

Need for and Development of Alternative Cysteamine Dose Formulation

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ABSTRACT

•Cystinosis is a rare yet devastating disorder. Currently, the principle therapeutic intervention is oral dosing of cysteamine, typically cysteamine bitartrate, every six hours. Cysteamine's odor and gastrointestinal symptoms have resulted in poor compliance (USCD Health Outcomes Survey). However, it has been shown that decreased compliance, even reduction of dosing from 6 to 9 hours with current dose formulation can result in poorer reduction of white cell cystine and worse renal function (Levtchenko et al 2006).

•Recently, Dohil and colleagues published their studies of directed intestinal administration of Cysteamine. When Cysteamine is delivered into the intestine, higher AUC and CMax of cysteamine results with a corresponding improvement in decreasing of white blood cell (WBC) cystine (Fidler et al 2006). In a pilot study of enteric coated (EC) Cysteamine, the UCSD group has successfully reduced dosing frequency to q12 hours with a similar or reduced total daily dosing of Cysteamine while resulting in similar or reduced WBC cystine levels (Dohil et al, 2008 presentation First International Cystinosis Research Symposium, Irvine CA)

•The Cystinosis Research Foundation has recently conducted an informal survey of 12 patient with cystinosis. All respondents felt a q12 hour dosing would improve their quality of life and/or their ability to comply with their prescription.

•Bennu Pharmaceuticals is currently developing an EC-Cysteamine formulation to bring a better tolerated q12 hour dosing alternative for patients with cystinosis, with clinical trials planned in 2009.

BACKGROUND

Bennu Pharmaceuticals Inc.

Bennu Pharmaceuticals Inc. (Bennu), a wholly-owned subsidiary of Raptor Pharmaceuticals Corp., is responsible for the clinical development of internally discovered therapeutic candidates based on Raptor Pharmaceutical Inc.'s novel drug delivery platforms, and in-licensed clinical-stage products. Bennu focuses on drug candidates that are: 1) new chemical entities in mid-to-late stage clinical development; 2) currently approved drugs with potential efficacy in additional indications; and 3) treatments that Bennu could repurpose or reformulate as potentially more effective or convenient treatments for their currently approved indications. On December 17, 2007, Bennu acquired a clinical product candidate, Delayed-Release cysteamine bitartrate (DR Cysteamine). Bennu received the exclusive worldwide license to DR Cysteamine, developed by clinical scientists at the University of California, San Diego, School of Medicine, by way of its acquisition by merger of Encode Pharmaceuticals, Inc., previously a privately held, development-stage pharmaceutical company. DR Cysteamine is being developed for the ultra-orphan indication, nephropathic cystinosis, and other genetic and metabolic diseases. For more information on all of our preclinical and clinical development programs, see www.raptorpharma.com. The name Bennu refers to a phoenix-like bird from Egyptian mythology, representing creation or renewal.

Delayed Release (DR) Cysteamine

Bennu's DR Cysteamine product candidate is an improved, enterically coated, delayed release oral formulation of cysteamine bitartrate, a drug used to treat nephropathic cystinosis (cystinosis), a rare lysosomal storage disease. Bennu's formulation will potentially require less frequent dosing and reduce gastrointestinal side effects, compared to the currently-marketed formulation of cysteamine bitartrate. These benefits are expected to greatly improve compliance and quality of life for cystinosis patients, who are typically children. Bennu obtained an exclusive, worldwide license to DR Cysteamine, as well as orphan drug designation from the FDA for DR Cysteamine for the treatment of nephropathic cystinosis, through its acquisition by merger of Encode Pharmaceuticals in December, 2007.

BACKGROUND, Continued

Cystinosis

Cystinosis is an inborn error of metabolism in which the transport of the amino acid cystine out of the lysosomes is abnormal. The disease, which typically begins to exhibit symptoms in the first year after birth, results in the accumulation of cystine crystals in various tissues and organs, including kidney, brain, liver, thyroid, pancreas, muscle and eye. Without treatment, cystinosis patients experience serious health consequences including renal failure and resultant transplant, growth failure, rickets, photophobia and blindness.

Cysteamine bitartrate, a cystine-depleting agent, is the only FDA and EMEA approved drug to treat cystinosis. Treatment with cysteamine bitartrate can delay or prevent kidney transplant in cystinosis patients. In its presently-available form, however, cysteamine bitartrate poses several challenges. It smells and tastes like rotten eggs, and results in halitosis and body odor. In many patients it causes severe gastrointestinal distress such as nausea and vomiting. It must be taken every six hours, requiring cystinosis patients to awake in the middle of the night to take their medicine. For these reasons, non-compliance with the dosing regimen for cysteamine bitartrate is common.

Clinical Results and Development Plan for Cystinosis

Clinical researchers at University of California, San Diego (UCSD), supported by the **Cystinosis Research Foundation**, have shown that delivery of cysteamine bitartrate into the small intestine instead of the stomach, may reduce many of the unpleasant side effects. In addition, they have shown that absorption of the drug is significantly higher when delivered to the small intestine versus the stomach. This suggests that a more selective release of the drug in the upper GI tract could lead to lower and less frequent dosing, which in turn could lead to reduced side effects and significantly better patient compliance. A recent presentation at the First International Cystinosis Research Symposium, Irvine CA, the UCSD group presented an extension of their work with enteric delivery of cysteamine using an oral capsule formulation.

