SGK1 Inhibitor LQT-1213 (Islasertib) Promotes Significant Reduction in QTc Prolongation in a Dofetilide-Induced Human Model of Long QT Syndrome (LQTS) in the WAVE I Clinical Study

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Background

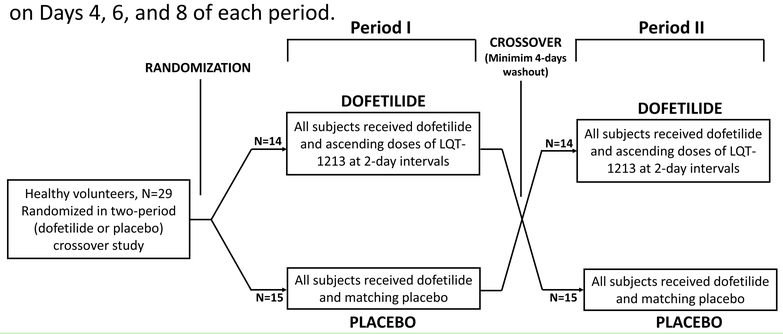
- Prolonged QT interval, due to mutations in cardiac ion channel genes (LQTS, Type 2), or pharmacological blockade of the human ether-a-gogo related (hERG) current, prolongs the QT interval and predisposes to Torsades de Pointe (TdP) and ventricular fibrillation.
- **S**erum and **G**lucocorticoid-regulated **K**inase **1** (SGK1) is a serine-threonine kinase that is activated downstream of insulin, glucocorticoid or calcium signaling pathways in the setting of cardiomyocyte stress.
- In vitro and in vivo activation of SGK1 in cardiomyocytes increases the late sodium current (INaL) leading to prolongation of the action potential duration (APD), and increased propensity for ventricular arrhythmias. While pharmacological or genetic inhibition of SGK1 mitigates the APD prolongation and arrhythmogenesis associated with cardiac stressors.
- Pharmacological inhibition of SGK1 was previously shown to reduce the APD/QTc interval in various preclinical models of congenital and acquired LQTS, including induced pluripotent stem cell cardiomyocytes (iPSC-CM's), guinea pigs, the LQT-2 rabbit model, and in vivo dogs.

AIM

The WAVE I clinical study was conducted to assess the efficacy and safety of LQT-1213, a potent and selective SGK1 inhibitor, in a human model of acquired Long QT Syndrome which may mimic Long QT Syndrome Type 2.

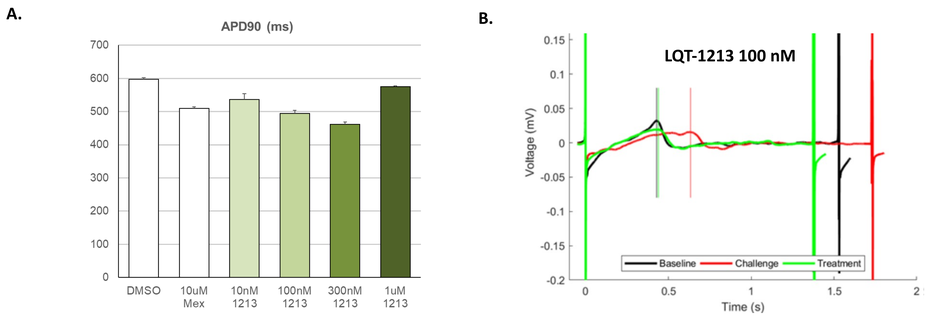
METHOD

- Wave 1 is a 2-treatment, 2-period crossover study.
- Healthy human volunteers were administered dofetilide - 500 µg BID, orally (Days 1-8) and concomitant LQT-1213 (0.25 mg/kg on Day 3 and 4, 0.50 mg/kg on Day 5 and 6, and 0.70 mg/kg on Day 7 and 8) or placebo depending on their treatment group assignment.
- Continuous 12-lead 24-hour Holter data were collected starting 2 hours before dosing on Day 1 to 8. Full PK sampling for dofetilide and LQT-1213 was conducted on Days 4, 6, and 8 of each period.



