HBI-3000: Pharmacological Conversion of Atrial Fibrillation with Unique Defense Against Excessive QT Interval Prolongation

Jay W. Mason MD[1], Denis Roy MD[2], Gary T. Elliott PhD[3], Suzanne J. Romano PhD[4], Charles Pollack MD[5], Mireille Gillings PhD[4], Jerome B. Riebman MD[4]

[1]Univ. Utah, Salt Lake City UT, U.S.
[2]Montreal Heart Institute, Univ. Montreal, Montreal, QC, Canada
[3]Galenic Strategies, Evergreen CO, U.S.
[4]HUYABIO International, San Diego CA, U.S.
[5]Univ. Mississippi Medical Center, Jackson, MS, U.S.

Acknowledgements: HUYABIO thanks our partners at the Shanghai Institute of Materia Medica (SIMM), especially Drs. Yiping Wang and Donglu Bai.

Author Disclosures

Jay W. Mason MD – Consultant to HUYABIO

Denis Roy MD – Consultant to HUYABIO

Gary T. Elliott PhD – Consultant to HUYABIO

Suzanne J. Romano PhD – HUYABIO employee

Charles Pollack MD – Consultant to HUYABIO

Mireille G. Gillings PhD - HUYABIO employee

Jerome B. Riebman MD - HUYABIO employee

Sulcardine Has An Intrinsic Mechanism to Protect from Excessive QT Prolongation

- Sulcardine sulfate, HBI-3000, is a **new antiarrhythmic drug (AAD) that blocks multiple cardiac ion channels** including $I_{Na\text{-}peak}$, $I_{Na\text{-}late}$, $I_{Ca,L}$ and I_{Kr} (hERG) with similar potencies.
- A major limitation of many AADs is **malignant proarrhythmia** due to excessive hERG channel block-mediated repolarization delay, manifested by **QT prolongation** due largely to prolongation of the J to T peak interval [JTp].
- At therapeutic doses sulcardine's ion channel flux during early repolarization is **perfectly balanced** to provide an **intrinsic mechanism of protection** from excessive QT prolongation, differentiating it from other AADs.

