46 (20.5%)	75 (29.8%)	49 (23.3%)	29 (16.5%)	27 (15.5%)	30 (20.5%)
Moderate	74 (23.0%)	34 (15.2%)	32 (12.7%)	37 (17.6%)	23 (13.1%)	18 (10.3%)	17 (11.6%)
Severe	54 (16.8%)	18 (8.0%)	9 (3.6%)	14 (6.7%)	17 (9.7%)	18 (10.3%)	16 (11.0%)
Not Evaluable[b]	67 (20.8%)	63 (28.1%)	62 (24.6%)	40 (19.0%)	37 (21.0%)	33 (19.0%)	26 (17.8%)
Missing	7 (2.2%)	13 (5.8%)	8 (3.2%)	8 (3.8%)	10 (5.7%)	18 (10.3%)	12 (8.2%)
Presence of Foreign Body Sensation (*n*%)[a]							
No	81 (25.2%)	64 (28.6%)	88 (34.9%)	94 (44.8%)	79 (44.9%)	88 (50.6%)	80 (54.8%)
Yes	57 (17.7%)	6 (2.7%)	10 (4.0%)	18 (8.6%)	9 (5.1%)	18 (10.3%)	13 (8.9%)
Not Evaluable[b]	164 (50.9%)	146 (65.2%)	142 (56.3%)	88 (41.9%)	76 (43.2%)	48 (27.6%)	38 (26.0%)
Missing	20 (6.2%)	8 (3.6%)	12 (4.8%)	10 (4.8%)	12 (6.8%)	20 (11.5%)	15 (10.3%)

[a] = Percentages were based on the number of eyes with non-missing values at the corresponding time point.
[b] = See *Section 11.2.2* for discussion of categorization of not evaluable.
Source: *Table 14.2.5.1*.

Source: May 6, 2010, Clinical Study Report Amendment, CAPTOC, 11.4.1.2 Secondary End Points

19% of eyes in the mITT Population had corneal haziness scores of zero (no haziness) at baseline. By Year 2, and continuing through Year 6, approximately 30% of eyes had

scores of zero. At Year 6, 32% (46/146) of eyes had no corneal haziness, 12% (18/146) of eyes had mild corneal haziness, 56% (8/146) of eyes had moderate corneal haziness, and 78% (11/146) of eyes had severe corneal haziness.

At baseline, 13% (42/322) of eyes in the mITT Population were without physician assessed photophobia, 24% (78/322) of eyes had mild photophobia, 23% (74/322) of eyes had moderate photophobia, and 16% (54/322) of eyes had severe photophobia. By Year 6, 31% (45/146) of eyes were without photophobia. There was a decrease in the number of eyes with severe photophobia from baseline (17% [54/322]) to Year 6 (11% [16/146]), with the lowest incidence at Year 2 (4% [9/252]).

The presence of a foreign body sensation decreased in eyes of patients from the mITT Population from baseline (18% [57/322]) to Year 6 (9% [13/146]). By Year 6, foreign body sensation was absent in 55% (80/146) of eyes.

6.1.6 Other Endpoints

None.

6.1.7 Subpopulations

Cystinosis is a rare autosomal recessive metabolic disorder. There were no subgroup analyses performed by sex or demographic group.

The results from CAPTOC indicate that for eyes with a lower baseline CCCS of <1, the response rate to Cystaran is lower than that in eyes with a higher baseline CCCS of ≥1. See Section 6.1.4.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

See Section 2.1 and 5.3 for a discussion of the evolution of the formulation of cysteamine hydrochloride ophthalmic solution.

Doses higher than 0.65% (more accurately, 0.44% cysteamine versus 0.65% cysteamine hydrochloride) were not pursued in humans because of findings of inflammatory reactions in animals.[12] Preclinical data with albino rabbits demonstrated a dose-response relationship for safety (an inflammatory reaction in rabbit eyes) following administration of ≥1% cysteamine ophthalmic solution every hour for 8 hours each day

12 Jain S, Kuwabara T, Gahl WA, Kaiser-Kupfer MI. Range of toxicity of topical cysteamine in rabbit eyes. J Ocul Pharmacol. 1988 Summer;4(2):127-31.

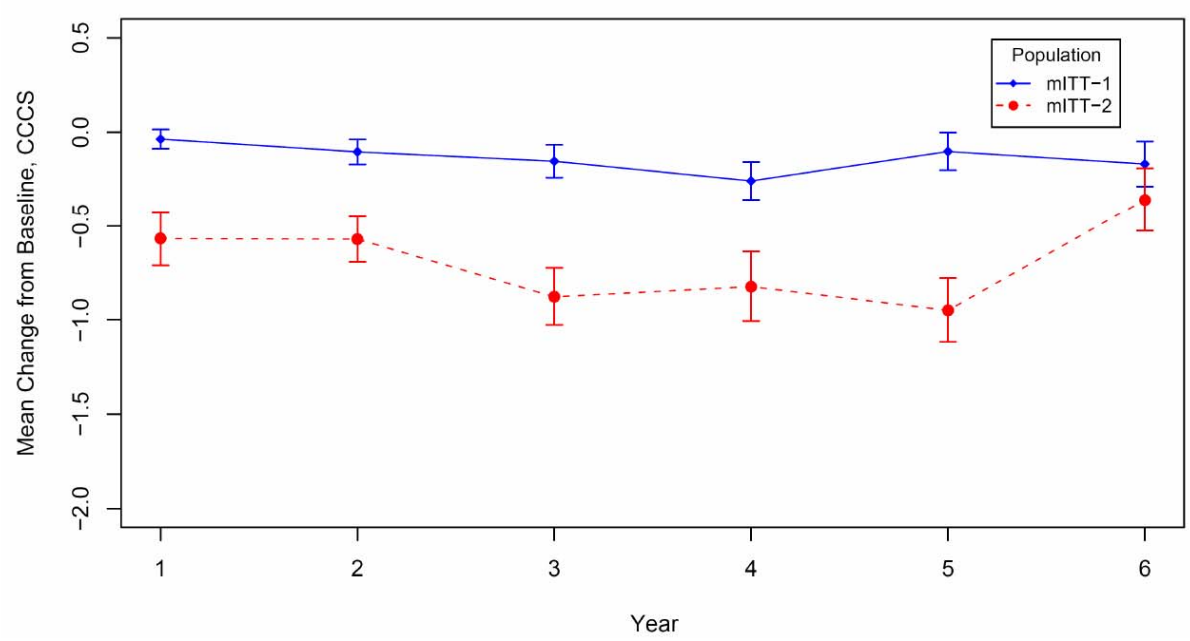
for 3 months but not with 0.5% cysteamine ophthalmic solution. See Pharmacology/Toxicology Review.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

