Pharmacokinetics and tolerability of iOWH032, an inhibitor of the cystic fibrosis transmembrane conductance regulator (CFTR) chloride channel, in normal volunteers and cholera patients

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Introduction

iOWH032 is a novel, low-molecular-weight compound being developed as an anti-secretory agent for the treatment of cholera toxin-induced secretory diarrhea, acting via inhibition of the cystic fibrosis transmembrane conductance regulator (CFTR) chloride channel.

The effects of secretory diarrhea on the pharmacokinetics of small molecules in the target patient population are poorly understood. The present study was conducted to compare the pharmacokinetic profiles of a single dose of 300 mg iOWH032 in healthy American volunteers (N=8), healthy Bangladeshi volunteers (N=8), and Bangladeshi cholera patients (N=14*) with severe diarrhea. In addition, the safety of iOWH032 was assessed in these different populations.

* 12 completed study participants; PK profiles (or partial profiles) were determined for two additional patients who withdrew from the study due to AEs.

Hypothesis

Absorption and disposition of iOWH032 in healthy volunteers and patients with cholera is not different.

Methods

Subjects, dosing, and sample collection

- Healthy US volunteers: As part of a single ascending dose study, six fasted, healthy, male and female US volunteers between 18 and 50 years each received a single 300-mg oral dose of iOWH032, administered as an aqueous suspension using xanthan gum. Two additional subjects received a matching placebo.
- Healthy Bangladeshi volunteers: Six fasted, healthy, male and female Bangladeshi volunteers between 18 and 22 years each received a 300-mg oral dose of iOWH032 administered as a fast-release tablet. Two additional subjects received a matching placebo.
- Bangladeshi patients with severe diarrhea: Twelve male Bangladeshi patients with a history of acute watery diarrhea of less than 24 hours duration, clinical signs of severe dehydration, and either stool dark-field microscopy or rapid strip test showing positive for *Vibrio cholera* were given a single 300-mg fast-release tablet of iOWH032 following rehydration and treatment with 1 g azithromycin as a standard of care. There were twelve completed study participants; PK profiles (or partial profiles) were determined for two additional patients who withdrew from the study due to AEs.

Each group provided a signed informed consent and complied with the inclusion and exclusion criteria described in the protocol. The study was approved by the respective Institutional Review Board/Independent Ethics Committee and conducted in accordance with the ethical principles of the Declaration of Helsinki.

Blood samples were collected from each subject predose and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 20, 24, 36, and 48 hours after dosing with iOWH032 and plasma was prepared by centrifugation for iOWH032 bioanalysis.

Bioanalysis

- Each plasma sample was analyzed using a validated LC-MS/MS bioanalytical method.
- After addition of [$^2H_2$]-iOWH032 as the internal standard, the samples were extracted by protein precipitation.
- Analytes of interest were separated by HPLC using a C18 reverse-phase column and isocratic elution.
- Each analyte was detected using an Applied Biosystems API-4000 mass spectrometer with turbo-ion spray ionization in negative ion mode and multiple ion monitoring.

All photos: PATH/Patrick Mckern

Methods continued

Pharmacokinetic Analysis

- The plasma profiles of intact iOWH032 from each subject were evaluated using a non-compartmental pharmacokinetic approach with WinNonlin 'v' 5.2 (Pharsight, CA).
- Cmax and Tmax were taken directly from the bioanalytical data.
- The terminal half-life was determined from a linear regression of the log of the plasma level versus time for the terminal portion of the curve; the number of points used for the regression was chosen following visual inspection of the data.
- The AUC was determined from the linear trapezoidal rule on the ascending portion of the curve and the log trapezoidal rule for the descending portion.