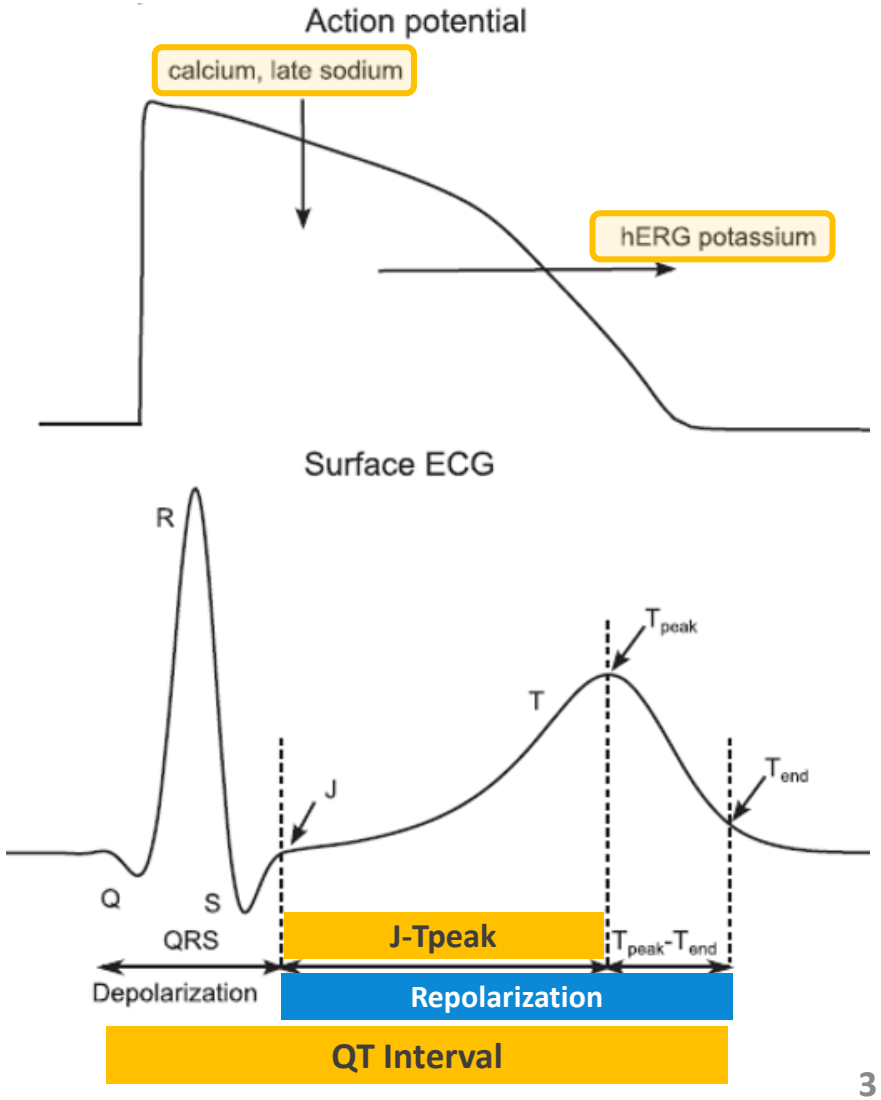


Figure adapted from Vicente at al, Clin Pharm & Therap. 99:214, 2016