In the eyes, cystine crystals initially appear in the central cornea and progress to the full thickness of the peripheral cornea and anterior two thirds of the central cornea with age. The natural history of corneal crystal accumulation indicates no spontaneous reduction in CCCS with age. The accumulation is at least partly responsible for clinical symptoms of photophobia, recurrent corneal erosions, secondary blepharospasm and loss of visual acuity that complicate longstanding cystinosis.

Cystaran (cysteamine hydrochloride ophthalmic solution) 0.44% is meant to be administered very hour while awake in each eye indefinitely.

Figure 2 - Mean change from baseline, CCCS ± standard error (SE) over time (mITT-1 and mITT-2 populations)



Source: May 6, 2010, Clinical Study Report Amendment, CAPTOC, 11.5 Efficacy Conclusion

6.1.10 Additional Efficacy Issues/Analyses

None.

7 Review of Safety

Safety Summary

7.1 Methods

See Section 5.3 for specific trial study designs.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Studies STP869294 (CAPTOC), 98 EI0109E, and 98 EI0109S were utilized to evaluate safety.

7.1.2 Categorization of Adverse Events

All adverse event terms in the three clinical trials (STP869294 (CAPTOC), 98 EI0109E, and 98 EI0109S) were coded using MedDRA Dictionary Version 9.0.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Pooled adverse event data was not submitted in the new drug application.

For the purposes of labeling the adverse event profile of cysteamine hydrochloride ophthalmic solution 0.44%, the data from STP869294 (CAPTOC) was utilized. CAPTOC enrolled 247 subjects; the trial duration was 19 years.

The adverse event profiles seen in 98 EI0109E, and 98 EI0109S are consistent with STP869294 (CAPTOC).

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

STP869294 (CAPTOC)

Because compliance was not analyzable in CAPTOC, the safety analyses were based on the assumption that all patients were on active treatment with ophthalmic cysteamine. As a conservative effort, these analyses actually encompassed times where patients may have been treated with cysteamine, placebo, or cystamine. The Table below provides the summary of study duration that details average treatment duration, minimum and maximum treatment duration, and how many patients were receiving treatment every year. For the Safety Population, the mean (±SD) treatment duration for the 247 patients was 5.8 ± 5.54 years. There were 4 patients that had been receiving treatment for the maximum duration of 19 years.

Table 14.1.5.1

Summary of Study Duration
ITT Population

	Total (N=247)
Duration on study (years)	
n	247
Mean	5.8
S.D.	5.54
Median	4.5
Min, Max	0.0, 19.0
Patients on study by year	
Baseline	247 (100.0)
1	180 (72.9)
2	176 (71.3)
3	153 (61.9)
4	137 (55.5)
5	128 (51.8)
6	113 (45.7)
7	102 (41.3)
8	94 (38.1)
9	85 (34.4)
10	74 (30.0)
11	63 (25.5)
12	55 (22.3)
13	47 (19.0)
14	34 (13.8)
15	25 (10.1)
16	15 (6.1)
17	10 (4.0)
18	7 (2.8)
19	4 (1.6)

Source: May 6, 2010, Clinical Study Report Amendment, CAPTOC, 12.1 Extent of Exposure

7.2.2 Explorations for Dose Response

Doses higher than 0.44% were not pursued in humans because of findings of inflammatory reactions in animals (rabbits). See Pharmacology/Toxicology Review.

7.2.3 Special Animal and/or In Vitro Testing

Per the Pharmacology/Toxicology Review dated 7/7/10:

The ophthalmic solutions were considered to be non-irritating following ocular administration every hour, 8 consecutive hours daily, of either Cysteamine Hydrochloride Ophthalmic Solution 0.55% (treated) or placebo for Cysteamine Hydrochloride 0.55% Ophthalmic Solution (untreated) in albino rabbits for 30 days.

The Applicant cites a published mechanistic study in which the cytotoxicity of cysteamine was investigated. It was shown that cysteamine produces hydrogen peroxide and inhibits glutathione peroxidase. Cysteamine appeared to stimulate production of cellular glutathione, but this may reflect an accumulation of cysteamine to levels that inhibit glutathione peroxidase.

Oral or subcutaneous administration of cysteamine resulted in acute perforating duodenal ulcers in a published study in rats. A single oral dose of 100 mg resulted in 70% mortality within 48 hours with all animals exhibiting evidence of duodenal ulcers. A dose of 100 mg SC was immediately lethal, while 50 mg SC resulted in 70% mortality within 48 hours, with perforating ulcers seen in half of the animals. Another study demonstrated a specific decrease in total duodenal mucosal HCO_3-ATPase activity in cysteamine-treated rats that was not seen in other segments of the intestines. This and a decrease in carbonic anhydrase activity were transient and associated with ulcer formation. Additional studies in rats: 1) demonstrated depression of sympathetic innervation and increased parasympathetic fiber activity associated with cysteamine induced ulcers, 2) suggested that the hepatoduodenal branch of the vagus nerve may play a role in cysteamine-induced duodenal ulcers, 3) demonstrated selective inhibition of alkaline phosphatase isoenzymes in the duodenal mucosa prior to any visible signs of ulcer formation following cysteamine treatment, and 4) suggested a role for iron in the pathogenesis of cysteamine-induced ulcers. A study in rats demonstrated that cysteamine is a relatively specific depleter of tissue somatostatin.

