Oral arsenic trioxide ORH-2014 pharmacokinetic and safety profile in patients with advanced hematologic disorders

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SUPPLEMENTAL METHODS

ORH-2014 Oral Formulation Development

A unique oral capsule formulation of ATO, ORH-2014, was developed using a proprietary lyophilization process. ATO was first solubilized in NaOH, and then neutralized with HCl to a pH of 7-8. Sodium lauryl sulfate was added, and the solution is lyophilized to obtain a cake (referred to as Lyopremix). The Lyopremix consisted of crystalline micron-sized ATO stabilized in a matrix of sodium lauryl sulfate. The Lyopremix was blended with compendial excipients such as mannitol, talc, and magnesium stearate, and was filled into hard-gelatin capsules (containing 5 or 10 mg of ORH-2014).

ORH-2014 Physical Properties Assessment

ORH-2014 particle size was measured by laser light scattering using the Mastersizer 3000 particle sizer (Malvern Panalytical, Malver, UK) with slight sonication to deagglomerate particles. Particles' surface area was measured using gas adsorption (Tristar II 3020 instrument; Micromeritics, Norcross, Ga.) with nitrogen as the adsorbate, a method based on the Brunauer-Emmett-Teller theory.[27] Scanning electron microscopy was used to obtain high resolution pictures to examine the structure of the Lyopremix and the morphology of ORH-2014.ORH-2014 dissolution profile was assessed with ORH-2014, 10 mg capsules in 900 mL of 0.1 N HCL in a United States Pharmacopeia Apparatus 2, with a paddle speed of 50 rpm. Arsenic was measured by inductively coupled plasma optical emission spectrometry (ICP-OES).

Toxicity and Other Study-Related Evaluations

Toxicity Assessment

Toxicities were graded using National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03. A DLT was defined as any of the following

toxicities experienced during the first 4 weeks of treatment, judged not related to underlying disease or concomitant medications: (i) Any treatment delay >2 weeks due to toxicity; (ii) any non-hematological toxicity Grade ≥3 (with some exception for manageable Grade 3 nausea, vomiting, diarrhea, and electrolyte abnormalities, anorexia, and fatigue); (iii) Grade 3 QTcF prolongations on at least 2 separate electrocardiograms (ECGs) (obtained ≥2 hours apart), unless associated with electrolyte abnormalities and resolved after their correction. Because bone marrow failure is typical in patients with hematologic malignancies, hematological toxicities and febrile neutropenia were not considered DLTs in this trial, unless they were clinically complicated, profound, prolonged, and not related to underlying disease. The window for DLT observations was the first 4 weeks of dosing, plus up to 14 days, if necessary, for evaluation of reversibility/persistence of events.

Safety Assessments and ECGs

Clinical laboratory parameters, vital signs, and the incidence and severity of adverse events (AEs) were monitored to assess safety and tolerability. Triplicate safety 12-lead ECGs were collected at Screening to determine subjects' eligibility, before dosing, and on Days 1, 2, 5, 8, 15, 16, 22, 23, and 29. ECGs were also recorded via continuous Holter monitoring from ~30 minutes pre-dose to ~24 hours post-dose on Day 1, and for ~8 hours on Days 5 and 15 to determine the effect of ORH-2014 on QTcF and other ECG parameters. Continuous ECG data were extracted in triplicate.

Bone Marrow Aspirates and Biopsies

Bone marrow aspirates and/or biopsies were obtained at Screening to establish the diagnosis (if a historical sample was unavailable), at the end of Week 12, and every 3-6 months if the subject continued on maintenance therapy.

PK Analysis

Blood samples for PK analysis were collected pre-dose and 0.5, 1, 2, 4, 8, 12, and 24 hours post-dose on Days 1, 15, and 22. Blood samples for trough PK analysis were also collected pre-dose on Days 5, 8, and 29. Concentration of total plasma arsenic as well as the main arsenical species ([AsIII], [AsV], [MMAV], [DMAV]) were measured using a validated inductively-coupled plasma mass spectrometry (ICP-MS) method performed by Frontage Laboratories (Exton, Pa.). The assay's lower limit of quantitation was 5 ng/mL. A correlation between total arsenic exposure and patient BMI was performed to determine whether flat dose administration is adequate.