Results

Table 1. Demographics (safety population)

Parameter	Part A (Healthy Bangladeshi volunteers)	Part B (Bangladeshi patients with severe diarrhea)
Sex		
Male (n [%])	4 (50%)	14 (100%)
Female (n [%])	4 (50%)	0
Age (years)		
Median (minimum, maximum)	19.0 (18, 22)	25.0 (18, 40)
Height (cm)		
Mean (SD)	161.6 (9.3)	160.4 (5.65)
Weight (kg)		
Mean (SD)	54.22 (12.4)	51.66 (6.3)
Body mass index (kg/m^2)		
Mean (SD)	20.548 (3.2)	20.037 (1.9)

Table 2. Summary of adverse events (AEs) by body systems

Summary of treatment-emergent adverse events (TEAEs), Part A

System Organ Class	Placebo (N = 2)		iOWH032 300 mg (N = 6)	
Preferred Term	Number (%) of subjects	Number of events	Number (%) of subjects	Number of events
Number of subjects with TEAEs	0 (0.0)		2 (33.3)	
Gastrointestinal disorders	0 (0.0)	0	2 (33.3)	2
Abdominal pain	0 (0.0)	0	1 (16.7)	1
Hematemesis	0 (0.0)	0	1 (16.7)	1

Summary of treatment-emergent adverse events (TEAEs), Part B

System organ class preferred term	Positive for *Vibrio cholerae* 01 (N = 14)	
	Number (%) of subjects	Number of events
Number of subjects with TEAEs	8 (57.1)	
Cardiac disorders	3 (21.4)	3
Sinus tachycardia	3 (21.4)	3
Gastrointestinal disorders	1 (7.1)	1
Gastritis	1 (7.1)	1
Investigations	4 (28.6)	4
Blood creatine phosphokinase increased	4 (28.6)	4
Metabolism and nutrition disorders	1 (7.1)	1
Tetany	1 (7.1)	1

Results continued

Summary of AEs by severity

- Two subjects in each part of the study reported AEs that were considered unlikely to be related to the study treatment:
  - Part A: One subject (16.7%) from the iOWH032 group reported abdominal pain that was considered unlikely to be related to the study treatment.
  - Part B: One subject (7.1%) reported increased blood creatine phosphokinase (CPK), which was considered unlikely to be related to the study treatment.
- All other AEs in both treatment groups were considered to be not related to the study treatments.
- In Part A, both reported AEs (abdominal pain and hematemesis) were mild in intensity and were reported in the iOWH032 group.
- In Part B, seven subjects (50%) reported mild events, while 1 subject (7.1%) each reported moderate (tetany) and severe (blood CPK increased) events.

Pharmacokinetics

The median of the plasma concentration of iOWH032 versus time curves for each of the groups are presented in Figure 1. The mean ± SD of the pharmacokinetic parameters for each of the groups are summarized in Table 1.

Healthy volunteers

iOWH032 was well absorbed in both the US and Bangladeshi healthy volunteer populations:

- Cmax of between 1,280 ± 491 ng/mL for Bangladeshi volunteers compared with 1,380 ± 539 ng/mL for US volunteers.
- Tmax of 4.8 hours for both Bangladeshi and US volunteers.
- AUC∞ of between 22,700 ± 10,400 ng*h/mL for Bangladeshi volunteers compared with 28,200 ± 12,200 ng*h/mL for US volunteers.
- Half-life slightly longer in the US healthy volunteers (11.5 ± 3.1 h) compared to the healthy Bangladeshi volunteers (8.5 ± 1.5 h).

Cholera patients

The exposure of iOWH032 was distinctly lower in the Bangladeshi cholera patients with severe diarrhea:

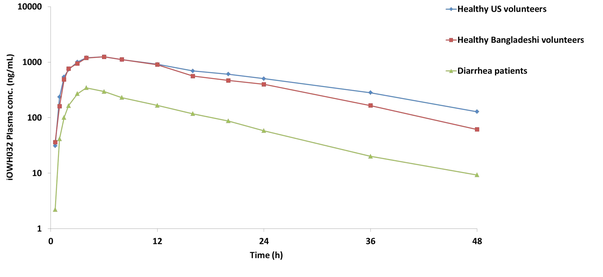
- Cmax of 482 ± 388 ng/mL for cholera patients compared with 1,280 ± 491 ng/mL for healthy volunteers.
- Tmax of 3.8 ± 1.6 h for cholera patients and 4.8 ± 2.6 h for healthy volunteers.
- AUC∞ of 6,250 ± 4,910 ng*h/mL for cholera patients and 22,700 ± 10,400 ng*h/mL for healthy volunteers.
- Half-life of 8.2 ± 1.4 h for cholera patients and 8.5 ± 1.5 h for healthy volunteers.

Table 3: Mean ± SD (CV%) of the pharmacokinetic parameters of iOWH032 following an oral 300-mg dose to healthy US and Bangladeshi volunteers and Bangladeshi patients with severe diarrhea

Parameter	Healthy US volunteers	Healthy Bangladeshi volunteers (Part A)	Bangladeshi patients with severe diarrhea (Part B)
Cmax (ng/mL)	1380 ± 539 (38.9)	1280 ± 491 (38.5)	482 ± 388 (80.5)
Tmax (h)	4.8 ± 3.7 (77.6)	4.8 ± 2.6 (54.2)	3.8 ± 1.6 (42.1)
AUClast (ng*h/mL)	28000 ± 12200 (43.6)	21800 ± 9740 (44.6)	6120 ± 4820 (78.8)
AUC∞ (ng*h/mL)	28200 ± 12200 (43.4)	22700 ± 10400 (45.7)	6250 ± 4910 (78.6)
Terminal $t_{1/2}$ (h)	11.5 ± 3.1 (26.9)	8.5 ± 1.5 (17.6)	8.2 ± 1.4 (7.1)

Results continued

Figure 1: Median plasma concentrations of iOWH032 following an oral dose to healthy US and Bangladeshi volunteers and Bangladeshi patients with severe diarrhea



Conclusions

- Oral iOWH032 was reasonably rapidly absorbed and at similar rates for all of the populations studied with Tmax averaging 3.8 to 4.8 hours (median 3 to 4 hours with a range of 3 to 12 hours).
- The Cmax was similar between the US (1,380 ± 539 ng/mL) and Bangladeshi (1,280 ± 491 ng/mL) healthy volunteers, as was the AUC∞ for the US (28,200 ± 12,200 ng*h/mL) and Bangladeshi (22,700 ± 10,400 ng*h/mL) healthy volunteers.
- The average Cmax and AUC∞ was distinctly lower for the Bangladeshi cholera patients with severe diarrhea (482 ± 388 ng/mL and 6,250 ± 4,910 ng*h/mL, respectively) compared to those of healthy Bangladeshi volunteers (1,280 ± 491 ng/mL and 22,700 ± 10,400 ng*h/mL, respectively) and with a much higher variability (CVs of approximately 40% for the healthy volunteers and 80% for the patients with severe diarrhea).
- Despite the differences in exposure, the half-life for the Bangladeshi healthy volunteers (8.5 ± 1.5 hours) was very similar to that of the patients with severe diarrhea (8.2 ± 1.4 hours), suggesting that the disease state has no effect on the clearance of iOWH032 and confirming the in vitro findings that azithromycin has no inhibitory interaction on the elimination of iOWH032.
- As the Tmax was similar for the two populations, the rate of absorption is probably unaffected, so the reduced absorption is most likely due to the decreased and variable transit time through the gastrointestinal tract of the patients with severe diarrhea.
- Pharmacokinetics of orally administered iOWH032 showed no ethnic differences between populations of healthy volunteers from the US and Bangladesh, but did show a pronounced reduction and higher variability of exposure (Cmax and AUC∞) for the Bangladeshi cholera patients with severe diarrhea. Patients with severe diarrhea are unlikely to be subject to unexpected high exposures of iOWH032 that could cause unwanted side effects.

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