7.2.4 Routine Clinical Testing

For CAPTOC, complete ophthalmologic examination included clinical assessment of photophobia and blepharospasm, observation for the presence of crystals in the cornea, on the surface of the lens, on iris, and on retina, and presence of posterior synechiae.

Visual acuity, psychophysical testing of dark adaptation and color perception, and electroretinography were performed depending on age and cooperation. Staining of corneal epithelium with fluorescein was noted. Slit-lamp photos were taken to assess extent of corneal crystal accumulation.

For 98 EI0109S, a complete ophthalmologic examination was performed, including manifest refraction, a clinical assessment of photophobia and blepharospasm, observation for the presence of crystals in the cornea, on the surface of the lens, iris, and retina, and for the presence of posterior synechiae. The presence of staining of corneal epithelium with fluorescein was noted. Slit-lamp photos were taken to assess extent of corneal crystal accumulation.

For 98 EI0109E**,** a complete ophthalmic examination was to be performed, including manifest refraction if indicated; a clinical assessment of photophobia (light sensitivity) and blepharospasm (eyelid twitching); observation for the presence of crystals in the cornea, on the surface of the lens, iris, and retina; and for the presence of posterior synechiae (adhesions between posterior iris and anterior lens surface). Visual acuity was assessed depending on age and was measured by the ETDRS eye charts or picture optotype visual acuity cards. Psychophysical testing of dark adaptation and color perception, and electroretinography was also assessed. Slit-lamp photographs of the cornea were taken by certified photographers following a standard protocol to assess the extent of corneal crystal accumulation.

7.2.5 Metabolic, Clearance, and Interaction Workup

All subjects were required to have a history consistent with cystinosis and be currently on Cystagon (oral cysteamine bitartrate) Capsules. Studies 98 EI0109E and 98 EI0109E required either >2 nmole half-cystine/mg protein in leukocytes or presence of corneal crystals consistent with cystinosis and distributed in corneal stroma observed by slit-lamp biomicroscopy.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The relevant potential adverse events for this drug class (cystine-depleting agents) were adequately monitored and evaluated. All subjects were concurrently treated with oral Cystagon (cysteamine bitartrate) Capsules for their cystinosis.

7.3 Major Safety Results

7.3.1 Deaths

CAPTOC
Eighteen deaths were reported in the three studies comprising the CAPTOC analysis. Two of the patient deaths (Patient 374973 and Patient 835249) were reported to FDA in IND Safety Reports.

Five patients (Patients 221252, 315632, 352157, 727697, and 883818) died with no cause provided.

Table 28. Cause of Death in Patients by Preferred Term: Safety Population

Patient Number (n = 18)	Cause of Death[a]
221252	No cause given
221478	Central nervous system lymphoma
268427	Therapeutic response unexpected (complications due to dialysis); Azotaemia
288466	Neuropathy; Azotaemia
292824	Pneumonia
315632	No cause given
352157	No cause given
374973	Renal failure
419131	Cardiac arrest; Peritonitis
665494	Congenital neurological disorder; Sudden infant death syndrome; Aspiration
717581	Respiratory failure
724841	Sepsis; Pneumonia aspiration
727697	No cause given
736117	Endocarditis; Sepsis
835249	Intestinal obstruction; Gastrointestinal infection; Renal failure
883818	No cause given
893478	Colon injury
997414	Myopathy; Depression

[a] = All AE terms were coded using MedDRA Dictionary Version 9.0.
Source: *Appendix 16.2.7.1.5*

Source: May 6, 2010, Clinical Study Report Amendment, CAPTOC, 12.3.2.1 Deaths

The Case Report Forms (CRFs) for all 18 patients were reviewed. For the five patients where no cause was provided, there was additional information in the CRFs for two.

Patient 21252 apparently rejected her renal allograft and refused dialysis. Patient 352157 was found unresponsive and died despite vigorous resuscitation attempts.

98 EI0109S AND 98 EI0109S

There were no deaths in these studies.

7.3.2 Nonfatal Serious Adverse Events

CAPTOC

Table 29. Serious Adverse Events Experienced in Patients by Preferred Term[a]: Safety Population

Patient Number (n = 11)	SAE
162668	Benign intracranial hypertension, Blindness
219255	Benign intracranial hypertension
266579	Benign intracranial hypertension
277782	Benign intracranial hypertension
374973	Renal failure
513837	Benign intracranial hypertension
558532	Benign intracranial hypertension
722165	Benign intracranial hypertension
835249	Intestinal obstruction, Gastrointestinal infection, Renal failure
966143	Optic disc disorder
989726	Benign intracranial hypertension

[a] = All AE terms were coded using MedDRA Dictionary Version 9.0.
Source: *Appendix 16.2.7.1.4*

Source: May 6, 2010, Clinical Study Report Amendment, CAPTOC, 12.3.2.2 Serious Adverse Events

Eight patients (Patients 162668, 219255, 266579, 277782, 513837, 558532, 722165, and 989726) reported benign intracranial hypertension. This resulted in blindness for one patient (Patient 162668). All of these subjects were on oral cysteamine treatment. There have been reports of benign intracranial hypertension (or pseudotumor cerebri; PTC) associated with oral cysteamine treatment that has resolved with the addition of

diuretic therapy. PTC may be more common in cystinotic patients because of concurrent medication and renal transplantation.

