HBI-3000: A Novel Drug for Conversion of Atrial Fibrillation - Phase 1 Study Results

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Introduction

- HBI-3000 (sulcardine sulfate trihydrate; Bai, et al. 2012) is a multi-ion channel blocker with effects on $I_{Na\text{-}Peak}$, $I_{Na\text{-}Late}$, $I_{Ca,L}$, and I_{Kr} with similar in vitro potencies across these various ion channels in human atrial cardiomyocytes. It is being developed by HUYA Bioscience International® (HUYABIO™) for the conversion of recent onset atrial fibrillation (AF).
- At the cellular level, HBI-3000 reduces maximum depolarization speed (V_{max}) and amplitude of the cardiac action potential (APA), decreases excitability and prolongs action potential duration (APD) and the effective refractory period (ERP) with modest rate dependency (Guo D, et al. 2011)
- In aggregate, HBI-3000 effects on ion channels have the potential to reduce conduction velocity, prolong APD and ERP and inhibit early afterdepolarizations (EADs)
- In multiple nonclinical models, HBI-3000 demonstrated antiarrhythmic effects with low risk for proarrhythmia
- We report here the safety, tolerability, pharmacokinetics (PK) and electrocardiogram (ECG) results of the first-in-human Phase 1 trial of intravenous (IV) HBI-3000 (NCT03397641)

Study Design

- A Phase 1, randomized, double-blind, placebo-controlled, serial cohort, dose-escalation study approved by the Medicines and Healthcare products Regulatory Agency (MHRA) and a UK National Research Ethics Committee was conducted at Quotient Sciences, Nottingham UK to assess the safety, tolerability and PK of HBI-3000 in healthy adult subjects. Extensive electrocardiography was also performed.
- Forty seven (47) subjects were randomized to 6 cohorts of 8 subjects each to receive 1 of 5 single ascending IV dose levels of HBI-3000 or placebo (6:2), with 2 cohorts receiving 600 mg
- PK samples were collected at pre-dose, 0.25, 0.5, 1, 2, 4, 6, 8, 12, 16, 24, 30, 36, 48 and 72 hours post-dose. Standard PK parameters were calculated.
- Continuous 12-lead Holter ECG data were recorded and ECGs were extracted at baseline (pre-dose) and 11 time points thereafter on Day 1 and at time-matched points on Day -1.
- Mean baseline subtracted (Δ) and baseline + placebo subtracted (ΔΔ) ECG intervals (QTcF, HR, PR, QRS, and P-wave duration [PDur]) and T-wave segments (J to T peak [JTp] and T peak to T end [TpTe]) were calculated at each PK time point, and values at C_{max} for each dose level were estimated by concentration-effect modeling.
- Vital signs and safety labs were monitored periodically throughout the 48 hours post-dose

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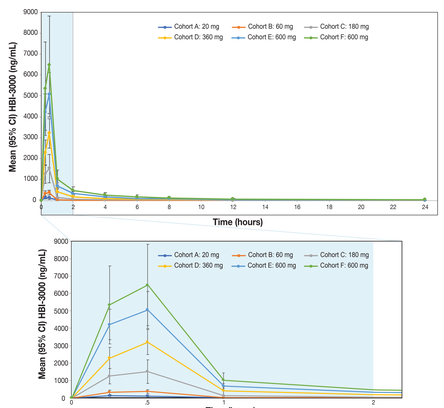
HUYABIO would like to thank our partners at the Shanghai Institute of Materia Medica (SIMM), especially Drs. Yiping Wang and Donglu Bai; Quotient Sciences for their work as the Phase 1 study site; and the team at AMPS for their expertise in processing the ECG data. We also thank HUYABIO colleagues Drs. Reid Bissonnette, Bob Goodenow, Yazhong Pei, Alain Rolland, Laurie Rosenberg, and Curtis Tyree for their scientific contributions to the Phase 1 program. *HBI-3000 AHA Poster Ver 1.0 12 Nov 2019*

Subject Dispositon

In total, 12 subjects were randomised to placebo and 35 were randomised to active treatment with HBI-3000 as follows:
6 subjects in each dose group received 20 mg, 60 mg and 180 mg; 5 subjects received 360 mg; and 12 subjects received 600 mg.

