Attenuation of Drug-Induced QT-Prolongation in Guinea Pig Isolated Heart and Anesthetized Dog Models of Drug-Induced QT Prolongation by Serum/Glucocorticoid Regulated Kinase 1 (SGK-1) Inhibitor

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Background

- Drug-induced QT prolongation (DI-QTP) via inhibition of hERG mimics Long QT Syndrome Type 2 (LQTS2) and is associated with Torsade de Pointes and sudden cardiac death.
- SGK1 inhibitors (SGK1-I) have recently been shown to reduce the action potential duration in a human heart cell model of DI-QTP but this effect has not yet been tested ex vivo or in vivo.

Objective

To test the efficacy of a novel SGK1-I in guinea pig (GP) and dog models of dofetilide-induced DI-QTP.

Methods

Langendorff Study: Hearts from 8 naïve male Dunkin-Hartley GP (range: 0.392−0.630 kg) were prepared for standard Langendorff procedures. The right atria was opened, and the atrioventricular node was mechanically ablated; pacing and recording of ECG data were conducted using a BARD 4F electrode catheter inserted into the right ventricle. Hearts were maintained at approximately 37°C; LVEDP was maintained at approximately 5 mmHg; and pacing was set at 110 bpm for the entire experimental period. ECGs were continuously recorded using the NOTOCORD-hem v4.3 data capture system, with measurements taken every 20 minutes.

Telemetered Dog Study: Non-naïve male and female beagle dogs (n=2/sex; F range: 8.0−8.7 kg; M range: 10.8−12.2 kg) were implanted with a Data Sciences International (St. Paul, MN) telemetry device for ECG evaluation of intravenous administration of an SGK1-I in the absence or presence of dofetilide-induced QT prolongation. The oral gavage administration of dofetilide (150 µg/kg) was followed by a 45-minute monitoring period after which dogs were anesthetized, allowed to stabilize for an average of 25 minutes (range: 19-29 minutes) prior to predose monitoring and then administered both a bolus (1.36 mg/kg over 1 minute) and IV dose (1.31 mg/kg; 0.5 mL/kg/h) of the SGK1-I. Control dogs were administered an equivalent volume of vehicle as a bolus and infusion. Parameters were continuously recorded from 30 minutes prior to dofetilide dosing to 30 minutes following SGK1-I dosing.

Data Analysis: Isolated heart values are presented as either mean ± SD or percent change vs baseline values normalized to dofetilide. Statistical analysis for the isolated heart study was conducted using a one-way ANOVA with Dunnett's post-hoc test. Statistical significance indicated at p<.05.

Values for the telemetered dog study are presented as either mean ± SD or absolute change values to either predose epochs or post-dofetilide dosing, as appropriate. Statistical analysis for the telemetered dog study was conducted using a paired t test on the difference between the baseline QTcH with anesthesia (with dofetilide on board) and the corresponding QTcH with vehicle vs the difference between the baseline QTcH with anesthesia (with dofetilide on board) and the corresponding QTcH with drug. Statistical significance indicated as p<.05.

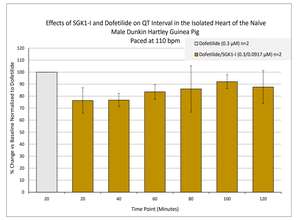
All statistical analyses were performed using GraphPad Prism 10.2.2.

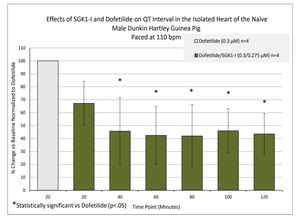
Results

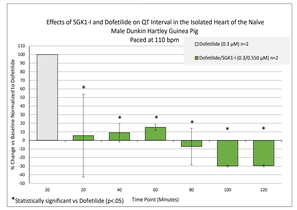
LANGENDORFF STUDY

- A total of 4 hearts were exposed to SGK1-I alone as a control; the baseline QTp in these hearts was 253 ± 8 ms.
  - Exposure of GP hearts to SGK1-I alone led to a concentration-dependent decrease in the QTp interval, with the maximum decrease in QTp interval noted at 100 minutes. following 0.275 µM (-15 ± 7 ms) and at 80 minutes following 0.550 µM (-21 ± 7 ms)
- Exposure of GP hearts to 0.3 µM dofetilide increased the paced QT interval (QTp) from a baseline value of 237 ± 17 ms to 274 ± 14 ms (+37 ± 14 ms; n = 4).