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Table 25. Summary of the Incidence of Non-Ocular SAEs (*n* and %) for the 12 Month Treatment Period: Safety Population	
System Organ Class Preferred Term[a]	**Safety Population (*n* = 16)**
Number of Patients With at Least One Non-Ocular SAE	**3 (18.8)**
General Disorders and Administration Site Conditions	**1 (6.3)**
Pyrexia	1 (6.3)
Infections and Infestations	**2 (12.5)**
Ear Infection	1 (6.3)
Influenza	1 (6.3)
Metabolism and Nutrition Disorders	**2 (12.5)**
Dehydration	1 (6.3)
Electrolyte Imbalance	1 (6.3)
Gastrointestinal Disorders	**2 (12.5)**
Abdominal Pain Upper	1 (6.3)
Gastritis Erosive	1 (6.3)
Gastrointestinal Inflammation	1 (6.3)
Vomiting	1 (6.3)

[a] = All AE terms were coded using MedDRA Dictionary Version 9.0.
Note: Patients are counted only once within each system organ class and within each preferred term.
Source: *Table 14.3.1.2, Appendix 16.2.7.1.2*

Source: December 17, 2009, Clinical Study Report, 98 EI0109E, 12.3.2 Narratives of Deaths, Ocular SAEs, and Certain Other Significant AEs

There were no ocular SAEs.

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There were four non-ocular SAEs reported in two patients. Patient 9002 experienced hypertension and headache that resulted in hospitalization and Patient 9011 experienced hypokalaemia and dehydration that resulted in hospitalization.

Dropouts and/or Discontinuations

See Section 6.1.3.

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The number of patients who completed the study and the number of patients who discontinued prematurely from the study could not be summarized because there was no provision in the CRF to capture these data. The nature of these studies involved continuous treatment under different protocols, and patients were able to continue receiving treatment as long as they returned to NEI. Patients are still receiving treatment under Protocol 86-EI-0062 at NEI. In addition, patients who may have discontinued taking the ophthalmic solution are able to receive treatment again under the same protocol whenever they return to NEI. Since there was no adherence to a regimented follow-up schedule, the cutoff date of July 2005 reflects a time when the last CRF was collected from NEI by STP. Because of this arbitrary cutoff date, there was a potential for patients to only have baseline data recorded. Because the protocol remains subject to open enrollment (and open re-enrollment), and the range of collection currently spans 19 years, no attempt was made to gather further data. In addition, because this protocol is the only means for patients to receive ophthalmic cysteamine solution, stopping this open enrollment was not an ethical option. This protocol has evolved into a treatment protocol.

A total of 247 patients were enrolled into the study through the three protocols. The mITT populations comprised all patients for whom a baseline CCCS score and a minimum of one post-baseline CCCS score exist.

7.3.4 Significant Adverse Events

See Section 7.3.2 and Section 7.4.1 of this review.

7.3.5 Submission Specific Primary Safety Concerns

See Section 7.3.2 and Section 7.4.1 of this review.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

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Table 23. Summary of the Incidence of the Most Common (≥2.0%) Ocular Adverse Events (*n* and %) for the Treatment Period: Safety Population	
System Organ Class Preferred Term[a]	**Total (N = 247) *n* (%)**
Number of Patients With at Least One AE	**169 (68.4)**
Eye Disorders	**166 (67.2)**
Photophobia	157 (63.6)
Conjunctival Hyperaemia	69 (27.9)
Eye Pain	48 (19.4)
Ocular Hyperaemia	43 (17.4)
Eye Irritation	42 (17.0)
Lacrimation Increased	21 (8.5)
Keratitis	19 (7.7)
Optic Disc Disorder	18 (7.3)
Vision Blurred	17 (6.9)
Dry Eye	13 (5.3)
Eyelid Oedema	12 (4.9)
Retinal Disorder	11 (4.5)
Conjunctivitis	10 (4.0)
Eye Pruritus	10 (4.0)
Blindness	7 (2.8)
Corneal Epithelium Disorder	6 (2.4)
Blepharitis	5 (2.0)
Erythema of Eyelid	5 (2.0)
General Disorders and Administration Site Conditions	**40 (16.2)**
Instillation Site Irritation	30 (12.1)
Instillation Site Pain	17 (6.9)
Adverse Drug Reaction	2 (0.8)[b]
Instillation Site Erythema	5 (2.0)

Table 23.	**Summary of the Incidence of the Most Common (≥2.0%) Ocular Adverse Events (*n* and %) for the Treatment Period: Safety Population**
System Organ Class **Preferred Term**[a]	**Total (N = 247)** ***n* (%)**
Infections and Infestations	**11 (4.5)**
Eye Infection	5 (2.0)

[a] = All AE terms were coded using MedDRA Dictionary Version 9.0.
[b] = There were a total of 7 patients experiencing adverse drug reactions; 2 ocular and 5 non-ocular. Although when separated out, ocular adverse drug reactions occurred in less than 2.0% of the population (0.8%), it continues to be included in this table because of its relevancy to the drug and indication. Please see below and *Table 24* for additional details.
Note: A patient experiencing multiple occurrences of an AE is counted only once within each system organ class and within each preferred term.
Source: *Table 14.3.1.2*.

Source: May 6, 2010, Clinical Study Report Amendment, CAPTOC, 12.2.2.3 Non-Ocular Adverse Events

The most common ocular adverse events in CAPTOC occurring in ≥ 10 % of patients were sensitivity to light, redness, and eye pain/irritation.