Pharmacokinetics

Figure 1. Mean HBI-3000 Plasma Concentrations Following a Single IV Infusion of 20, 60, 180, 360, or 600 mg HBI-3000



- Median plasma time to maximum concentration (T_{max}) following a single IV dose was 0.5 hour [95% confidence intervals (CI) ranging from 0.25-0.50] over the higher dose range of 180 mg to 600 mg HBI-3000
- Mean maximum plasma concentration (C_{max}) for HBI-3000 IV doses of 20 mg to 600 mg (Cohorts E and F) ranged from 131 to 5580 ng/mL, with a range of area under the concentration-time curve from time 0 to 24 hours ($AUC_{[0\text{-}24]}$) from 89.7 to 5810 ng•hours/mL
- Increases in exposure, as measured by C_{max} and AUC from time 0 to last measurable concentration ($AUC_{[0\text{-}last]}$) were approximately dose proportional or slightly greater than proportional over the 180 mg to 600 mg dose range
- Exposures rapidly declined (~10-fold) within 1-2 hours post infusion (Figure 1), likely associated with distribution into peripheral compartments

References:
Bai at al., Discovery of N-(3,5-bis(1-pyrrolidylmethyl)-4-hydroxybenzyl)-4- methoxybenzenesulfamide (sulcardine) as a novel anti-arrhythmic agent. Acta Pharm Sinic. 2012; 33: 1176–1186.
Guo, D, et al. Electrophysiological Properties of HBI-3000: A New Antiarrhythmic Agent with Multiple-channel Blocking Properties in Human Ventricular Myocytes. J Cardiovasc Pharm 2011;57:79-85.
Johannesen L, et al. Differentiating drug-induced multichannel block on the electrocardiogram: randomized study of dofetilide, quinidine, ranolazine, and verapamil. Clin Pharmacol Ther. 2014; 96:549–558.

Electrocardiogram

Dose-related increases in ECG parameters were observed following HBI-3000 administration, with maximum effect invariably occurring at the highest dose level (600 mg) at the end of infusion (T_{max} 0.5 hour) (Figures 2-5). The concentration-effect models combining all doses of HBI-3000 are summarized (Table 1), and example plots are shown (Figures 6-9).

Figures 2-5. ΔΔECG Parameters over Time

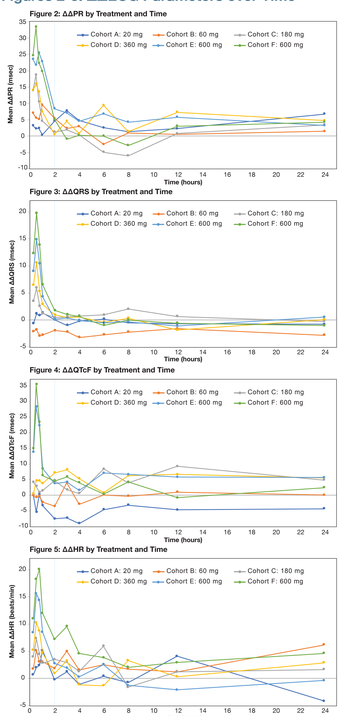
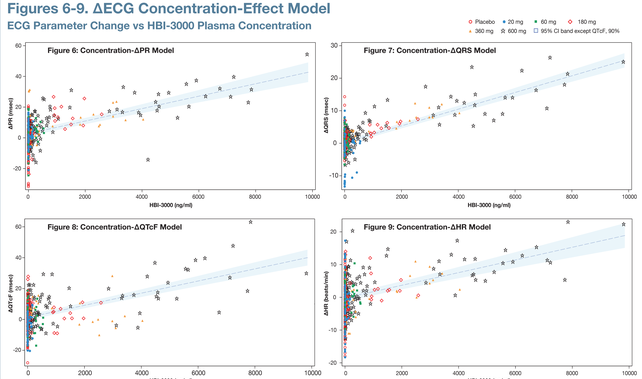


Table 1. Predictions of ΔΔECG at C_{max} by Dose level Using a Concentration-Effect Regression Model, Values Are Mean (95% CI) Except for QTcF (90% CI)