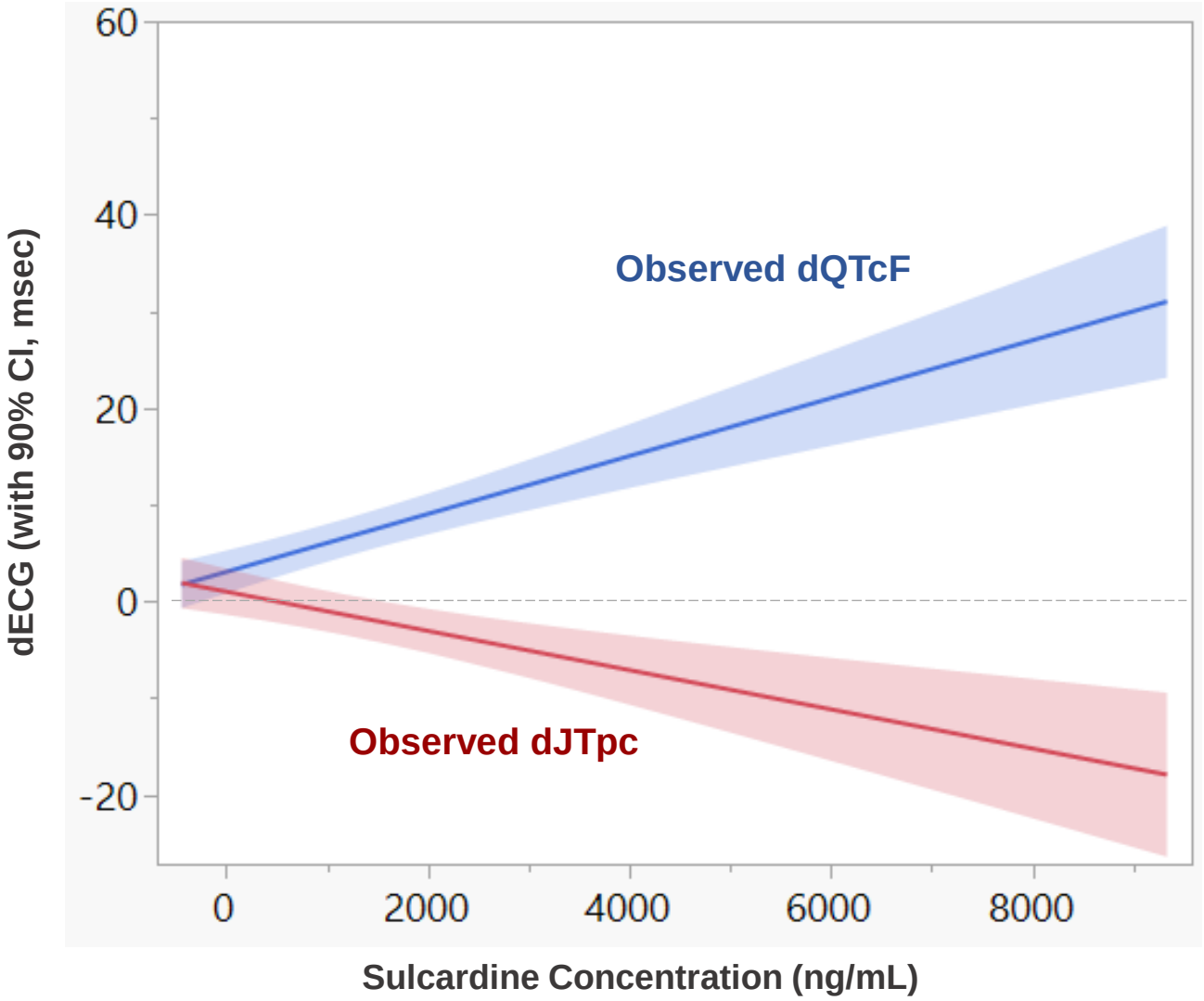
Sulcardine's Protective JTp Effect Was Investigated in AF Patients

