Concentration-QT analysis for BAY 2927088 indicates no clinically relevant QTc interval prolongation

PI-012

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INTRODUCTION

- Sevabertinib (BAY 2927088) is an oral tyrosine kinase inhibitor currently being investigated in SOHO-01 (NCT05099172), a Phase I/II, open-label, multicenter, first-in-human study being conducted with adult patients with advanced non-small cell lung cancer (NSCLC) harboring activating mutations in epidermal growth factor receptor (*EGFR*) and/or human epidermal growth factor receptor 2 (*HER2*), also known as Erb-B2 receptor tyrosine kinase 2 genes[1,2]
- Preliminary results from SOHO-01 demonstrated a manageable safety profile and promising anti-tumor activity of sevabertinib[3]
- Sevabertinib is also being investigated in SOHO-02 (NCT06452277), a Phase III, open-label, randomized, active-controlled, multicenter trial, to assess the efficacy of sevabertinib as a first-line treatment for patients with *HER2*-mutated NSCLC[4]
- Investigation of potential drug effects on QT intervals corrected for heart rate (QTc) is a regulatory requirement as per guidance E14 from the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use[5]
- A prespecified statistical analysis was performed to investigate the relationship between observed sevabertinib plasma concentration and QTc (C-QTc) in patients with advanced cancers harboring activating gene mutations in *EGFR* or *HER2*

OBJECTIVE

- The primary objective was to explore the influence of sevabertinib concentration on QTc interval

METHODS

Study design

- Key eligibility criteria included advanced NSCLC with any *EGFR* or *HER2* mutation, an Eastern Cooperative Oncology Group performance status of 0 or 1, and progression on ⩾1 line of systemic therapy
- Patients were recruited into 3 parts: dose escalation (ESC) and backfill (BF) to assess safety, tolerability, maximum tolerated dose (MTD)/maximum acceptable dose (MAD), and pharmacokinetics; dose expansion (EXP) to assess early efficacy, including overall response rate and duration of response; and dose extension (EXT) to assess further efficacy and safety (Table 1)
- Patients were administered sevabertinib in 21-day cycles with continual oral administration as a tablet or a liquid service formulation either once daily (QD) or twice daily (BID) at the following doses: 10, 20, 30, 40, or 60 mg
- To evaluate the impact on cardiac function, single or triplicate 12-lead electrocardiogram (ECG) readings were performed during cycle 1 at screening and before dosing and were time-matched to plasma concentration sampling at 1, 2, 4, 6, and 24 h after dosing on days 1 and 15. On day 8, additional readings were performed before dosing and 2 h after dosing. Results were evaluated centrally at an ECG core laboratory
- Plasma concentrations were measured on days 1 and 15 of cycle 1 before dosing and 1, 2, 4, 6, and 24 h after dosing. On day 8, an additional measurement was collected before dosing
- Additional plasma concentration measurements and ECG readings continued to be collected through cycles 5 and 30, respectively
- Data from all patients with QTc corrected using the Fridericia method (QTcF) data after baseline with paired concentration measurements were used for this analysis

Statistical analyses

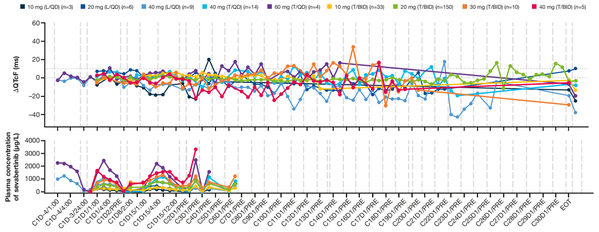
- In this analysis, only centrally evaluated ECGs were used, which includes data from the dose-escalation and backfill groups and part of the data from the dose-expansion groups; data from the dose-extension groups were not considered in this analysis; "*N*" represents the number of patients actually treated as of the database cut-off date
- To test for absence of hysteresis (delay effect) between change from baseline in QTc (ΔQTc) and drug plasma concentration, mean plasma concentration and mean change from baseline in QTcF (ΔQTcF) per time point were used
- The C-QTc linear mixed effects (LME) approach to analyzing ΔQTcF included: (1) fixed effects for the slope of the concentration–effect relationship, mean intercept in the absence of treatment effect, and the difference of the individual baseline QTcF and the mean QTcF baseline of all patients; and (2) random effects for slope and intercept
- To test the assumption of linearity between exposure and ΔQTcF, mean and 90% confidence intervals (CIs) of ΔQTcF at the plasma concentration deciles were reported with the resulting model
- As no hypotheses were tested, all statistical analyses were exploratory in nature

