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**CROFLEMER, FIRST-IN-CLASS ANTI-DIARRHEAL AGENT, POSITIVE
CLINICAL RESULTS TO BE DISCUSSED AT 13TH ANNUAL US-JAPAN CMSP
IN KOLKATA, INDIA**

**Glenmark Pharmaceuticals Limited targets introduction of crofelemer for 2010 to
address disease that kills millions**

South San Francisco, California, April 8, 2009 - Napo Pharmaceuticals, Inc., (“Napo”) announces that oral presentations regarding the safety, efficacy and mechanism of action of crofelemer in clinical trials in severe acute dehydrating watery diarrhea and cholera, as well as the preclinical results for other small molecule cystic fibrosis transmembrane conductance regulator (CFTR) chloride channel blockers, will be presented at the upcoming U.S. - Japan CMSP: 13th International Conference on Emerging Infectious Diseases (EID) in the Pacific Rim – Focused on Enteric Diseases, April 6-9 in Kolkata, India. Data will also be presented on other pre-clinical anti-secretory agents. Glenmark Pharmaceuticals Limited (“Glenmark”) is currently undertaking clinical trials on crofelemer in India and anticipates introduction in the country in 2010. Glenmark has both developmental and marketing rights for the molecule in 140 countries around the world including India.

Pradip K. Bardhan of the International Center for Diarrheal Disease Research (“ICDDR”) in Bangladesh will be summarizing the results from two clinical studies that evaluated the safety and efficacy of Napo’s novel anti-secretory anti-diarrheal agent, crofelemer (NP-303), in the treatment of adult acute infectious diarrhea (conducted in India by Glenmark) and cholera (conducted at the ICCDR in Bangladesh). The study of the effects of crofelemer in adult infectious diarrhea, predominantly from enterotoxigenic Escherichia coli (ETEC) infection, was conducted without the use of any antibiotics, while the study in adult patients suffering from cholera infection was conducted in combination with a single oral dose of azithromycin. These results collectively show that crofelemer represents a first-in-class treatment option as an antisecretory agent for the treatment of acute dehydrating watery diarrhea, with or without the use of antibiotics.

Perhaps the most important application of crofelemer is to address the devastating morbidity and mortality of ~2.5 million children under 5 who die each year primarily in developing countries, from the devastation of diarrhea and dehydration of cholera and watery diarrhea due to multiple etiologies and the global crisis in access to clean water. Cholera, for example, results in death for >50% of its victims without adequate rehydration. Current standard-of-care therapy focuses on rehydration therapy and antibiotic therapy to target the infectious agent. There are no current therapies for cholera which decrease the secretion of fluid into the small intestine. Patients are at maximum risk during the first 6-18 hours. Crofelemer demonstrated significant reduction

(approximately 32%) in stool volume output in the first 6 hours, a trend which continued through the first 24 hours of observation — the period of time where patients are often in a life-threatening situation due to severe dehydration. In the severe acute watery diarrhea study, overall clinical success was achieved in about 75% of the crofelemer group, including statistically significant results on all seven measurements of diarrhea symptoms. Both these studies was conducted in adults.

A separate presentation will be given by Dr. Alan S. Verkman of the Departments of Medicine and Physiology at the University of California, San Francisco, California, discussing the mechanism of action of crofelemer as a first-in-class, small molecule dual inhibitor of CFTR chloride channel and calcium activated chloride channel (“CaCC”). Furthermore, this presentation will provide some of the preclinical results with other novel small molecule inhibitors of CFTR (“second gen CFTR”), which have been exclusively licensed by Napo from the University of California regents.

(See Abstracts below)

Lisa A. Conte, CEO of Napo Pharmaceuticals, Inc. commented: "Napo is thrilled that the important results of the trials of crofelemer for cholera and for severe adult acute infectious diarrhea are being presented in such a forum and I would like to thank Glenmark, Dr. Bardhan and the ICDDR for their contributions. We look forward to Glenmark’s anticipated introduction of crofelemer in India in 2010 and in other countries thereafter. Napo is committed to the development of crofelemer for pediatric populations and collaboration with both crofelemer and second gen CFTR to address the global impact of diarrhea diseases.”

Napo’s commercial licensee for crofelemer in the United States, Salix Pharmaceuticals, Inc., expects to file an NDA for the indication of chronic diarrhea in people living with HIV/AIDS in the first half of 2010. Crofelemer is in the final Phase 3 study for this indication and has been fast-tracked by the FDA.