Hypothesis: We proposed that by shortening JTp sulcardine would reduce early repolarization prolongation and thereby limit overall QT prolongation in patients with AF.

Methods:

- Ten patients in AF with onset within 72 hours received 350 mg of sulcardine IV (the anticipated clinical dose) over 30 min in a Phase 2 open-label study.
- Sulcardine plasma concentrations and ECG intervals (from 5-min summary ECGs) were obtained at baseline and several time points after treatment.
- Mean baseline-subtracted, heart rate-corrected QTcF (dQTcF) and JTp (dJTpc; Johannesen's method) were calculated at each time point.
- Relationships between plasma concentration, dQTc prolongation, and dJTPc were examined.
- These patient data were compared to similar analyses in normal volunteers in two earlier studies.

In Acute AF, Sulcardine Induced Modest QTcF Prolongation with A Uniquely Strong JTpc *Reduction*



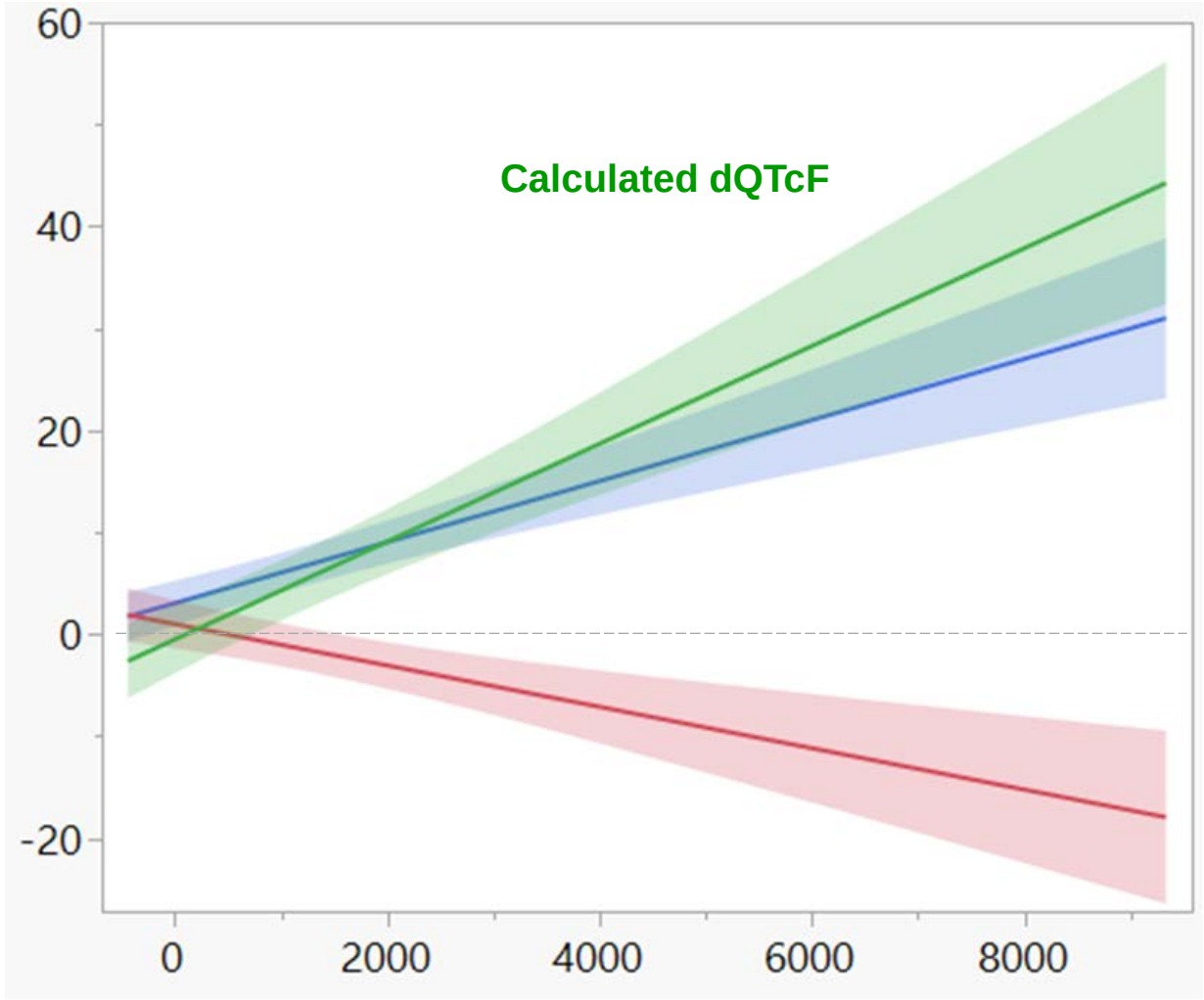
Observed dQTcF

- Modestly prolonged, less than expected
- Changes linear with plasma concentration

Observed dJTpc

- Strong linear *reduction* as seen in Phase 1
- Unique among AADs used to treat AF

In Acute AF Patients, The Sulcardine-Induced JTpc Reduction Offsets QTcF Prolongation



