Centralised Analysis of Phase I ECG Dataset of Resminostat, a New Oral Histone Deacetylase Inhibitor (HDACi)

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Background

Resminostat (4SC-201) is a newly developed, specific, potent, pan-HDAC inhibitor with broad anti-tumour activity in preclinical models and promising clinical characteristics. Resminostat was investigated for the first time in a completed phase I study in an open-label, dose escalation design in patients with advanced stages of solid tumors. The last patient came off study treatment in June 2009. Resminostat is currently in Phase II clinical development in various oncological indications, i.e. hepatocellular carcinoma, Hodgkin Lymphoma, and colorectal cancer.

In general, prolongation of the QT interval has been reported from clinical studies with other HDAC inhibitors. It is hypothesized that this is a class effect associated with inhibition of maturation of hERG – a component of potassium ion channels. QT interval prolongation poises a potential risk of malignant cardiac arrhythmia, however it is important to note that the QT abnormalities reported from HDAC inhibitor clinical investigations have, with very few exceptions, not translated into clinically relevant events.

This data set represents the first central ECG analysis in patients treated with oral, single-agent resminostat at different doses levels administered in Phase I.

Methods

Phase I Study Design

19 Patients were treated at increasing oral daily dose levels from 100 mg to 800 mg in repeated 14-day cycles consisting of 5 consecutive treatment days followed by a 9-day rest period. Cardiac function was monitored by pulse rate, blood pressure, troponin levels and continuous ECG telemetry. In addition, standard 12-lead rest ECGs were conducted frequently to aid in the determination of potential effects on QT interval prolongation. An intensive profile consisting of 18 single ECGs was performed from Day 1 to 5 during Cycle 1, and a reduced number of ECGs in the following cycles, if there were no clinically relevant findings. ECGs were recorded at the following time points during treatment days:

Cycle 1	**Days 1-4**	**predose, +1, +2, +3, +4, +5, +6, +8, +10, +24 hr**
	Day 5	**predose, +1, +2, +3, +4, +5, +6, +8, +10 hr**
	Day 8	**+72 hr after the last drug administration on Day 5**
Cycles 2 - 4	**Days 15, 29, and 43**	**predose, +1, +2, +4 hr**

In addition to standard ECG measurements, patients were to be in-patients after oral treatment on Day 1, to undergo continuous ECG monitoring with telemetry for at least 24 hr after drug intake on Day 1 of Cycle 1. In the case of clinically relevant changes in cardiac parameters during Cycle 1, e.g. QT interval greater than 470 ms, the intensive ECG measurements and the continuous ECG monitoring were to be repeated in further cycles.

Subsequent to the on-site clinical assessment, original paper ECGs were sent to a core lab, scanned and stored on a computer disk for ECG interpretation. This was conducted by means of computer-assisted, on-screen measurement of electrocardiographic intervals by manual point-to-point determination using image analysis software (Sigma Scan Pro 5.0, SPSS Inc., Chicago, IL). All ECGs were interpreted and interval measurements were performed by a board certified cardiologist.

All measurements were done in congruence with current regulatory requirements (1, 2). In each ECG, the PR, QRS and QT intervals and heart rate (R-R interval) were measured in lead II across 3 consecutive beats using markers for the respective ECG intervals. The mean of the three corresponding ECG measurements for each ECG interval was calculated. Where measurement was not possible in lead II, lead V2 was used in stead. Where measurement was not possible in lead V2 either, lead V5 or another suitable lead was used. All data were entered into an SQL-database for data storage and further statistical analysis.

Statistical methods

Summary statistics for the ECG variables PR, QRS, QT, HR, QTcB and QTcF are presented comprising mean, standard deviation, minimum and maximum. Graphical analysis of ECG interval data was performed using scatter plots of ECG intervals versus study day with mean +/- standard deviation as reference lines.

All statistical analyses were performed using the SPSS Statistical Package Release 13.0 (SPSS Inc., Chicago, IL).

Results

19 patients were evaluated individually and in a descriptive manner. Overall analyses for each of the escalating dose cohorts were performed. As patient #19 dropped out from the study at an early stage, only ECG measurements of the first two study days were available. Therefore, this patient was not included in the overall analysis of the dose cohort (800 mg level).

Heart Rate (HR)

At baseline, heart rate was normal (i.e., below 100 bpm) in all patients. In most patients, an increase in heart rate was observed after administration of resminostat. A HR increase of up to 22 beats per minute was detected reaching its maximum usually 3 to 5 hours after drug administration. In all dose groups, time course of HR was variable. Increases in HR were most marked after doses > 400 mg/day. Drug-induced changes in HR appeared attenuated on Day 5. Effects of resminostat on HR were also evident during treatment cycles 2 to 4.

