IQ-CSRC PROSPECTIVE QTc STUDY

Study Design and Choice of Drugs

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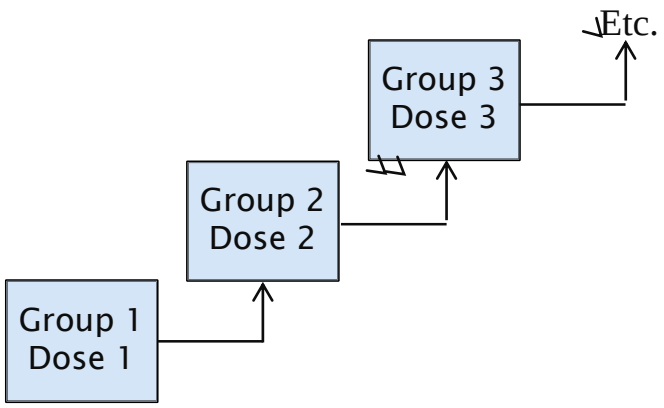
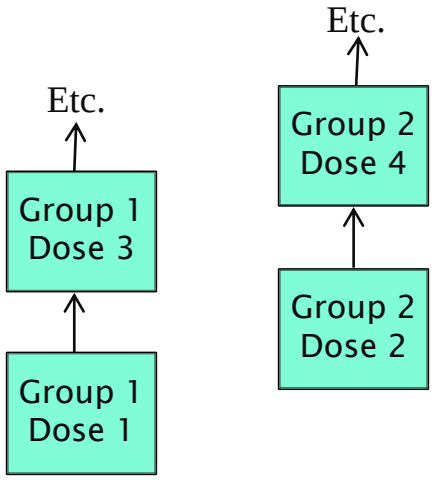
Background

- SAD studies can reliably assess QTc prolongation if proper ECG collection, centralized ECG analysis and CEM are used
- First-in-Human SAD studies assess PK/tolerability at the future therapeutic and supratherapeutic doses
  - Commonly includes supratherapeutic dose in TQT study
- Typical SAD designs using healthy subjects:

5-8 PARALLEL SEQUENTIAL COHORTS
N = 8 per cohort (6 on active, 2 on placebo)

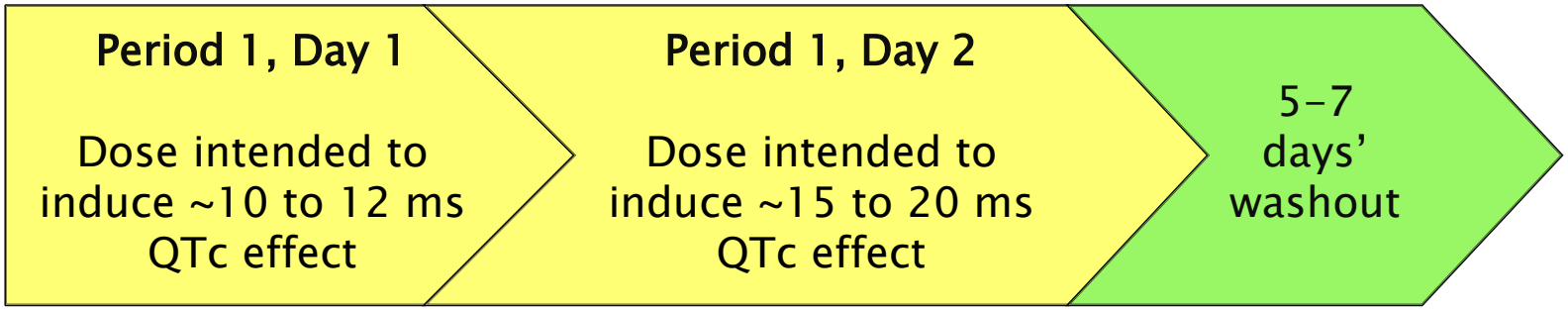


2-3 ALTERNATING PANELS
N = 9-12 per cohort (active)



Study design

- Goal: mimic the typical SAD as much as possible
- Double-blind, randomized, placebo controlled study
- Population: 20 male and female healthy subjects
- Each subject was to undergo 3 treatment periods
- Fixed dosing sequence (low → high) on 2 consecutive days in each period:



- Standardized robust experimental conditions as in TQT studies
- Continuous ECG acquisition and processing as in TQT studies
- Primary analysis based on exposure QTc - response modeling.