Table 25.	**Summary of the Incidence of the Most Common (≥2.0%) Non-Ocular Adverse Events (*n* and %) for the Treatment Period: Safety Population**
System Organ Class Preferred Term[a]	**Total (N = 247) *n* (%)**
Number of Patients With at Least One AE	**169 (68.4)**
Nervous System Disorders	**63 (25.5)**
Headache	34 (13.8)
Visual Field Defect	32 (13.0)
Benign Intracranial IIypertension	8 (3.2)
General Disorders and Administration Site Conditions	**5 (2.0)**
Adverse Drug Reaction	5 (2.0)[b]
Gastrointestinal Disorders	**8 (3.2)**
Vomiting	8 (3.2)

[a] = All AE terms were coded using MedDRA Dictionary Version 9.0.
[b] = There were a total of 7 patients experiencing adverse drug reactions; 2 ocular and 5 non-ocular. Please see *Section 12.2.2.2* and *Table 24* for additional details.
Note: A patient experiencing multiple occurrences of an AE is counted only once within each system organ class and within each preferred term.
Source: *Table 14.3.1.2*.

Source: May 6, 2010, Clinical Study Report Amendment, CAPTOC, 12.2.2.3 Non-Ocular Adverse Events

The most common non-ocular adverse events in CAPTOC occurring in ≥ 10 % of patients were headache and visual field defect.

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Table 15. Summary of the Incidence of Ocular Treatment-Emergent AEs (*n* and %) for the 12 Month Treatment Period: Safety Population		
System Organ Class Preferred Term[a]	**Treatment**	
	Formulation 5 (*n* = 16)	**Formulation 3 (*n* = 16)**
Number of Eyes With at Least One Ocular TEAE	**11 (68.8)**	**8 (50.0)**
Eye Disorders	**1 (6.3)**	**1 (6.3)**
Eye Discharge	1 (6.3)	1 (6.3)
Eye Irritation	1 (6.3)	1 (6.3)
Eye Pain	1 (6.3)	0 (0)
Eye Pruritus	1 (6.3)	1 (6.3)
Foreign Body Sensation in Eye	1 (6.3)	1 (6.3)
Photophobia	1 (6.3)	1 (6.3)
General Disorders and Administration Site Conditions	**11 (68.8)**	**8 (50.0)**
Instillation Site Erythema	4 (25.0)	4 (25.0)
Instillation Site Irritation	10 (62.5)	7 (43.8)
Instillation Site Pain	5 (31.3)	2 (12.5)
Instillation Site Reaction	1 (6.3)	2 (12.5)

[a] = All AE terms were coded using MedDRA Dictionary Version 9.0.
Note: An eye experiencing an AE is counted only once within each system organ class and within each preferred term.
Source: *Table 14.3.1.1.2.*

Source: December 17, 2009, Clinical Study Report, 98 EI0109E, 12.2.2.1 Ocular TEAEs

The most common ocular adverse events with Formulation 3 in 98 EI0109E were installation site pain and redness.

Table 24. Summary of the Incidence of Non-Ocular TEAEs (*n* and %) for the 12 Month Treatment Period: Safety Population	
System Organ Class Preferred Term[a]	**Safety Population (*n* = 16)**
Number of Patients With at Least One Non-Ocular TEAE	**7 (43.8)**
Gastrointestinal Disorders	**2 (12.5)**
Abdominal Pain Upper	1 (6.3)
Gastritis Erosive	1 (6.3)
Gastrointestinal Inflammation	1 (6.3)
Vomiting	1 (6.3)
General Disorders and Administration Site Conditions	**3 (18.8)**
Pyrexia	1 (6.3)
Unevaluable Event	2 (12.5)
Immune System Disorders	**1 (6.3)**
Seasonal Allergy	1 (6.3)
Infections and Infestations	**3 18.8)**
Ear Infection	1 (6.3)
Gastroenteritis, Viral	1 (6.3)
Influenza	1 (6.3)
Injury, Poisoning and Procedural Complications	**1 (6.3)**
Hand Fracture	1 (6.3)
Metabolism and Nutrition Disorders	**3 (18.8)**
Dehydration	2 (12.5)
Electrolyte Imbalance	1 (6.3)
Skin and Subcutaneous Tissue Disorders	1 (6.3)
Rash	1 (6.3)

[a] = All AE terms were coded using MedDRA Dictionary Version 9.0.
Note: Patients are counted only once within each system organ class and within each preferred term.
Source: *Table 14.3.1.2*, *Appendix 16.2.7.1.1*.

Source: December 17, 2009, Clinical Study Report, 98 EI0109E, 12.2.3.2 Non-Ocular TEAEs

The most common non-ocular adverse events in 98 EI0109E were “unevaluable events” coded as general disorders and dehydration.

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Table 23. Summary of the Incidence of Ocular TEAEs (*n* and %) for the 6 Month Treatment Period – Safety Population		
System Organ Class Preferred Term[a]	**Treatment**	
	Formulation 5 (*n* = 20)	**Formulation 3 (*n* = 20)**
Number of Eyes With at Least One Ocular TEAE	**14 (70)**	**5 (25)**
Eye Disorders	**5 (25)**	**3 (15)**
Eye Irritation	1 (5)	2 (10)
Lacrimation Increased	1 (5)	0 (0)
Ocular Hyperaemia	4 (20)	3 (15)
Vision Blurred	1 (5)	1 (5)
General Disorders and Administration Site Conditions	**14 (70)**	**5 (25)**
Instillation Site Erythema	7 (35)	4 (20)
Instillation Site Irritation	11 (55)	1 (5)
Instillation Site Lacrimation	1 (5)	0 (0)
Instillation Site Pain	11 (55)	1 (5)
Infections and Infestations	**1 (5)**	**1 (5)**
Conjunctivitis Infective	1 (5)	1 (5)

[a] = All AE terms were coded using MedDRA Dictionary Version 9.0.
Note: An eye experiencing an AE is counted only once within each system organ class and within each preferred term.
Source: *Table 14.3.1.1.2*.

Source: December 17, 2009, Clinical Study Report, 98 EI0109S, 12.2.2.1 Ocular TEAEs

The most common ocular adverse events with Formulation 3 in 98 EI0109S were installation site redness and eye irritation.