ECG parameters (PR, QRS, QTc)

PR interval duration was normal at baseline in all patients (< 200 ms). Corresponding to the increase in HR, a shortening of the PR and QT intervals were found in a dose-dependent manner. However, at the highest dose level of 800 mg, no decrease in PR interval was observed after drug administration despite an HR increase. Slowing of atrioventricular conduction might be caused by the increased vagal tone in these patients developing adverse events like nausea and vomiting on that dose level.

QRS interval duration was normal at baseline in all patients (< 120 ms). After resminostat intake, no major changes in QRS interval duration were observed during all treatment cycles.

QT/QTcF interval values were prolonged at baseline in one patient (> 450 ms). After administration in Cycle 1, a decrease in QT interval was observed that paralleled increases in HR. Similar effects of resminostat on QT/QTc values were evident during Cycles 2 to 4. Correction of QT intervals for heart rate was performed using Fridericia's formula (QTcF). There was no evidence to suggest a dose-dependent change in QTcF.

In most of the patients, the variation of QTcF was relatively high, however the incidence of QTcF and QTcB outliers was very small. Absolute values of QTcB or QTcF higher than 480 ms were not found in these analyses, and only in once case (patient 19) a value between 450 ms and 480 ms was observed 8 hours after drug administration on Day 1 in Cycle 1.

Differences in QTcF or QTcB between baseline and on-treatment values could be observed also in some patients. For results of the highest dose cohort, please refer to Table 1.

ECG parameters (including T-wave)

At dose levels ≥ 400 mg, unspecific flattening of the T-wave and slight depression of the ST-segment were observed frequently. However, in some patients such findings were already present at baseline.

Special attention was paid to the evaluation of the six patients included in the highest dose cohort (800 mg once-daily). Increases in HR were associated with increases in QTcB in all six patients after drug administration. It is known that in cases of increased HR, QT interval correction according to Bazett results in overcorrection. Therefore, QT correction acc. to Fridericia is the more relevant method for resminostat.

Neither cases of severe arrhythmias, nor cases of Torsade de pointes were observed.

Table 1: Categorical analysis of QTc for the highest dose cohort (800 mg)

Pat. ID	Cycle	Study Day	ΔQTcF>30ms	ΔQTcF>50ms	ΔQTcB>30ms	ΔQTcB>50ms
17	1	01	0	0	1	0
		03	0	0	1	0
	2	15	0	0	1	0
	Total		*0*	*0*	*3*	*0*
18	1	01	0	0	2	0
		02	0	0	3	0
	2	15	0	0	1	0
	Total		*0*	*0*	*6*	*0*
19	1	01	2	0	4	0
	Total		*2*	*0*	*4*	*0*
20	1	01	0	0	4	0
		02	0	0	3	0
		05	0	0	3	0
	3	29	2	0	2	2
		33	0	0	3	1
	Total		*2*	*0*	*15*	*3*
21	2	15	0	0	2	0
	Total		*0*	*0*	*2*	*0*
22	1	03	0	0	1	0
	2	15	1	0	2	0
	3	33	0	0	1	0
	Total		*1*	*0*	*4*	*0*
23	2	15	0	0	2	0
	3	29	1	1	3	1
		33	1	0	3	0
	4	43	1	0	2	0
		47	1	0	1	0
	Total		*4*	*1*	*11*	*1*

Conclusions

- Centralised analysis of the Phase I ECG data set did not reveal any signal for a drug-induced prolongation of the QTc interval by orally administered resminostat up to the highest dose of 800 mg once-daily.
- Drug administration was frequently associated with moderate increases in heart rate.
- At dose levels ≥ 400 mg, unspecific flattening of the T-wave and slight depression of the ST-segment were observed frequently.
- No dose-limiting toxicities acc. to CTC-AE criteria were seen with regard to cardiac safety in all dose cohorts evaluated.
- No severe arrhythmias were observed under treatment with oral resminostat.

References

1. Committee for Proprietary Medicinal Products (CPMP). Points to consider: the assessment of the potential for QT interval prolongation by non-cardiovascular drugs. The European Agency for the Evaluation of Medicinal Products 1997.
2. ICH Harmonized Tripartite Guideline: The clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs. Step 4 (May 12, 2005).

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