Randomization Schema

Cohort	Subject	Period 1	Period 2	Period 3
1	1	A	B	C
1	2	B	C	A
1	3	C	A	B
1	4	C	B	A
1	5	B	A	C
1	6	A	C	B
1	7	P	C	B
1	8	C	P	A
1	9	B	A	P
1	10	A	B	C
2	11	D	E	F
2	12	E	F	D
2	13	F	D	E
2	14	F	E	D
2	15	E	D	F
2	16	D	F	E
2	17	P	F	E
2	18	F	P	D
2	19	E	D	P
2	20	D	E	F

Incomplete block design:
Of subjects on each active, 2 were also dosed with placebo

- 2 cohorts (n=10 each)
- Placebo pooled from both cohorts
- 9 subjects were to receive each of 6 active treatments
- 6 subjects were to receive placebo
- Goal: have at least 5 on placebo and 6 on each active

A - Ondansetron
B - Quinine
C - Dolasetron
D - Moxifloxacin
E - Dofetilide
F - Levocetirizine
P - Placebo

ECG collection and analysis

- All experimental conditions were analogous to the TQT study
- Fasting for 8 hours before and 4 hrs after dosing on Day 1 and 2
- 3rd party dosing with subjects blindfolded
- Standardized composition and timing of meals
- Strict control of the autonomic tone for 15 minutes (10 min before and 5 min after the nominal time point for ECG extraction)
- Vital signs and blood draws only after the nominal ECG time point.
- Continuous digital 12-lead ECG recording from 1 hour prior to dosing on Day 1 to 24 hours after the dose on Day 2
- Nominal time points for ECG extraction:
  - Baseline: -30, -20, and -10 minutes prior to first dose on Day 1
  - Post-dose: 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours after dosing on both days

ECG processing and interval measurement

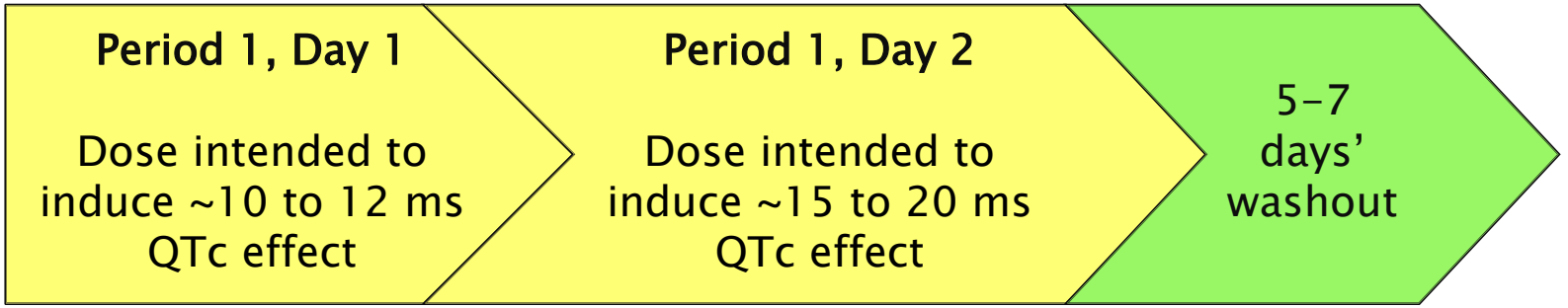
- Ten ECG replicates (10-sec each) extracted during the 5-minute window preceding each nominal timepoint
- A computerized algorithm used that allows extraction of high quality ECGs with low heart rate variability based on predefined criteria
- QT interval measured with the High Precision QT technique
  - All beats in a replicate classified as ‘high-confidence’ or ‘not high’
  - QT interval measured with COMPAS, a computerized algorithm
  - ‘High confidence’ beats accepted without human over-read
  - ‘Not high’ beats over-read by human and either accepted or rejected; no mixing of human- and computer-made measurements
  - Typically results in 90-100 QT measurements per timepoint
- PR and QRS intervals measured semi-automatically