Table 30. Summary of the Incidence of Non-Ocular TEAEs (*n* and %) for the 6 Month Treatment Period: Safety Population	
System Organ Class Preferred Term[a]	**Safety Population (*n* = 20)**
Number of Patients With at Least One Non-Ocular TEAE	**4 (20.0)**
Infections and Infestations	**1 (5.0)**
Oral Infection	1 (5.0)
Investigations	**1 (5.0)**
Blood Creatinine Increased	1 (5.0)
Metabolism and Nutrition Disorders	**1 (5.0)**
Dehydration	1 (5.0)
Hypokalaemia	1 (5.0)
Nervous System Disorders	**1 (5.0)**
Headache	1 (5.0)
Surgical and Medical Procedures	**1 (5.0)**
Orthopedic Procedure	1 (5.0)
Vascular Disorders	**1 (5.0)**
Hypertension	1 (5.0)
[a] = All AE terms were coded using MedDRA Dictionary Version 9.0. Note: Patients are counted only once within each system organ class and within each preferred term. Source: *Table 14.3.1.2*	

Source: December 17, 2009, Clinical Study Report, 98 EI0109S, 12.2.3.3 Non-Ocular TEAEs

7.4.2 Laboratory Findings

In CAPTOC, leukocyte cystine and fibroblast assays were to be performed on blood samples collected at baseline and at study termination. Per the May 6, 2010, Clinical Study Report Amendment, CAPTOC,16.1.10.1 Laboratories Used in the Study, no clinical laboratory data were collected.

7.4.3 Vital Signs

The CAPTOC CRF did not provide a location for this information to be captured; these data were not recorded.

Vital signs (measured only at baseline) were recorded for 98 EI0109E.

Vital signs (measured only at baseline) were recorded for 98 EI0109S.

7.4.4 Electrocardiograms (ECGs)

The protocols did not require ECGs to be performed.

7.4.5 Special Safety Studies/Clinical Trials

There were no special safety studies or clinical trials conducted for this application.

7.4.6 Immunogenicity

Not applicable. Drug product is not expected to be immunogenic.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

The CAPTOC analysis collapsed adverse events across all treatment groups in the three studies; therefore, AEs are not strictly categorized according to treatment group. The adverse event tables for CAPTOC conservatively capture events for placebo and for Formulations 1, 2, 3, and 4.

The overall incidence of ocular TEAEs in 98 EI0109E was greater in eyes treated with Formulation 5 (11/16 [68.8%]) compared with eyes treated with Formulation 3 (8/16 [50.0%]).

The overall incidence of ocular TEAEs in 98 EI0109Ewas greater in eyes receiving Formulation 5 (14/20 [70%]) than eyes receiving Formulation 3 (5/20 [25%]).

7.5.2 Time Dependency for Adverse Events

There was no specific time dependency for adverse events explored.

7.5.3 Drug-Demographic Interactions

Cystinosis is a rare autosomal recessive metabolic disorder. There were no subgroup analyses performed by sex or demographic group.

7.5.4 Drug-Disease Interactions

There were no specific drug-disease interactions explored with the exception of the systemic cystinosis for which all subjects received Cystagon (cysteamine bitartrate) Capsules.

7.5.5 Drug-Drug Interactions

There were no specific drug-drug interactions explored with the exception of Cystagon (cysteamine bitartrate) Capsules which all subjects received for the systemic cystinosis.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Cysteamine has not been tested for its carcinogenic potential in long-term animal studies.

Cysteamine was not mutagenic in the Ames test. It produced a negative response in an in vitro sister chromatid exchange assay in human lymphocytes but a positive response in a similar assay in hamster ovarian cells.

Repeat breeding reproduction studies were conducted in male and female rats. Cysteamine was found to have no effect on fertility and reproductive performance at an oral dose of 75 mg/kg/day (450 mg/m2/day, 0.4 times the recommended human dose based on body surface area). At an oral dose of 375 mg/kg/day (2,250 mg/m2/day, 1.7 times the recommended human dose based on body surface area), it reduced the fertility of the adult rats and the survival of their offspring.

7.6.2 Human Reproduction and Pregnancy Data

There are no adequate and well-controlled studies of ophthalmic cysteamine in pregnant women. Cystaran should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

The following information is from the oral cysteamine product:

Teratogenic Effects: Pregnancy Category C.

Teratology studies have been performed in rats at oral doses in a range of 37.5 to 150 mg/kg/day (about 0.2 to 0.7 times the recommended human maintenance dose on a body surface basis) and have revealed cysteamine bitartrate to be teratogenic. Observed teratogenic findings were cleft palate, kyphosis, heart ventricular septal defects, microcephaly, and exencephaly.

(b) (4)

7.6.3 Pediatrics and Assessment of Effects on Growth

The safety and effectiveness of Cystaran (cysteamine hydrochloride ophthalmic solution) 0.44% in pediatric patients have been established for the treatment of corneal cystine crystal accumulation in patients with cystinosis.

Cystinosis often presents with growth retardation and renal tubular Fanconi syndrome in the first year of life and, if untreated, leads to renal failure by the age of 10 years.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Cysteamine hydrochoride is a non-narcotic and does not have abuse potential.

All patients with cystinosis expected to receive Cystaran will also be receiving the oral Cystagon (cysteamine bitartrate) Capsules. See Section 2.4 of this review regarding the adverse event profile of Cystagon Capsules.

7.7 Additional Submissions / Safety Issues

The 120-day Safety Update, submitted on July 2, 2010, provided no new safety information regarding Cystaran (cysteamine hydrochloride ophthalmic solution) 0.44% since the original submission of March 3, 2010.

8 Postmarket Experience

This product is not approved or marketed in any country.