Bennu plans to initiate an expanded study of its final proprietary formulation in collaboration with the UCSD researchers in 2008, and to apply to the FDA for market approval of DR Cysteamine for the treatment of cystinosis in 2009

To further understand the current issues facing a subset of patients active in the Cystinosis Research Foundation, a survey of patients attending a meeting of the GRF in La Jolla California was conducted. Bennu Pharmaceuticals provided resources for the compilation of the results of the anonymous survey.

METHODS

► Survey distributed at Cystinosis Research Foundation

Meeting, June 2008

-Conducted by Cystinosis Research Foundation

-Surveys were completed and collected anonymously with no patient specific identifiers collected

- After review by CRF, third party tabulation of results performed

-Results provided to Bennu Pharmaceuticals Inc. by CRF

► Characteristics of Respondents

-11 completed Surveys, representative of 12 patient experiences

-8 respondents were parents of patients with Cystinosis (1 parent respondent had 2 children with Cystinosis); 3 respondents were patients

SURVEY QUESTIONS

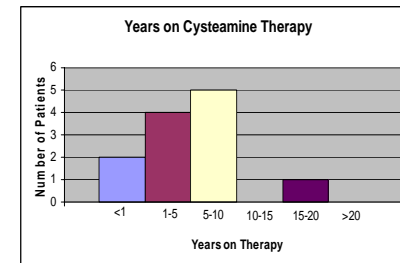
If you are a patient with Cystinosis or a parent of a child with Cystinosis, the Cystinosis Research Foundation would appreciate it if you could spend a few minutes of your time while at the meeting this weekend to complete this survey. This will be an anonymous survey, please do not include your age, name or where you live on this form. This survey will be used to help the Cystinosis Research Foundation work with companies doing research for therapies for Cystinosis.

- Is the parent or child (or patient with cystinosis) completing this survey?
 Parent Child /Patient with Cystinosis
- Do you take Cystagon™ (Cysteamine)? Yes No
- Do you currently take Enteric Coated (Twice a day) Cystagon™/Cysteamine as part of a study? Yes No
- Have you taken Enteric Coated (Twice a day) Cystagon™/Cysteamine as part of a study?
 Yes No
- How many years have you been receiving Cystagon™/Cysteamine?
 <1 1-5 5-10 10-15 15-20 >20
- How many times a day does your doctor say to take the Cystagon™/Cysteamine?
 Twice a day Three times a day Four times a day
 Other (please list): _____
- Are you always able to take the full dose of Cystagon™/Cysteamine that your doctor prescribes? Yes No
- Do you think you would take Cystagon™/Cysteamine more regularly if you only had to take it twice a day? Yes No
- How many times a day do you take Cystagon™/Cysteamine?
 Twice a day Three times a day Four times a day
 Other (please list): _____
- If miss a dose of Cystagon™/Cysteamine, what is the most frequent reason you miss a dose?
 Forgot it Over slept/Couldn't wake up Felt Sick
 Didn't like the smell of the pill Don't like how it makes me smell to others Other (please list): _____
- If you miss a dose of Cystagon™/Cysteamine, please check all applicable reasons why you have missed a dose in the past:
 Forgot it Over slept/Couldn't wake up Felt Sick
 Didn't like the smell of the pill Don't like how it makes me smell to others Other (please list): _____
- If there was a form of Cystagon™/Cysteamine that only had to be taken every 12 hours (twice a day) would you think that would help to take all your doses?
 Yes No
- What times during the day do you regularly take the Cystagon™/Cysteamine medicine currently? Please fill in the hours and list "am" (after midnight/morning) or "pm" (afternoon/evening).

- What times, would you take the medication if you only had to take it twice a day?

- What is the worst thing about taking Cystagon™/Cysteamine?
 Waking up at night? Taste? Smell of pill? Upset stomach? Bloating? Nausea? Vomiting? Body Odor?
 Other (Please list): _____
- Do you have extra acid on your stomach for which your doctor has prescribed an acid reducer? Yes No
- If yes, which one?
 Nexium Prilosec Zantac Cimetidine
 Other (List): _____
- In addition do you take any of the following over-the-counter medications:
 Tums Maalox Peptobismol
 Other (List): _____
- Have you had a kidney transplant? Yes No
- If yes, do you still take Cystagon™/Cysteamine? Yes No
- Would you possibly be interested in participating in a study to reduce the number of doses of Cysteamine?
 Yes No

RESULTS



Key Survey Responses

- All patients previously or currently on Cystagon; 10 currently on q6 hr; 1 on q8 hrs (post transplant); 1 on DR-Cysteamine q12 hrs currently
- 6 patients responded that they do not take the full dose prescribed, however ALL respondents noted one or more reasons "a dose of Cystagon™/Cysteamine were missed.
- Main reason cited by respondents for missing doses: 5 "forgot", 3 "forgot", 2 "overslept" 1 had multiple listing and 1 listed other
- Total of reasons doses were missed included 7 "forgot", 7 "felt sick", 4 "overslept/couldn't wake up", 1 "didn't like how it makes me smell", 1 other
- All respondents thought q12 hour dosing would improve their ability to take cysteamine more regularly

CONCLUSION

Bennu Pharmaceutical is committed to developing a q12 hour DR Cysteamine to improve the quality of lives of patients with cystinosis.

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Bennu Pharmaceuticals Inc. thanks the Cystinosis Research Foundation for its efforts in conducting this survey and providing the results to Bennu.