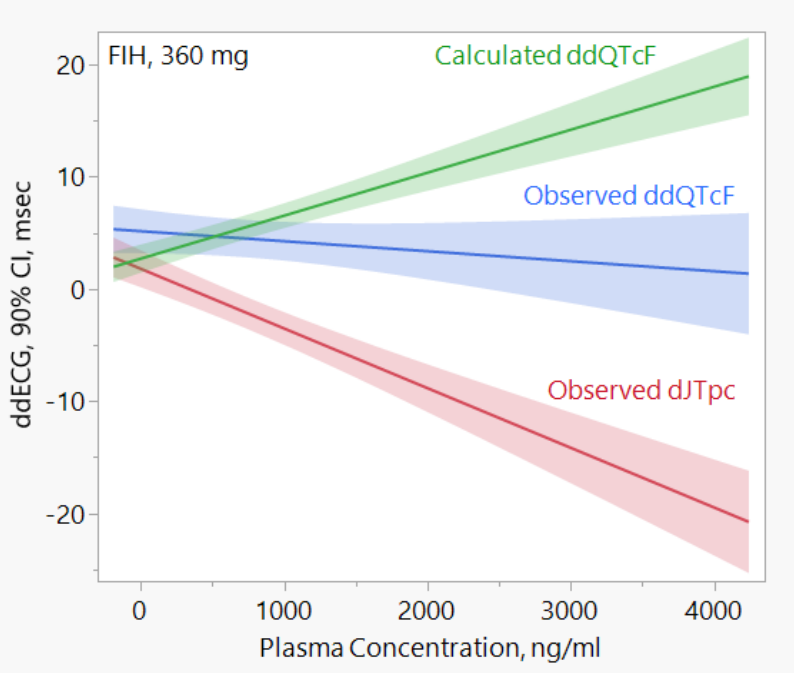
Calculated dQTcF without JTpc reduction

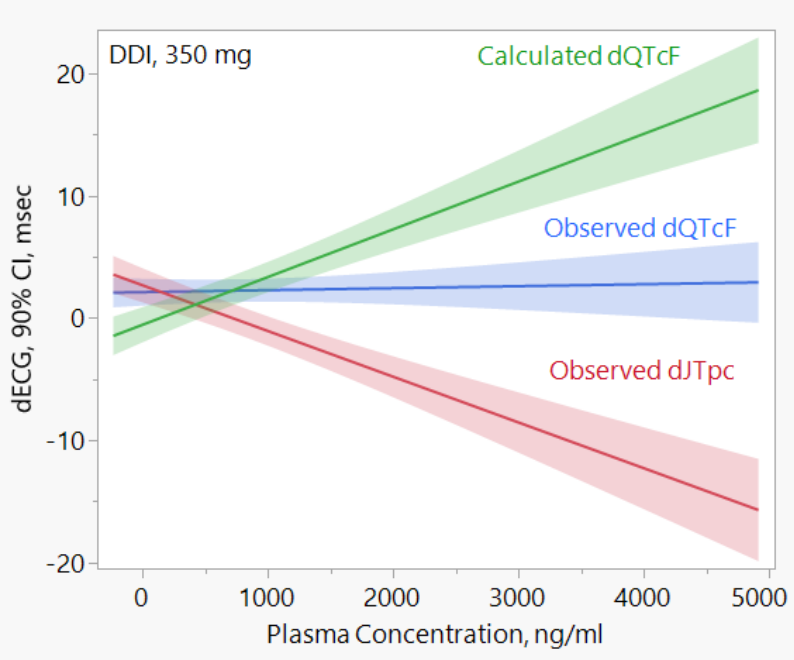
- **Greater dQTcF prolongation than observed**
- **dQTcF would have been 27% higher at Cmax if no change in JTpc had occurred**

Sulcardine's uniquely strong JTp shortening acts as a mechanism to limit excessive QT prolongation, reducing proarrhythmic risk

The Phase 2 Results from AF Patients Validate Findings from Phase 1 Subjects in SR

- Similar results were found in two Phase 1s of healthy volunteers in sinus rhythm. In a first in human (FIH) study and a drug-drug interaction (DDI) study, therapeutic doses of sulcardine (350-360 mg IV) also reversed the lengthening of JTpc.[1,2]
- This **uniquely shortened JTpc *reduced*** the extent of observed **QTcF prolongation** by 76% and 42% at Cmax in the two studies.





1. Mason et al., Circulation. 2019;140:A11495.
2. Mason et al., Presentation: European Society of Cardiology Congress 2024; Sept 01, 2024; London, UK.

Conclusion: Sulcardine Demonstrates Uniquely Powerful Self-Defense Against Excess QT Prolongation

Hypothesis Validation

- Three separate studies in human subjects and AF patients consistently showed JTp shortening with blunting of the extent of QT prolongation due to a **unique pattern of channel fluxes that shortens early repolarization**.

Novel Protective Mechanism

- We believe this effect is mediated by sulcardine's inhibition of $I_{Na\text{-}late}$ and $I_{Ca,L}$, both of which shorten the JTp interval. This protective profile is probably **unique among QT prolonging drugs used to treat AF** because the necessary inward and outward channel effects occur at therapeutic doses of sulcardine.

Well Tolerated by AF Patients

- Acute IV sulcardine (HBI-3000) was **well-tolerated in acute AF** and resulted in no clinically significant safety findings. Further investigation of this promising drug is underway.