Data Analyses

PK Data Analyses

Plasma arsenic concentrations time-curves were derived and the following PK parameters were calculated using standard noncompartmental or compartmental methods using the Phoenix WinNonlin software version 8.1 (Certara, Princeton, NJ): C_{max}, time to C_{max} (t_{max}), AUC_{0-24} and AUC extrapolated to infinity ($AUC_{0-\infty}$), clearance (CL/F), and accumulation ratio (AR). The mean and coefficient of variation (CV%) were calculated. The terminal elimination half-life and other regression-based parameters were not calculated as they were considered unreliable due to the longer than expected half-life over the 24-hour sampling.

Safety, ECG, and Efficacy Analyses

Preliminary efficacy was assessed by the number of subjects with CR or PR according to the International Working Group (IWG) response criteria for the appropriate diseases.[28,29] Descriptive statistics and changes from baseline were calculated for safety, ECG, and efficacy parameters. No formal statistical analyses were conducted.

All authors had access to the primary clinical trial data. To obtain original data, contact the corresponding author.

SUPPLEMENTAL DATA

PK parameters AsIII

	ORH-2014 5 mg		ORH-2014 10 mg			ORH-2014 15 mg			IV ATO 0.15 mg/kg
	Day 1 (N=3)	Day 15 (N=3)	Day 1 (N=6)	Day 15 (N=5)	Day 22 (N=2)	Day 1 (N=3)	Day 15 (N=3)	Day 22 (N=3)	Day 25
C_{max}, ng/mL	3.11 (1.06)	4.85 (1.17)	12.94 (7.35)	15.34 (12.25)	24.33 (5.59)	17.39 (5.24)	27.37 (13.85)	25.43 (10.74)	
$AUC_{0\text{-}24,}$ ng•h/mL	24.14 (8.67)	28.95 (9.65)	114.2 (55.7)	110.9 (155.5)	241.3 (126)	183.2 (28.23)	264.3 (160)	254.9 (167)	332
T_{max}, h†	2.5 [2.0, 4.0]	2.0 [1.0, 4.0]	2.2 [1.0, 4.0]	2.4 [1.0, 4.0]	1.4 [1.0, 2.0]	2.0 [1.0, 4.0]	1.6 [1.0, 2.0]	1.6 [1.0, 2.0]	2.0
$T_{½}$, h	7.4 (1.9)	12	7.9 (1.6)	16.1 (2.3)	13	7.8 (2.4)	14.2 (2.3)	13.2 (1.5)	10 - 14
RA	NA	1.20 (0.10)	NA	1.05 (0.64)	1.38 (0.54)	NA	1.44 (0.75)	1.94 (0.68)	2

Geometric mean (SD) data are presented, unless otherwise noted.

RA = AUC_{last} (Day N)/AUC_{last} Day 1

* Shaded cells are historical values for IV ATO (Trisenox®) calculated from data in NDA #21-248.

† Median [min, max].

PK parameters AsV

	ORH-2014 5 mg		ORH-2014 10 mg			ORH-2014 15 mg		
	Day 1 (N=3)	**Day 15 (N=3)**	**Day 1 (N=6)**	**Day 15 (N=5)**	**Day 22 (N=2)**	**Day 1 (N=3)**	**Day 15 (N=3)**	**Day 22 (N=3)**
C_{max}, ng/mL	0.82 (0.16)	0.25 (0.09)	2.5 (1.6)	1.93 (1.4)	3.58 (2.7)	4.8 (1.2)	27.37 (13.85)	25.43 (10.74)
$AUC_{0\text{-}24,}$ ng•h/mL	1.69 (1.2)	5.97 (3.5)	14.2 (8.5)	14.79 (15.2)	34.47 (2.4)	29.3 (24.2)	264.3 (160)	254.9 (167)
T_{max}, h†	1.6 [1.0, 4.0]	1.6 [1.0, 2.0]	2.2 [1.0, 4.0]	2.0 [1.0, 2.0]	2.8 [1.0, 8.0]	2.5 [2.0, 4.0]	1.6 [1.0, 2.0]	1.6 [1.0, 2.0]
$T_{½}$, h	ND	ND	ND	ND	ND	6.4 (0.4)	12.6 (4.9)	10.7 (1.9)
RA	NA	3.54 (7.1)	NA	1.03 (0.93)	1.84 (1.21)	NA	1.76 (0.64)	1.89 (1.12)