C_{max} Arithmetic Mean (Dose)	QTcF (msec)	HR (beats/min)	PR (msec)	QRS (msec)	PDur (msec)	JTp (msec)	TpTe (msec)
135 ng/mL (20 mg)	**1.40** (-2.1, 4.9)	**1.74** (-0.5, 4.0)	**5.08** (1.4, 8.7)	**-0.08** (-1.5, 1.4)	**3.17** (-0.5, 6.9)	**-2.87** (-7.6, 1.8)	**1.95** (-0.5, 4.4)
378 ng/mL (60 mg)	**2.35** (-1.1, 5.8)	**2.21** (-0.1, 4.5)	**6.06** (2.4, 9.7)	**0.54** (-0.9, 2.0)	**3.71** (0.0, 7.4)	**-5.28** (-10.0, -0.6)	**2.20** (-0.2, 4.6)
1530 ng/mL (180 mg)	**6.89** (3.4, 10.4)	**4.44** (2.2, 6.7)	**10.73** (7.0, 14.4)	**3.50** (2.0, 5.0)	**6.24** 2.5, 9.9)	**-15.09** (-20.2, -10.0)	**3.37** (0.9, 5.8)
3120 ng/mL (360 mg)	**13.50** (9.8, 17.2)	**7.70** (5.2, 10.2)	**17.53** (13.5, 21.6)	**7.81** (6.2, 9.4)	**9.93** (6.0, 13.9)	**-24.60** (-30.6, -18.6)	**5.07** (2.5, 7.7)
5280 ng/mL (600 mg)	**23.77** (19.4, 28.2)	**12.75** (9.7, 15.8)	**28.10** (23.1, 33.1)	**14.50** (12.6, 16.4)	**15.67** (11.1, 20.3)	**-28.10** (-34.7, -21.5)	**7.72** (4.7, 10.7)
Slope - Linear	0.004	0.002	0.004	0.003	0.002	1.007E-6 Quadratic	0.001
P value	<0.0001	<0.0001	<0.0001	<0.0001	<0.001	<0.0001	<0.0001

Figures 6-9. ΔECG Concentration-Effect Model
ECG Parameter Change vs HBI-3000 Plasma Concentration



- HBI-3000 induced dose-proportional changes in all ECG parameters, which were relatively brief, returned to near baseline in 2 to 4 hours, and closely reflected changes in PK exposures:
  - Heart rate (HR) increased with a strong exposure-response pattern
  - The increases in QRS and PDur are consistent with block of $I_{Na\text{-}Peak}$
  - The increase in the PR interval, due in part to the increase in PDur, is consistent with both $I_{Na\text{-}Peak}$ and $I_{Ca,L}$ inhibition
  - Prolongation of TpTe is consistent with I_{Kr} block, which would be expected, in isolation, to lengthen JTp as well. The observed dose-related reduction of JTp is likely due to counteraction of the effect of HBI-3000 on I_{Kr} through inhibition of both $I_{Na\text{-}Late}$, and $I_{Ca,L}$.

Disclosures: [1] None. [2] Other - Consultant; Significant; HUYABIO. [3] Honoraria; Modest; HUYABIO, Milestone Pharmaceuticals Inc, Research Grant; Modest; Servier Canada.

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Safety

- Single IV infusion of HBI-3000 was well tolerated, with no study discontinuations, serious or dose limiting adverse events, or cardiac arrhythmias observed across doses tested (Tables 2 and 3)
- Mean values for systolic and diastolic blood pressure (BP) were within normal range at all time points. Relevant changes in BP (small decrease in systolic BP with no significant change in mean arterial BP) were observed only at the 600 mg dose and were limited to the first 4 hours post-dose.

Table 2. Summary of All Treatment Emergent Adverse Events (TEAEs)

TEAEs by Category	All Placebo (N=12)	All Active (N=35)	Dose of HBI-3000 20 mg (N=6)	60 mg (N=6)	180 mg (N=6)	360 mg (N=5)	600 mg (N=12)
Total	9	20	2	4	0	2	12
Related	1	6	0	0	0	0	6
Leading to infusion stop	0	0	0	0	0	0	0
Leading to trial stop	0	0	0	0	0	0	0
Severe	0	0	0	0	0	0	0
Serious	0	0	0	0	0	0	0
Leading to death	0	0	0	0	0	0	0

Table 3. Summary of Possibly Related Adverse Events (AEs)

Possibly Related AEs	All Placebo, N=12 n (%)	All 600 mg, N=12 n (%)
Dysgeusia	0	2 (17%)
Dizziness	0	1 (8%)
Headache	0	1 (8%)
Paraesthesia	0	1 (8%)
Hypoesthesia oral	0	1 (8%)
Administration site extravasation	1 (8%)	0

Summary of Conclusions

- These results demonstrate that HBI-3000 elicits ECG changes consistent with its mechanism as a potent inhibitor of multiple cardiac ion channels that play a role in onset and maintenance of AF
- The HBI-3000 mediated strong reduction of JTp may predict freedom from arrhythmias associated with I_{Kr} block (Johannesen L, et al. 2014)
- The PK profile of HBI-3000 with attendant rapid redistribution to peripheral compartments may be well suited for pharmacologic cardioversion of acute/paroxysmal atrial fibrillation as an alternative to electrical cardioversion, avoiding prolonged residual effects on cardiac conduction and risk of drug induced arrhythmia
- Based on these results the drug is now entering Phase 2 in recent onset AF