A Randomized Controlled Crossover Trial for Nephropathic Cystinosis Demonstrates a Twice Daily "Gastroresistant" Cysteamine is Not Inferior to Every Six Hour Cystagon.

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Introduction

- Nephropathic Cystinosis (OMIM 219800; 219900) is an autosomal recessive, systemic disease caused by defective cystinosin transport of cystine from intracellular organelles such as the lysosome.
- Kidney failure is an inevitable consequence of untreated disease, and multiple organ failure over time ensues as well if the disease is untreated after kidney transplantation.
- Cysteamine bitartrate immediate release {CBIR; Cystagon®} is the only Rx for cystinosis that prevents/delays kidney failure and the other consequences, but requires lifelong adherence to q6h dosing.
- This schedule and CBIR-associated side effects cause non-adherence, suboptimal treatment, ensuing kidney failure, and other disease-related problems.
- An efficacious delayed-release (DR) formulation is desirable.

Patients & Methods

- Patients with Nephropathic Cystinosis, their native kidneys, and eGFR > 30 mL/min/1.73m^2 and a WBC [cystine] ≤ 2 nmol ½ cystine/mg protein {prepared from WBC}, as evidence of adherence to Cystagon®.
- WBC cystine was used as a surrogate marker of disease control.
- We powered an open-label, randomized, controlled, crossover trial to show that a new DR ("gastroresistant") cysteamine bitartrate {RP103}, was non-inferior to Cystagon®, in maintaining the surrogate marker, WBC [cystine] at baseline or < 0.3 nmol ½ cystine/mg protein (non-inferiority margin): **Figure 1, below**.

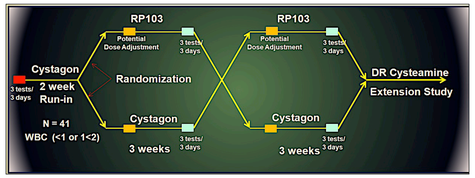


Figure 1.

- Subjects were stratified by their WBC [cystine] baseline value (0-1; >1-2) before being randomized to Cystagon® or RP103, for 3 weeks, and then crossed over to the other therapy.
- Total daily dose (TDD) of RP103 was started at 70% of Cystagon® TDD, and adjusted once based on WBC [cystine].
- Cystagon was administered q6h; RP103 was administered q12h.
- Patients stopped gastro-protective agents when on RP103.

Surrogate Endpoint of the Study

WBC cystine measurement. The white blood cell cystine content was used as a surrogate marker of control for the cystemaine products. However, variability exists in the measured cystine content in cells. Some of the variability arises from the method used to determine the amount of protein to which the cystine content is indexed. There is no explicit reference in the Cystagon® Package Insert as to which protein assay should be used to determine WBC cystine. Some laboratories have used the Lowry assay and historical results reported by these laboratories have been cited in publications, making the Lowry assay somewhat of a reference method, by default.

The method for the analysis of cellular total protein in white blood cells (WBC) for the current study was the bicinchoninic acid assay (BCA) total protein method. However, consistent and systematic differences were noted between the total protein results reported by the BCA and Lowry methods [5]. Based on these experiments, it was determined that the Lowry vs. BCA protein results had to be adjusted as follows:

protein amount[Lowry] = protein amount[BCA] * 1.6999 - 0.0648.

Statistical Analyses

The Intention to Treat (ITT) population for efficacy analyses was defined as all patients who completed the Run-In Period and the two 3 week crossover periods. The ITT population for safety analyses is defined as all patients who received at least one dose of either Cystagon® or RP103, starting with the first day of the Run-In Period.

The per-protocol (PP) population is defined as all patients from the ITT population for efficacy less three patients who had a 3-day average WBC cystine level > 2 nmol ½ cystine/mg protein during one of the periods under Cystagon® and were therefore considered as "not well controlled" under Cystagon®.

The initial sample size calculation and the pre-determined non-inferiority margin were based on a study of weekly steady state serial measures of WBC cystine levels from seven patients treated with Cystagon® followed by treatment with a different enteric-coated cysteamine bitartrate (EC-Cysteamine) [Dohil, R., et al., Twice-daily cysteamine bitartrate therapy for children with cystinosis. J Pediatr, 2010. 156: 71-75 e1-3].

Statistical analyses were performed with SAS Software version 9.2 (SAS Institute, Cary, North Carolina).

Pharmacokinetic / Pharmacodynamic Analyses.

Pharmacokinetic parameters were determined and then analyzed using non-compartmental methods to obtain estimates of parameters, (Phoenix WinNonlin standard, version 6.2, Pharsight Corp, Cary, NC).

Results

Table 1. Baseline characteristics for all enrolled patients (ITT) and for patients (PP) with a mean WBC < 2 nmol ½ cystine/ mg protein; "well-controlled") during all periods under Cystagon®. Two sibling patients withdrew voluntarily unrelated to the study. Values presented are the mean ± SD unless otherwise noted.