Geometric mean (SD) data are presented, unless otherwise noted.

RA = AUC_{last} (Day N)/AUC_{last} Day 1

† Median [min, max].

ND = not determined due to insufficient data

PK parameters DMA

	ORH-2014 5 mg		ORH-2014 10 mg			ORH-2014 15 mg		
	Day 1 (N=3)	**Day 15 (N=3)**	**Day 1 (N=6)**	**Day 15 (N=5)**	**Day 22 (N=2)**	**Day 1 (N=3)**	**Day 15 (N=3)**	**Day 22 (N=3)**
C_{max}, ng/mL	4.68 (1.11)	20.35 (3.68)	6.49 (2.78)	24.7 (12.6)	45.46 (31.9)	7.27 (8.2)	42.82 (18.9)	41.32 (20.9)
$AUC_{0\text{-}24,}$ ng•h/mL	71.53 (26.5)	134.8 (18.1)	74.92 (29.5)	277 (354.5)	910.6 (636.9)	75.27 (80.8)	604.1 (551.4)	819.2 (448.4)
T_{max}, h†	24 [24.0, 24.0]	4.3 [0, 8.0]	24 [24.0, 24.0]	16.3 [1.0, 24.00]	12 [0.0, 24.0]	24 [24.0, 24.0]	8.2 [0.0, 24.0]	12 [0.0, 24.0]
$T_{½}$, h	ND	ND	ND	ND	ND	ND	ND	ND
RA	NA	1.88 (1.02)	NA	3.53 (3.00)	10.12 (3.70)	NA	8.03 (0.74)	10.88 (5.26)

Geometric mean (SD) data are presented, unless otherwise noted.

RA = AUC_{last} (Day N)/AUC_{last} Day 1

† Median [min, max].

ND = not determined due to insufficient data

PK parameters MMA

	ORH-2014 5 mg		ORH-2014 10 mg			ORH-2014 15 mg		
	Day 1 (N=3)	**Day 15 (N=3)**	**Day 1 (N=6)**	**Day 15 (N=5)**	**Day 22 (N=2)**	**Day 1 (N=3)**	**Day 15 (N=3)**	**Day 22 (N=3)**
C_{max}, ng/mL	1.25 (0.33)	4.55 (1.18)	3.51 (1.38)	10.21 (4.45)	1.27 (4.6)	5.56 (2.09)	22.01 (10.87)	24.25 (10.95)
$AUC_{0\text{-}24,}$ ng•h/mL	20.59 (5.62)	29.46 (8.59)	53.24 (25.21)	107.4 (121.5)	268.3 (108.3)	68.23 (34.01)	338.8 (269.5)	481.38 (235.6)
T_{max}, h†	12 [12.0, 12.0]	5.3 [0.0, 8.0]	19 [12.0, 24.0]	10 [8.0, 4.00]	4.3 [0.0, 8.0]	24.0 [24.0, 24.0]	4.2 [0.0, 12.0]	8.0 [0.0, 12.0]
$T_{½}$, h	ND	ND	ND	ND	ND	ND	ND	ND
RA	NA	1.43 (0.76)	NA	1.81 (2.56)	4.71 (3.08)	NA	4.97 (1.73)	7.06 (0.1)

Geometric mean (SD) data are presented, unless otherwise noted.

RA = AUC_{last} (Day N)/AUC_{last} Day 1

† Median [min, max].

ND = not determined due to insufficient data