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About Napo Pharmaceuticals, Inc.

Napo Pharmaceuticals, Inc. focuses on the development and commercialisation of proprietary pharmaceuticals for the global marketplace in collaboration with local

partners. Napo was founded in November 2001, and is based in California, USA with a subsidiary in Mumbai, India.

Napo's late-stage proprietary gastro-intestinal compound, crofelemer, is in various stages of clinical development for four distinct product indications, including a late-stage Phase 3 program:

- CRO-HIV for AIDS diarrhoea, Phase 3
- CRO-IBS for diarrhoea irritable bowel syndrome ("D-IBS"), Phase 2
- CRO-ID for acute infectious diarrhoea (including cholera), Phase 2
- CRO-PED for paediatric diarrhoea, Phase 1

The FDA has granted fast-track status to CRO-IBS and CRO-HIV.

Crofelemer, a proprietary patented agent, is extracted from *Croton lechleri*, a medicinal plant which can be sustainably harvested from several countries in South America. Napo also plans to develop an early clinical stage product, NP-500, for the treatment of insulin resistant diseases of Type II diabetes and metabolic syndrome (Syndrome X; pre-diabetic syndrome). Napo also has a plant library of approximately 2,300 medicinal plants from tropical regions, and Napo has entered two screening relationship associated with this collection.

Currently, products are based on the chemical and biological diversity derived from plants with medicinal properties, but future products may be in-licensed from other sources.

In December 10, 2008 Napo announced the licensing of crofelemer to Salix Pharmaceuticals, Inc. for all indications in North America, Europe (excluding certain smaller countries), and Japan, and certain indications worldwide, including chronic diarrhea in people living with HIV/AIDS which is currently in Phase 3. Crofelemer is also licensed to Glenmark Pharmaceuticals, Ltd. of Mumbai, India in 140 emerging and developing countries for diarrhea indications; and to AsiaPharm, Ltd. in greater China for diarrhea indications.

For more information please visit www.napopharma.com.

Abstract for the clinical effects of crofelemer is provided below:

Safety and efficacy of a novel anti-secretory anti-diarrheal agent Crofelemer (NP-303), in the treatment of adult acute infectious diarrhea and cholera, with or without the use of antibiotics

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The effects of crofelemer were evaluated in patients with acute dehydrating watery diarrhea caused by various bacterial pathogens, such as enterotoxigenic strains of *Escherichia coli* (ETEC) and *Vibrio cholerae* infection. Crofelemer was evaluated in adult Indian patients with acute watery diarrhea of less than 24 hour duration with suspected bacterial infections, without the use of antibiotics. In this study, patients received oral doses of placebo or crofelemer at a dose of 250 mg every 6 hours for 2 days on the background of oral rehydration therapy only. The use of antibiotics was prohibited in this study. A total of 98 patients were randomized into this study (47 in placebo group and 51 in the crofelemer group). The key endpoint of this study was the resolution of watery diarrhea within 48 hours from the initiation of therapy. Other endpoints evaluated included stool weight and stool frequency. Crofelemer was well tolerated and there were no drug related adverse events. Twelve patients in the placebo group and four patients in the crofelemer group required antibiotic rescue therapy. Crofelemer at 250 mg every 6 hours was superior to placebo in improving the watery diarrhea and overall clinical success was achieved in about 75% of the crofelemer group compared to 37% in the placebo group. Stool cultures showed that 78% of the patients had *ETEC*, 15% had *Salmonella*, 2% had *Shigella* and about 5% had suspected viral pathogens.

In another study, a total of 100 adult patients, from Bangladesh, between the ages of 18 and 55, with acute, severely dehydrating watery diarrhea with confirmed cholera were treated with crofelemer on a background of an antibiotic (azithromycin) and oral rehydration therapy. After a four hour period of rapid rehydration therapy, patients were randomized 1:2:2 to placebo or 125 mg or 250 mg oral dose of crofelemer. Crofelemer or placebo doses were administered about one hour after the oral administration of azithromycin (1 gm dose). The primary objective was to evaluate the safety and effects of crofelemer on reducing the watery stool output normalized to body weight (mL/kg) in the first 24 hours on the background of azithromycin and rehydration therapy. Crofelemer was well tolerated and there were no drug related adverse events in this study. Both doses of crofelemer produced approximately 25-30% reduction in median watery stool volumes in the 0-6 and 0-12 hour period following initiation of therapy. Crofelemer showed a strong trend in the reduction of watery stool output in the 0-6 hour and 0-12 hour intervals ($p=0.07$). Upon exclusion of three outlier patients, the crofelemer dose of 125 mg produced a statistically significant reduction in the normalized stool output ($p=0.028$) and the dose of 250 mg crofelemer showed a strong trend for reduction of watery stool output ($p=0.07$).