	ITT: Intent-To-Treat	PP: Per Protocol
N	*43*	*38*
Age (year)	11.7 ± 4.2	11.9 ± 4.4
Children (2 < age <= 12)	27	25
Adolescents (12 < age <= 21)	15	15
Adults (>21)	1	1
Male (n / %)	24 / 56 %	22 / 58 %
Height (cm)	139.5 ± 18.9	139.1 ± 19.1
Weight (kg)	36.0 ± 14.2	34.5 ± 12.1
BMI: Body Mass Index (kg/m^2)	17.8 ± 2.8	17.2 ± 2.1
BSA: Body Surface Area (m^2)	1.17 ± 0.30	1.14 ± 0.28
eGFR: Estimated Glomerular Filtration Rate (mL/min)	86 ± 34	87 ± 35
Daily Cystagon® Dose (mg/day)	1,849 ± 536	1,801 ± 511
Daily Cystagon® Dose (mg/kg/day)	55.8 ± 15.2	56.5 ± 14.6
WBC Cystine (nmol ½ cystine/ mg protein)		0.63 ± 0.31
WBC Cystine < 1 nmol ½ cystine/ mg protein		33 (87%)

Table 2: Treatment effect as determined by mixed effects model.

RP103 Achieved Non-Inferiority with CBIR (1^0 Endpoint)

Per –Protocol (PP) Population (N=38)	Cystagon®	RP103
WBC cystine level (LS Mean) in mg ½ cystine/mg protein	0.54 ± 0.05	0.62 ± 0.05
Treatment effect (LS mean ± SE; 95.8% CI)	0.08 ± 0.04 ; 0 to 0.16	
Intent-to-Treat (ITT) Population (N=41)	**Cystagon®**	**RP103**
WBC cystine level (LS Mean) in mg ½ cystine/mg protein	0.97 ± 0.19	0.70 ± 0.19
Treatment effect (LS mean ± SE; 95.8% CI)	-0.27 ± 0.36 ; -0.63 to 0.09	

Pharmacokinetics and Pharmacodynamics

RP103 Maintained WBC Cystine Below Therapeutic Threshold of 1.0 for 12 Hours

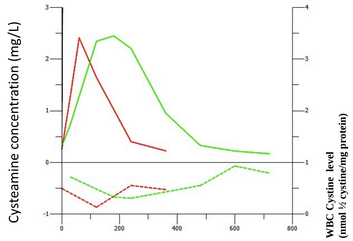
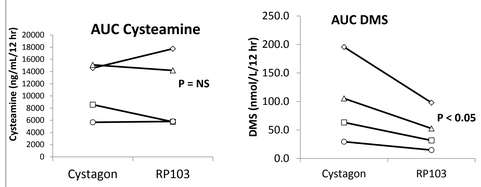


Figure 2: Mean cysteamine concentration and WBC cystine level after a single dose of Cystagon® (in red) or a single dose of RP103 (in green) in 38 patients (Per-Protocol population).

Endpoint Achieved with Lower Daily Dose of RP103

- Reducing daily drug exposure was a goal for the study and an important safety parameter
- Initial dose of RP103 set at 70% of run-in dose of Cystagon
- One pre-set dose adjustment of RP103 allowed
  - Based on intermediate WBC cystine level
- 33% of RP103 subjects remained at initial dose
  - 67% increased dose
- On average, 18% less drug needed to achieve non-inferiority endpoint (82% of total daily dose of CBIR except for one patient at 100% CBIR).

Study of Halitosis: Effect of RP103 in 4 patients



AUC DMS, the halitosis-producing metabolite of cysteamine was reduced (p < 0.05) with RP103 compared to CBIR.

Table 3: Principal pharmacokinetic parameters for cysteamine after a single dose at steady state

	Cystagon®	RP103
C_{max} (mg/L)	2.73 ± 1.36	3.70 ± 1.72
T_{max} (min)	72 ± 31	187 ± 89
$AUC_{0\text{-}12h}$ (min*mg/L)	357 ± 150	739 ± 334
t½ (min)	90 ± 23	254 ± 408
Cl/F (L/min)	1.33 ± 0.50	1.11 ± 0.58
Vd/F (L)	180 ± 112	356 ± 376
AUC_{inf}_D (min*mg/L)	0.85 ± 0.30	1.05 ± 0.45

There were no differences in the principal pharmacokinetic parameters between the two products.

Safety

- No unexpected safety issues were experienced in the study with either drug.
- Five of the total of seven SAEs reported in the study were associated with gastrointestinal events (vomiting, nausea, abdominal pain), possibly due to underlying disease.
  - One due to traumatic bone fracture; one planned knee surgery.
- One serious adverse event (SAE) reported during the study as "possibly related" to RP103
  - Scored as "Gastric Intolerance" (vomiting, nausea, abdominal distress).
  - Subject successfully rechallenged and included in the efficacy analysis [and currently in safety extension study].
- All SAEs were resolved.

Conclusions

- RP103 kept WBC [cystine] to levels no different than CBIR in "well-controlled" patients wth cystinosis.
- The total daily dose of RP103 was less than CBIR, and with equivalent pharmacokinetics.
- The disabling side-effect of halitosis may be improved with RP103.
- 87% of proton-pump inhibitor usage was discontinued during the RP-103 arm [data not shown].
- No new adverse events were seen with RP103 compared to CBIR.
- **Twice-daily RP103 for the care of nephropathic cystinosis represents a hope fro long-term control of the disease and possible removal of need for kidney transplantation.**

We thank the patients, their families, and study coordinators at each site for dedication and excellence of care.

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