9 Appendices

9.1 Additional Tables/Analyses

STP869294 (CAPTOC) Cysteamine Formulations

Table 1. Comparison of Protocol and Treatments Associated with the CAPTOC

Protocol	Treatment	Dates
86-EI-0062	Formulation 1 vs Placebo[a]	March 20, 1986
86-EI-0062Amendment 1	Formulation 2 vs Placebo[a]	April 15, 1988
86-EI-0062 Amendment A	Formulation 3 vs Formulation 2	May 20, 1992
92-EI-0230	Formulation 3 vs Formulation 2	July 13, 1992
86-EI-0062 Amendments B-D	Formulation 3 OU	July 2, 1993
94-EI-0116	Formulation 4 vs Formulation 3	February 22, 1994
98-EI-0109S[b]	Formulation 5 vs Formulation 3	September 21, 1998
98-EI-0109E[b]	Formulation 5 vs Formulation 3	November 3, 1998

[a] = Responders received active treatment in both eyes.
[b] = Only baseline data from Protocol 98-EI-0109S and Protocol 98-EI-0109E used in CAPTOC analysis.

Source: May 6, 2010, Clinical Study Report Amendment, CAPTOC, 9.2 Discussion of Study Design, Including the Choice of Control Groups

STP869294 (CAPTOC) Baseline Characteristics

Table 10. Baseline Characteristics				
	Population			
Baseline Characteristic	ITT[a] (N = 494)	mITT[a] (N = 322)	mITT-1[a] (N = 184)	mITT-2[a] (N = 138)
Photo-rated CCCS				
Number of Evaluable Eyes	453	319	181	138
Mean ± SD	2.6 ± 0.79	2.5 ± 0.86	2.4 ± 1.00	2.7 ± 0.58
Median	3.0	3.0	3.0	3.0
Minimum, Maximum	0.0, 3.0	0.0, 3.0	0.0, 3.0	0.5, 3.0
Score (*n*%)				
0	10 (2.0%)	7 (2.2%)	7 (3.8%)	0 (0.0%)
>0.00-1.00	29 (5.9%)	29 (9.0%)	24 (13.0%)	5 (3.6%)
>1.00-2.00	44 (8.9%)	31 (9.6%)	16 (8.7%)	15 (10.9%)
>2.00-3.00	370 (74.9%)	252 (78.3%)	134 (72.8%)	118 (85.5%)
Missing	41 (8.3%)	3 (0.9%)	3 (1.6%)	0 (0.0%)

[a] = Refers to the total number of eyes.
Source: *Table 14.1.3.1*, *Table 14.1.3.2*, *Table 14.1.3.3*, *Table 14.1.3.4*.

Table 11. Baseline Characteristics				
	Population			
Baseline Characteristic	ITT[a] (N = 494)	mITT[a] (N = 322)	mITT-1[a] (N = 184)	mITT-2[a] (N = 138)
Corneal Haziness				
Severity (*n*%)				
None	95 (19.2%)	62 (19.3%)	6 (3.3%)	56 (40.6%)
Mild	37 (7.5%)	24 (7.5%)	4 (2.2%)	20 (14.5%)
Moderate	40 (8.1%)	31 (9.6%)	4 (2.2%)	27 (19.6%)
Severe	30 (6.1%)	15 (4.7%)	2 (1.1%)	13 (9.4%)
Not Evaluable	266 (53.8%)	172 (53.4%)	156 (84.8%)	16 (11.6%)
Missing	26 (5.3%)	18 (5.6%)	12 (6.5%)	6 (4.3%)
Photophobia (Physician Assessment)				
Severity (*n*%)				
None	48 (9.7%)	42 (13.0%)	20 (10.9%)	22 (15.9%)
Mild	93 (18.8%)	78 (24.2%)	62 (33.7%)	16 (11.6%)
Moderate	93 (18.8%)	74 (23.0%)	38 (20.7%)	36 (26.1%)
Severe	90 (18.2%)	54 (16.8)	24 (13.0%)	30 (21.7%)
Not Evaluable	157 (31.8%)	67 (20.8)	38 (20.7%)	29 (21.0%)
Missing	13 (2.6%)	7 (2.2%)	2 (1.1%)	5 (3.6%)
Foreign Body Sensation (*n*%)				
No	131 (26.5%)	81 (25.2%)	12 (6.5%)	69 (50.0%)
Yes	95 (19.2%)	57 (17.7%)	14 (7.6%)	43 (31.2%)
Not Evaluable	236 (47.8%)	164 (50.9%)	150 (81.5%)	14 (10.1%)
Missing	32 (6.5%)	20 (6.2%)	8 (4.3%)	12 (8.7%)

[a] = Refers to the total number of eyes.
Source: *Table 14.1.3.1*, *Table 14.1.3.2*, *Table 14.1.3.3*, *Table 14.1.3.4*.

Source: May 6, 2010, Clinical Study Report Amendment, CAPTOC, 11.2.2 Disease Characteristics

98 EI0109E Baseline Characteristics

Table 4. Baseline Corneal Cystine Crystal Score (Per-Protocol Population)		
	Treatment	
Baseline Parameter	Formulation 5 (n = 15)	Formulation 3 (n = 15)
Corneal Cystine Crystal Score (CCCS)[a]		
Mean ± SD	2.583 ± 0.556	2.683 ± 0.438
Minimum, Maximum	1.25, 3.00	1.75, 3.00
Median	2.750	3.000
Score (n%)[b]		
0	0 (0%)	0 (0%)
>0-1	0 (0%)	0 (0%)
>1-2	3 (20.0%)	2 (13.3%)
>2-3	12 (80.0%)	13 (86.7%)

[a] = Median of 2 scores or Grader 3 decision.
[b] = Percentages were based on the number of eyes with non-missing values.
Source: *Table 14.1.3.2.*

