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 maturational arrest of NER – a component of potassium ion channels. QT interval prolongation poses a potential risk of malignant cardiac arrhythmia, however it is important to note that the QT abnormal risk factors 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 pre-dose, +1, +2, +3, +4, +5, +6, +8, +10, +24 hr
- **Day 5**: pre-dose, +1, +2, +3, +4, +5, +6, +8, +10, +24 hr
- **Day 8**: +72 hr after the last drug administration on Day 5

Cycles 2 - 4: Days 15, 29, and 43 pre-dose, +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. ECG parameters were 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 pre-dose, +1, +2, +3, +4, +5, +6, +8, +10, +24 hr
- **Day 5**: pre-dose, +1, +2, +3, +4, +5, +6, +8, +10, +24 hr
- **Day 8**: +72 hr after the last drug administration on Day 5

Cycles 2 - 4: Days 15, 29, and 43 pre-dose, +1, +2, +4 hr

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 dedicated software for ECG analysis. The mean of the three corresponding measurements for each ECG interval was calculated. Where measurement was not possible in lead II, lead V2 was used instead. 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 utilizing the entire set 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 observed during the 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, QT)**

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.

QT/QTc interval values were prolonged at baseline in one patient (QTcF > 450 ms). After administration in Cycle 1, a decrease in QTcF interval was observed that paralleled increases in HR. Similar effects of resminostat on QT/QTc intervals were evident during all treatment cycles.

Differences in QTcF or QTcB between baseline and on-treatment values could be observed also in some patients. For differences of the highest dose cohort, please refer to Table 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 doses levels ≥ 400 mg, unspecific flattening of the T-wave and slight depression of the ST-segment were observed frequently.**
- **No dose-limiting toxicities according 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


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

<table>
<thead>
<tr>
<th>Cycle</th>
<th>Study Day</th>
<th>QTcF</th>
<th>QTcB</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0.03</td>
<td>0.03</td>
</tr>
</tbody>
</table>

**Table 2: Statistical analysis of QTc for the highest dose cohort (800 mg)**

<table>
<thead>
<tr>
<th>Cycle</th>
<th>Study Day</th>
<th>QTcF</th>
<th>QTcB</th>
</tr>
</thead>
</table>