

Advancing iOWH032

Novel antisecretory drug for the treatment of cholera

GLOBAL BURDEN OF DIARRHEAL DISEASE

Diarrheal disease kills an estimated 1.3 million people each year. A disease of poverty and poor sanitation, it remains one of the leading causes of death among children younger than five years, claiming more than half a million lives and accounting for 9 percent of global child deaths. Infectious diarrhea is caused by pathogens that disrupt the absorptive and/or secretory processes of the gut epithelium. Among the pathogens most commonly responsible, *Vibrio cholerae* bacteria account for almost 6 percent, or 29,000, of diarrheal deaths annually in children younger than five.¹ The onset of diarrhea is rapid and can last from hours to days, accompanied by copious fluid loss and rapid life-threatening dehydration. If left untreated, the mortality rate increases up to 60 percent, with death occurring within hours to days. However, with immediate and appropriate treatment, the mortality rate can be reduced to 1 percent.²

Without adequate prevention and treatment options, survivors of severe diarrheal disease are often left weakened and vulnerable to reinfection and other opportunistic illnesses, leading to an unrelenting cycle of poor health and poverty. Alongside important interventions like good nutrition, vaccination, improved access to clean water and sanitation, and the wider use of oral rehydration solution (ORS), expanded use of safe, effective, and affordable drugs for the most common causes of illness is a necessary part of the solution.

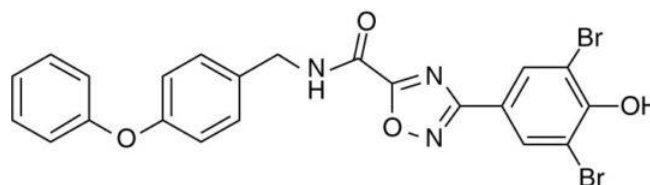
USE OF ANTISECRETORY DRUGS TO TREAT DIARRHEA

Antisecretory drugs are intended for use as adjuncts to the standard of care. Supplementing ORS with an antisecretory drug would allow ORS to rehydrate more effectively by decreasing the amount of fluid lost through secretion. It would also provide more rapid relief of symptoms, facilitating the care of patients and improving the perceived impact of the treatment. Faster rehydration and reduction of diarrhea symptoms could improve acceptance of ORS and increase its uptake as a standard of care in endemic countries. Additionally, adoption of a broad-spectrum antisecretory drug with ORS may help displace the (often inappropriate) use of antibiotics to treat diarrhea.

iOWH032 FOR CHOLERA

PATH and its partners are developing iOWH032 as a complement to ORS. Acting via inhibition of the cystic fibrosis transmembrane conductance regulator chloride channel, iOWH032 is a novel, low-molecular-weight compound intended to reduce fluid and electrolyte loss in cases of cholera toxin-induced secretory diarrhea (see Figure 1). iOWH032 is expected to reduce mortality by making rehydration with ORS or intravenous (IV) fluids more efficient, and by accelerating the turnover of in-patients in large outbreak situations.³

Figure 1. Molecular composition of iOWH032.



BENEFITS OF TREATMENT WITH iOWH032

Patient care. Treatment with iOWH032 would benefit patients directly as well as benefiting the health care infrastructure in which they are treated. For patients, the treatment would reduce the duration of acute symptoms of cholera and decrease the time at peak risk for the consequences of dehydration, allowing for more rapid recovery, reduced loss of productivity, and lower cost of care. Use of iOWH032 is intended to also decrease the burden on available health care resources through the overall shortened need for care, and lessen time under intensive care for the most severe cases. A more efficient treatment regimen would particularly benefit management in acutely resource-constrained situations, such as a public-sector response to a cholera outbreak, allowing for substantially improved treatment and patient outcomes.

While effective treatment for cholera in children has been available for decades (ORS and zinc), the overall effectiveness has been limited by a lack of adoption. Caregivers often underdose ORS in children, and potentially inappropriate treatments such as antibiotics are frequently

utilized in lieu of ORS. Treatment of children suffering from cholera with iOWH032 would fill the gap between the potential and actual effectiveness of ORS. Adoption of iOWH032 would directly improve treatment outcomes by reducing the duration of acute symptoms and decreasing the time spent at peak risk for dehydration. Where ORS is provided but underdosed, use of an antisecretory drug would improve hydration in children by decreasing fluid loss through secretion. Where antibiotics are used as an adjunct to ORS, iOWH032 would provide a more effective substitute with a broader spectrum.



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Cost of care. The cost of treatment with iOWH032 may be offset by lower costs of other treatments and reduced caregiver time devoted to the ill child. A 2016 study of the cost of treating pediatric diarrhea in Rwanda provides some perspective on the potential impact of shortening the duration or intensity of treatment: the investigators found that the average cost of hospitalization for diarrhea was US\$44 (~\$9/day for an average five-day hospitalization), of which some \$15 (\$3/day) was for medication (including IV fluids, ORS, and antibiotics) and \$22 (~\$4/day) was for other health care costs. A liter of IV fluid may cost \$1 or more, and 10 liters of replacement fluid may be required before a cholera patient is stabilized and can be managed with oral fluids.⁴ The cost of IV fluid replacement multiplied by thousands of cases that may occur in an epidemic reflects the high cost of treatment. Use of an antisecretory drug in the treatment of cholera in both adults and children could reduce the IV fluid requirement, improve patient management, and reduce costs for patients and their families.

PROJECT HIGHLIGHTS

2006: Funding received from the Bill & Melinda Gates Foundation to develop a novel antisecretory drug to safely reduce stool output and shorten duration of diarrheal episodes. Collaboration begun with BioFocus DPI to apply their medicinal chemistry expertise to identify new drug candidates.

2011: Investigational New Drug Application for iOWH032 approved by the United States Food and Drug Administration.

2012: Phase 1 clinical trials for iOWH032 successfully concluded. The drug candidate was found to be safe and well tolerated in healthy volunteers.

2013: Two-part bridging study to assess pharmacokinetics, safety, and tolerability in Bangladeshi adult volunteers and male cholera patients completed. Valuable information was obtained about how the drug is absorbed and metabolized in cholera patients.⁵

2018: With funding from the United Kingdom’s Department for International Development, a challenge trial is planned to test the efficacy of iOWH032 as a treatment for cholera to provide data to inform a go/no-go decision regarding further clinical development leading to regulatory approval and product introduction. If successful, a proof-of-concept Phase 2 trial in an endemic setting will follow (to be funded).

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