Table 6. Baseline Ophthalmic Examination (Per-Protocol Population)		
	Treatment	
Baseline Parameter	Formulation 5 (n = 15)	Formulation 3 (n = 15)
Corneal Haziness (n%)[a]		
None	9 (60%)	9 (60%)
Mild	3 (20.0%)	3 (20%)
Moderate	3 (20.0%)	2 (13.3%)
Severe	0 (0%)	1 (6.7%)
Photophobia (Patient Assessment) (n%)[a,b]		
None	1 (6.7%)	1 (6.7%)
Mild	6 (40.0%)	6 (40.0%)
Moderate	6 (40.0%)	5 (33.3%)
Severe	2 (13.3%)	3 (20.0%)
Photophobia (Physician Assessment) (n%)[a]		
No	2 (13.3%)	2 (13.3%)
Yes	13 (86.7%)	13 (86.7%)
Presence of Foreign Body Sensation (n%)[a]		
No	8 (53.3%)	8 (53.3%)
Yes	7 (46.7%)	7 (46.7%)

[a] = Percentages were based on the number of eyes with non-missing values.
[b] = No further information was provided in the study protocol to define the procedure for patient assessed photophobia in young patients.
Source: *Table 14.1.3.2.*

Source: December 17, 2009, Clinical Study Report, 98 EI0109E, 11.2.2 Disease Characteristics

98 EI0109S Baseline Characteristics

Table 4. Baseline Corneal Cystine Crystal Score (Per-Protocol Population)		
	Treatment	
Baseline Parameter	**Formulation 5 (n = 18)**	**Formulation 3 (n = 18)**
Corneal Cystine Crystal Score (CCCS)[a]		
Mean ± SD	0.931 ± 0.954	1.014 ± 0.979
Min, Max	0.00, 2.75	0.00, 2.75
Median	0.625	0.625
Score (n%)[b]		
0	6 (33.3%)	3 (16.7%)
>0-1	5 (27.8%)	8 (44.4%)
>1-2	5 (27.8%)	4 (22.2%)
>2-3	2 (11.1%)	3 (16.7%)

[a] = Median of 2 scores or Grader 3 decision
[b] = Percentages were based on the number of eyes with non-missing values.
Source: *Table 14.1.3.2.*

Table 8. Baseline Ophthalmic Examination (Per-Protocol Population)		
	Treatment	
Baseline Parameter	**Formulation 5 (n = 18)**	**Formulation 3 (n = 18)**
Corneal Haziness (n%)[a]		
None	18 (100%)	18 (100%)
Mild	0 (0%)	0 (0%)
Moderate	0 (0%)	0 (0%)
Severe	0 (0%)	0 (0%)
Photophobia (Patient Assessment) (n%)[a]		
None	12 (66.7%)	12 (66.7%)
Mild	6 (33.3%)	6 (33.3%)
Moderate	0 (0%)	0 (0%)
Severe	0 (0%)	0 (0%)
Photophobia (Physician Assessment) (n%)[a]		
No	13 (72.2%)	13 (72.2%)
Yes	5 (27.8%)	5 (27.8%)
Presence of Foreign Body Sensation (n%)[a]		
No	18 (100%)	18 (100%)
Yes	0 (0%)	0 (0%)

[a] = Percentages were based on the number of eyes with non-missing values.
Source: *Table 14.1.3.2.*

Source: December 17, 2009, Clinical Study Report, 98 EI0109S, 11.2.2 Disease Characteristics

Release and Stability Specification

Table 3.2.P.5.1-1. Release and Stability Specifications for Cysteamine HCl Ophthalmic Solution			
Test	**Release Acceptance Criteria**	**Stability Acceptance Criteria**	**Analytical Procedures**
Description	Clear, colorless solution	Clear, colorless solution	Visual
pH	4.00–4.60	3.80–4.80	USP <791>
Osmolality	360-420 mOsmol/kg[a]	360-420 mOsmol/kg[a]	*M-239*
Deliverable Volume	Meets requirements	NA	USP <698>
Particulate Matter (b) (4)	(b) (4)		
Identification UPLC	The retention time of the cysteamine HCl peak in the chromatogram of the test sample preparation corresponds to the cysteamine HCl peak in the chromatogram of the standard preparation.	NA	*M-1017*
UV-Vis	The UV-vis spectrum (between (b) (4) for the cysteamine HCl in the product sample preparation concordant with the UV-vis spectrum of cysteamine HCl in the cysteamine HCl standard preparation.	NA	
Cysteamine HCl	(b) (4)		
Specified Impurities/Degradation Product (b) (4)	(b) (4)		
Individual Unspecified Impurities/Degradation Products			

Table 3.2.P.5.1-1. Release and Stability Specifications for Cysteamine HCl Ophthalmic Solution			
Test	**Release Acceptance Criteria**	**Stability Acceptance Criteria**	**Analytical Procedures**
Total Specified and Unspecified Impurities/Degradation Products of Cysteamine HCl	(b) (4)		
Benzalkonium Chloride	(b) (4)		*M-1015*
	(b) (4)		
Sterility	Meets requirements	Meets requirements	*M-226*, USP <71>
Preservative Challenge[b]	Meets requirements	Meets requirements	*M-03* USP <51>
Bacterial Endotoxin	(b) (4)	NA	USP <85>

[a] = Specification for previously proposed commercial formulation (supporting stability studies) was 260-330 mOsmol/kg.
[b] = Preservative challenge testing will only be conducted on the development and validation batches.
NA = Not applicable.

Source: July 30, 2010 submission, 3.2.P.5.1 Specifications

9.2 Advisory Committee Meeting

No Advisory Committee Meeting was held. There were no new issues raised in the review of the application which were thought to benefit from an Advisory Committee Meeting.

9.3 Labeling Recommendations

The following labeling submitted by the applicant on August 30, 2010, is acceptable.

7 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200740	ORIG-1	SIGMA TAU PHARMACEUTICALS INC	(Cysteamine hydrochloride ophthalmic solution) 0.65% Sterile

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

WILLIAM M BOYD
08/30/2010

WILEY A CHAMBERS
09/02/2010