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

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Introduction

HBI-3000 (suilsodine sulfa triamide) (Bai et al., 2012) is a multi-channel blocker of effects on \( I_{Na-Late} \) and \( I_{Kr} \) with similar in vitro potency across these three channels in human atrial cardiomyocytes. It is being developed by HUYA Bioscience International (HUYA/BIO) for the conversion of recent onset atrial fibrillation (AF).

At the cellular level, HBI-3000 reduces maximum depolarization speed (\( V_\text{max} \)) and amplitude of the cardiac action potential (AP), decreases excitability and prolongs action potential duration (APD) in a time-dependent manner with a modest rate dependency (Gou 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 depolarizations (EADs).

In multiple animal models, HBI-3000 demonstrated anti-arrhythmic effects with low risk for proarrhythmia.

We report here the safety, tolerability, pharmacokinetics (PK) and electrocardiographic (ECG) results of the first-in-human Phase 1 trial of intravenous (IV) HBI-3000 (NCT03979471).

Study Design

A Phase 1, randomized, double-blind, placebo-controlled, serial cohort, dose-escalation study approved by the Medical and Healthcare products Regulatory Agency (MHRA) and a UK National Research Ethics Committee was conducted at Quotient Bioscience International, 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 (8), with 2 cohorts receiving 60 mg.

PK samples were collected at pre-dose, 0.25, 0.5, 1, 2, 4, 6, 13, 16, 24, 30, 48, and 72 hours post-dose. Standard PK parameters were calculated.

Continuous lead Holter ECG data were recorded and ECGs were extracted at baseline (pre-dose) and at 11 time points thereafter on Day 1 and at time-matched points on Day -1.

Mean baseline subtracted (+40 ms) and baseline subtracted (40 ms) ECG parameters (QTcF, QTc, HR, PR, and P-wave duration [PD]) and T-wave segments (T offset [τT], T offset to T onset [Tc], and Tc to Tp [Tp]) were calculated at each PK time point, and values at Cmax for each dose level were estimated by concentration-effect modeling.

Vital signs and safety labs were monitored periodically throughout the study.

Pharmacokinetics

In total, 12 subjects were randomized to placebo and 35 were randomized 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.

Subject Disposition

All Placebo, \( N=12 \)

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 dose levels (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 (usual decrease in systolic BP with no significant change in diastolic BP) were observed only at the 600 mg dose and were limited to the first 4 hours post-dose.

Dosages of HBI-3000 and number of subjects: Placebo, \( N=12 \), Cohort A: 20 mg, \( N=12 \), Cohort B: 60 mg, \( N=12 \), Cohort C: 180 mg, \( N=12 \), Cohort D: 360 mg, \( N=12 \), Cohort E: 600 mg, \( N=12 \).

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

<table>
<thead>
<tr>
<th>TEAEs</th>
<th>Placebo</th>
<th>Cohort A: 20 mg</th>
<th>Cohort B: 60 mg</th>
<th>Cohort C: 180 mg</th>
<th>Cohort D: 360 mg</th>
<th>Cohort E: 600 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>0</td>
<td>2</td>
<td>4</td>
<td>30</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Leading to stop</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Leading to trial stop</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<td>0</td>
</tr>
<tr>
<td>Serious</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Leading to hospitalisation</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>None.</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Mean baseline subtracted (40 ms) and baseline + placebo subtracted (0 ms) ECG parameters (QTcF, QTc, HR, PR, and P-wave duration [PD]) and T-wave segments (T offset [τT], T offset to T onset [Tc], and Tc to Tp [Tp]) were calculated at each PK time point, and values at Cmax for each dose level were estimated by concentration-effect modeling.

• Median plasma time to maximum concentration (\( T_{\text{max}} \)) following a single IV dose was 0.5 hour (95% confidence intervals (CI) ranging from 0.25-0.65) over the higher dose range of 180 mg to 600 mg HBI-3000.

• Maximum plasma concentration (\( C_{\text{max}} \)) for HBI-3000 IV peaked within 1-2 hours post-dose. Standard PK parameters were calculated.

• Increases in exposure, as measured by Cmax from time 0 to last measurable concentration (AUC \( _{\text{0-}24} \)) and baseline + placebo subtracted ECG parameters (QTcF, QTc, HR, PR, and P-wave duration [PD]) and T-wave segments (T offset [τT], T offset to T onset [Tc], and Tc to Tp [Tp]) were calculated at each PK time point, and values at Cmax for each dose level were estimated by concentration-effect modeling.

• Vital signs and safety labs were monitored periodically throughout the study.

Electrocardiogram

Heart rate (HR) increased with a strong exposure-response pattern with \( T_{\text{max}} \) ranging from 0.25-0.50 over the higher dose range of 180 mg to 600 mg of HBI-3000. Exposures rapidly declined (~10-fold) within 1-2 hours post-dose.

Increases in exposure, as measured by Cmax from time 0 to last measurable concentration (AUC \( _{\text{0-}24} \)) for HBI-3000 IV and AUC from time 0 to last measurable concentration (AUC \( _{\text{0-}24} \)) following oral administration of HBI-3000 were summarized (Table 1), and example plots are shown (Figures 6-9).

Mean baseline subtracted (+40 ms) and baseline subtracted (40 ms) ECG parameters (QTcF, QTc, HR, PR, and P-wave duration [PD]) and T-wave segments (T offset [τT], T offset to T onset [Tc], and Tc to Tp [Tp]) were calculated at each PK time point, and values at Cmax for each dose level were estimated by concentration-effect modeling.

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:

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Summary of Conclusions

• These results demonstrate that HBI-3000 exerts ECG changes consistent with its mechanism as a potent inhibitor of multiple cardiac ion currents. Its effects were dose-dependent and remained consistent with its mechanism as a potent inhibitor of multiple cardiac ion currents.

• The HBI-3000 mediated strong reduction of JTp may be consistent with its mechanism as a potent inhibitor of multiple cardiac ion currents.

• 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.

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• The increase in the PR interval, due in part to the increase in PDR, is consistent with both \( I_{Na-Late} \) and \( I_{Kr} \) inhibition.

• Proarrhythmia of Tp wave is consistent with \( I_{Na-Late} \) block, which would be expected, in isolation, to lengthen JTp as well. The observed dose-related reduction of \( I_{Na-Late} \) is likely due to concomitant inhibition of all the \( I_{Na-Late} \) currents, leading to death

• HBI-3000 is a possibly useful alternative to electrical cardioversion, avoiding prolonged cardioversion with a consistent with its mechanism as a potent inhibitor of multiple cardiac ion currents.

• The PK profile of HBI-3000 with attendant rapid redistribution to peripheral compartments may be well suited for pharmacologic cardioversion of acute/persistent atrial fibrillation as an alternative to electrical cardioversion, avoiding prolonged residual effects on cardiac conduction and risk of drug induced arrhythmia.