IQ-CSRC vs. Typical SAD study

	SAD	IQ CSRC
Total subjects on active	~30-48 on 1 drug (5-8 dose cohorts)	8 or 9 per drug x 2 doses
Total subjects on placebo	10-16	6 x 2 doses
Double-blind randomized design	Yes	Yes
Dose range evaluated	Low to High (MTD)	Medium to high (low exposures captured during elimination)
PK and ECG schedule	Robust (PK); Minimal to robust (ECG) Pre-dose baseline on day 1	Robust for both PK and ECG; Pre-dose baseline on Day 1
Experimental conditions	+ to +++	+++
ECG collection and processing	+ to +++	+++

Choice of study drugs

QT- positive	QT-negative	Placebo
Ondansetron Quinine Dolasetron Moxifloxacin Dofetilide	Levocetirizine	PO and IV



Dose justification (1 of 3)

Drug	Dose Justification	
	Day 1	Day 2
ZOFRAN (ondansetron)	**56 mg PO**** Dose has not been tested in TQT study. However, the anticipated QT effect is 10 to 12 ms. Cmax: ~ 281 ng/mL	**32 mg by 15-min IV inf.** Based on the TQT study results, mean ΔΔQTc= 19.5 ms.
QUALAQUIN (quinine)	**648 mg PO**** In a PK study in HV (n=24) the mean change from baseline QTc at Tmax was 12 ms. Cmax ~ 3.9 µg/mL. Expected increase in QTc of 12 ms based on the PK/PD model.	**648 mg PO q8h x 4** (3 doses on Day 1 and a morning dose on Day 2) After the 4th dose (75% of Cmax), the anticipated concentration is 5.1 µg/mL and the anticipated QTc is 19 ms.

**Dose recommended by FDA

Dose justification (2 of 3)

Drug	Dose Justification	
	Day 1	Day 2
ANZEMET (dolasetron)	**100 mg PO**** Cmax ~ 278 ng/mL, as extrapolated from the 200 mg dose in the USPI. The Cmax from 100 mg IV was 310 [SD= 65.7] ng/mL in the TQT study.	**150 mg IV by 15-min IV inf.** Dose chosen for an expected QTcF of about 20 ms, based on: • Linear PK in the 50-200 mg IV dose range • From TQT modeling, plasma hydrodolasetron concentrations above ~444 ng/mL will result in QTcF increases of ≥20 ms.
AVELOX (moxifloxacin)	**400 mg PO**** Cmax: ~ 2.95 µg/mL Mean ΔΔQTc = 10-14 ms	**800 mg IV** Mean ΔΔQTc ~20 ms,

**Dose recommended by FDA

Dose justification (3 of 3)

Drug	Dose Justification	
	Day 1	Day 2
TIKOSYN (dofetilide)	**0.125 mg PO** Cmax: ~ 2.1 ng/mL ΔQTc = 10 to 11 ms	**0.25 mg PO** ΔQTc = 20 ms
XYZAL (levocetirizine)	**5 mg PO** (therapeutic dose)	**30 mg PO** (supra-therapeutic dose in the TQT study) Mean ΔΔQTc 1.1 ms [31] Cmax: ~ 1.3 µg/mL

Acknowledgements

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