These results collectively show that crofelemer represents a first-of-a-kind treatment option as an antisecretory agent for the treatment of acute dehydrating watery diarrhea, with or without the use of antibiotics.

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Cellular antisecretory mechanisms of crofelemer and small-molecule chloride channel blockers

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Intestinal fluid secretion, as occurs in cholera, involves chloride secretion across enterocytes into the gut lumen through apical membrane chloride channels and the basolateral membrane $\text{Na}^+/\text{K}^+/\text{2Cl}^-$ cotransporter (NKCC). Na^+ and K^+ channels are also involved in intestinal fluid transport. The principle route for apical chloride secretion in cholera and other enterotoxin-mediated secretory diarrheas is the cystic fibrosis transmembrane conductance regulator (CFTR), a cAMP-regulated chloride channel. Calcium-activated chloride channels (CaCCs) provide another route for chloride secretion, and may be preferentially activated in some viral and drug-induced diarrheas.

Crofelemer, a purified proanthocyanidin oligomer extracted from the bark latex of the medicinal plant *Croton lechleri*, is currently in clinical trials for secretory diarrheas. We investigated the antisecretory mechanisms of crofelemer by determination of its effect on the principle membrane transport processes and signaling pathways in intestinal fluid transport. Using cells lines expressing human transport proteins, crofelemer did not affect epithelial Na^+ or K^+ channels, or G-protein regulation of cAMP. Crofelemer was a partial antagonist of CFTR, with maximum inhibition of 65-90 % depending on activating agonist, with IC_{50} in the range 20-60 μM . Crofelemer action at an extracellular site on CFTR produced a voltage-independent block by patch-clamp, without effect on the potency of glycine hydrazide or thiazolidinone CFTR inhibitors. Crofelemer action resisted washout, with <20% reversal of CFTR inhibition after 4 hours. Crofelemer was also a partial antagonist of the intestinal CaCC, with maximum inhibition of 85 % and IC_{50} of $\sim 40 \mu\text{M}$. Crofelemer inhibited CaCC in human airway epithelia with similar potency. The dual inhibitory action of Crofelemer on pro-secretory Cl^- channels, and its lack of effect on pro-absorptive Na^+ channels, may account for its clinical antisecretory activity.

For target-based antisecretory therapy we identified, by high-throughput screening, several classes of small-molecule CFTR and CaCC inhibitors. Thiazolidinones such as $\text{CFTR}_{\text{inh}}-172$ inhibit CFTR with IC_{50} down to 200 nM by binding to an intracellular site on CFTR and stabilizing its closed channel state (Ma et al. J. Clin. Invest. 2002, 110:1651-1658; Thiagarajah et al. Gastro. 2004, 126:511-519). Glycine hydrazides such as GlyH-101 block the CFTR pore at its external entrance (Muanprasat et al., J. Gen. Physiol. 2004, 124:125-137). Polyethyleneglycol (PEG) and lectin conjugates of GlyH analogs inhibit CFTR externally with nanomolar potency, are not absorbed in the intestine, and block fluid secretion in models of cholera (Sonawane et al., Gastro. 2007, 132:1234-1244; Chem. Biol. 2008, 15:718-728). We recently identified a third class of CFTR blockers with IC_{50} down to 50 nM, which are being optimized for testing in cholera models. Several classes of CaCC inhibitors were identified by a phenotype screen using human intestinal cells (de la Fuente et al. Mol. Pharm. 2008, 73:758-768), including 3-acyl-2-aminothiophenes that inhibited human intestinal CaCC with IC_{50} under 1 μM . These and new potent inhibitors appear to target the recently identified CaCC, TMEM16A. The antisecretory efficacy of these compounds remains to be tested. Finally, using a cAMP 'pathway' screen, we recently identified thiophenecarboxylate PDE activators that suppress cyclic nucleotides and reduce intestinal fluid secretion (Tradtrantip et al. Mol. Pharmacol. 2009, in press). Our results support the utility of antisecretory therapy for diarrheas in developing countries.

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