Effect of SGK1-I and Dofetilide on the QTp Interval







- SGK1-I attenuated the dofetilide-induced QTp prolongation in a concentration-dependent manner when compared to the post-dofetilide values:
  - Exposure to 0.0917 µM SGK1-I slightly reduced the dofetilide-induced QTp prolongation over the 120-minute monitoring period, with the maximum change noted at 20 minutes into SGK1-I infusion when QTp was 76% of the dofetilide response (n=2).
  - Exposure to 0.275 µM SGK1-I significantly reduced the dofetilide-induced QTp prolongation from 40−120 minutes, with the maximum change (42% of the dofetilide response) seen at 60 and 80 minutes (n=4).
  - Exposure to 0.550 µM SGK1-I completely abrogated the QTp prolongation, significantly reducing the QTp interval at all time points; the maximum change (-30% when normalized to the dofetilide response) was noted at 120 minutes (n=2).

TELEMETERED DOG STUDY

- No adverse clinical observations were noted during the conduct of this study.
- Baseline hemodynamic and ECG values were similar prior to either dofetilide (non-anesthetized) or vehicle/SGK1-I dosing (anesthetized).

Baseline Hemodynamic and ECG Values in Telemetered Beagle Dogs

Group[a]	Time Period	Baseline Values (Mean ± SD)							
		Hemodynamic Parameters					ECG Parameters		
		SAP (mmHg)	DAP (mmHg)	MAP (mmHg)	PP (mmHg)	HR (bpm)	QRS Duration (ms)	PR Interval (ms)	QTcH Interval (ms)
Dofetilide Oral Gavage (150 µg/kg) + Vehicle Bolus (0 µg/kg), Vehicle Infusion (0 µg/kg)[b]	Pre-Dofetilide (non-anesthetized)	161 ± 19	96 ± 8	120 ± 11	65 ± 18	97 ± 10	40 ± 2	94 ± 15	213 ± 8
	Pre-Vehicle (anesthetized)	75 ± 7	46 ± 5	56 ± 6	29 ± 5	79 ± 7	42 ± 4	107 ± 15	367 ± 27
Dofetilide Oral Gavage (150 µg/kg) + SGK1-I Bolus (1366 µg/kg), SGK1-I Infusion (1308 µg/kg)	Pre-Dofetilide (non-anesthetized)	174 ± 8	108 ± 4	132 ± 3	67 ± 8	93 ± 10	39 ± 2	94 ± 13	211 ± 7
	Pre-SGK1-I (anesthetized)	73 ± 5	44 ± 6	55 ± 6	29 ± 4	70 ± 5	42 ± 4	107 ± 14	391 ± 34

[a] Pooled; n = 4 (Female: n = 2; Male: n = 2).
[b] Vehicle was 5% NMP/20% SBE-β-cyclodextrin in PBS (pH 7.5 ± 0.2).
bpm, beats per minute; DAP, diastolic arterial pressure; HR, heart rate; MAP, mean arterial pressure; No., number; PP, pulse pressure; SAP, systolic arterial pressure; SD, standard deviation.