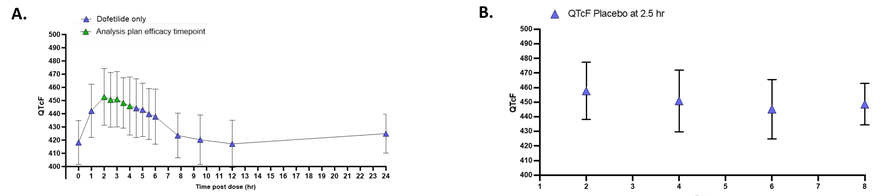
Result

1. LQT-1213 shortens APD in LQT2 patient derived iPSC-CMs and iPSC-CM model of acquired Long QT syndrome.



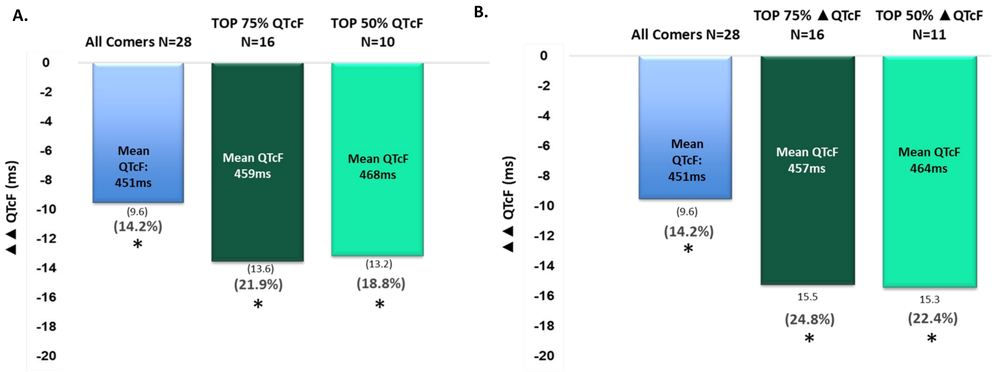
LQT-1213 decreases APD90 of G604S-KCNH2 iPS-CMs, iPS-CMs from a LQT2 patient (A, from: Kim et al., 2023 Heart Rhythm O2. 2023 Feb 16;4(4):268-274) and dofetilide-induced increase in FPD in iPS-CM's (B).

2. Dofetilide increased QTcF in healthy human volunteers



A. Dofetilide treatment led to a predictable and acute increase the QTcF of healthy volunteers; green triangles (△) indicate the timepoints of the primary endpoint analysis of QTcF shortening.
B. Consistent with the dofetilide product monograph, QTcF response lessened during the 8 days of treatment.

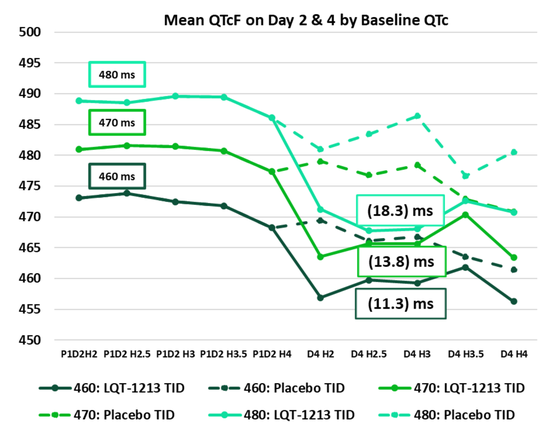
3. Primary Endpoint: LQT-1213 demonstrated significant reductions of dofetilide-induced QTcF prolongation



A. Day 4, 2 hr post-dose, placebo-corrected change from baseline QTcF (ΔΔQTcF) with top 75% and 50% of doetilide responders (based on longest QTcF values) demonstrate LQT-1213 produces statistically and clinically significant placebo corrected QTcF reductions (*P<0.05). B. Significant effect of LQT-1213 on day 4 – 2 hr post dose to reduce the ΔΔQTcF, based on largest ΔQTcF values following administration of dofetilide versus baseline, of 75% and 50% of dofetilide responders (*P<0.05).

Result

4. Patients achieving higher QTcF values on dofetilide alone had greater reductions in their placebo–corrected QTcF as a function of absolute QTcF



Greater QTcF reductions were consistently observed in individuals with larger dofetilide-induced QTc prolongation.

CONCLUSIONS

- Treatment with LQT-1213 demonstrated a statistically and clinically significant reduction in dofetilide-induced QTc prolongation – a model which mimics Long QT Syndrome Type 2.
- QTc shortening effects of LQT-1213 were more pronounced in patients with longer dofetilide-induced QTcF intervals and the largest increases in QTcF-interval from baseline.
- Administration of LQT-1213 was not associated with any clinically significant safety findings in healthy adult subjects also receiving dofetilide. LQT-1213 dosing demonstrated no effects on the PR or QRS intervals. No patients receiving any dose of LQT-1213, experienced prolongation of QTcF.
- **Overall, the WAVE 1 study provides evidence that inhibition of SGK-1 with LQT-1213 has promise as a novel therapeutic to reduce QTcF**.

DISCLOSURES

- The Wave 1 study is sponsored by Thryv Therapeutics Inc.
- Saumya Das, Philip Sager, Pirouz Shamszad, Doug Wight, Alexandre Brkovic and Sabindra Pradhananga have received salary and equity from Thryv Therapeutics.
- Jay Mason and Jan Matousek are consultants for Spaulding Clinical Research.
- Michael J. Ackerman is a consultant for Abbott, Boston, Scientific, Bristol Myers Squibb, Daiichi Sankyo, Invitae, Thryv Therapeutics, and Medtronic.