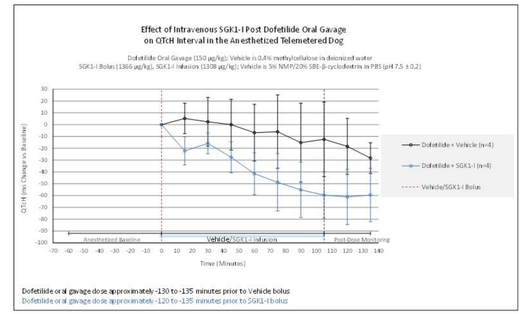
- No effects were noted on any hemodynamic parameter (MAP, SAP, DAP, PP and HR) after dofetilide or subsequent dosing with either vehicle or the SGK1-I.
- No effects were seen on the QRS duration following administration of dofetilide or subsequent dosing with vehicle or the SGK1-I.
- No effects were noted for the PR interval following dofetilide or subsequent vehicle dosing while a very slight decrease in the PR interval was noted (-8 ± 22 ms) at 120 minutes post SGK1-I bolus.
- Dofetilide prolonged the QTcH interval from its baseline by 19 ± 6 ms in vehicle-treated dogs and by 20 ± 3 ms in SGK1-I-treated dogs.
- As expected, the QTcH interval further increased following anesthesia; however, the absolute QTcH values were similar prior to vehicle and SGK1-I administration (see Table 2).
- IV administration of SGK1-I (1.36 mg/kg, bolus dose) + 1.31 mg/kg (maintenance dose) substantively decreased the QTcH interval while vehicle only mildly decreased the QTcH interval at the end of the 105-minute infusion period as well as during the post-dose monitoring period when assessed as change from the post-anesthetic baseline.

Absolute QTcH Changes from Respective Baseline Values

Changes in QTcH Interval at Defined Experimental Periods (ms; Mean ± SD)				
Group[a]	45 minutes post dofetilide bolus[b]	Time Post Vehicle/SGK1-I Bolus[c]		
		105 min	120 min	135min
Dofetilide Oral Gavage (150 µg/kg) + Vehicle Bolus (0 µg/kg), Vehicle Infusion (0 µg/kg)[d]	-19 ± 6	-12 ± 31	-18 ± 24	-28 ± 13
Dofetilide Oral Gavage (150 µg/kg) + SGK1-I Bolus (1366 µg/kg), SGK1-I Infusion (1308 µg/kg)	-20 ± 3	-60 ± 20	-61 ± 23	-59 ± 23

[a] Pooled: n = 4 (Female: n = 2; Male: n = 2).
[b] Change from pre-dofetilide (non-anesthetized) baseline value.
[c] Change from (anesthetized) baseline value prior to vehicle/SGK1-I bolus.
[d] Vehicle was 5% NMP/20% SBE-β-cyclodextrin in PBS (pH 7.5 ± 0.2).

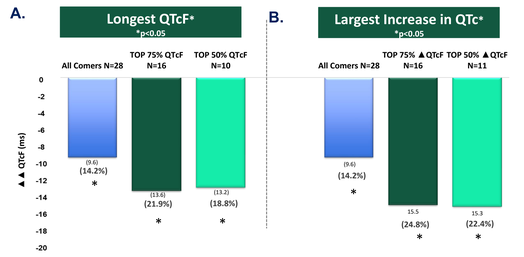
QTcH Interval Absolute Change from Baseline following Vehicle or SGK1-I Dosing



Dofetilide oral gavage dose approximately -130 to -135 minutes prior to Vehicle bolus
Dofetilide oral gavage dose approximately -120 to -135 minutes prior to SGK1-I bolus

HUMAN CONFIRMATORY STUDY

SGK1-I Demonstrated Significant Reductions of Dofetilide-Induced QTcF Prolongation in a Dofetilide-Induced Human Model of LQTS in WAVE I Clinical Trial (NCT05906732)



A. Day 4: 2-hour post-dose, placebo-corrected change from baseline QTcF (ΔΔQTcF) with top 75% and 50% of dofetilide responders (based on longest QTcF values) demonstrate SGK1-I produces statistically and clinically significant placebo corrected QTcF reductions (*p < .05).
B. Significant effect of SGK1-I on Day 4 at 2 hours 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 < .05). Data presented as a poster at ACC2024.

Conclusions

Consistent with previously reported findings in a human heart cell model of drug-induced QT prolongation, a robust attenuation of drug-induced QT prolongation by a novel SGK1-I was observed in both guinea pig (ex vivo) and dog (in vivo) models. The preclinical study findings are further confirmed in a human study (Das et al., J Am Coll Cardiol. 2024 Apr, 83 (13_Supplement) 185), which further warrants the continued development of SGK1-I as a novel therapeutic for DI-QTP and Long QT Syndrome Type 2.

References

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Disclosures

CorDynamics, Inc. is a Contract-Research Organization that was contracted by Thryv Therapeutics, Inc. to conduct the preclinical studies.