RESULTS

QTcF intervals

- For the ΔQTcF, the variability within the dose groups greatly increased with time after baseline. The overall mean changes appeared to be the lowest for the dose groups with the most patients, and as the number of patients in each dose group decreased across treatment cycles, the variability increased (Figure 1)
- For this analysis, all observations for patients with ⩾1 change from baseline ΔQTcF were included, regardless of whether a simultaneous plasma concentration measurement was collected

Figure 1. Mean ΔQTcF *vs* time by dose group



Upper panel: dotted lines, horizontal: ΔQTcF = 0 ms; dotted lines, vertical: borders of different cycles and days; colored dots: mean changes from baseline for the different dose groups. Lower panel: median plasma concentrations for the different dose groups

C, cycle; D, day; EOT, end of treatment; L, liquid service formulation; ms, milliseconds; PRE, before dosing; T, tablet formulation

Table 1. Coding of dose groups and distribution among parts of SOHO-01

Dose level	10 mg (L/QD)	20 mg (L/QD)	40 mg (L/QD)	40 mg (T/QD)	60 mg (T/QD)	10 mg (T/BID)	20 mg (T/BID)	30 mg (T/BID)	40 mg (T/BID)
ESC *Sevabertinib dose increased in stepwise fashion from 10 mg QD to MTD/MAD (min. 3 patients evaluable for DLT pre-dose level)*	X	X	X	X	X		X	X	X
BF *BF run concurrently with ESC (max. 24 patients per cohort)*	X	X	X	X	X		X	X	X
BA *Subgroup of ESC for BA assessment*			X		X				
EXP *8 groups (A, B1, B2, C, D, E, F, G) planned. EXP may start at a dose level evaluated in ESC/BF*						X	X		
EXT *Initiation of EXT will depend on benefit-risk profile observed during EXP*							X		

BA, bioavailability; DLT, dose-limiting toxicity; L, liquid service formulation; T, tablet formulation

Table 2. Patients (observations) per dose group (PKS/QTS data set)

Visit	10 mg (L/QD)	20 mg (L/QD)	40 mg (L/QD)	40 mg (T/QD)	60 mg (T/QD)	10 mg (T/BID)	20 mg (T/BID)	30 mg (T/BID)	40 mg (T/BID)
Cycle 1 (number of observations)	3 (28)	6 (65)	9[a] (109)	14 (160)	4[b] (71)	33 (250)	150 (1144)	10 (100)	5 (48)

[a]4 of 9 patients were in the bioavailability group (day −4 as baseline); [b]All 4 patients were in the bioavailability group (day −4 as baseline)

L, liquid service formulation; PKS/QTS, pharmacokinetics QT analysis set; T, tablet formulation

Qualification of model assumptions

- Overall, 11,657 centrally assessed ECGs and 3064 plasma concentrations from 260 patients were received
- 1975 observations of total paired plasma concentration and ΔQTcF interval were available for C-QTc analyses from 234 patients, 62.4% of whom were female and 37.6% were male (Table 2)
- In general, no systematic change in heart rate with dose or plasma concentration was observed, although some dose groups (tablet 40 mg BID and liquid 10 mg QD) showed a mean change from baseline above and close to 10 beats per minute, likely due to the small sample size and considerable inter-individual variability. A small trend of lower heart rates on days 1 and 15 of cycle 1 compared with baseline was present, likely due to patient relaxation and experience over the course of the study (Figure 2)
- Linear regression analysis showed a small statistically significant dependence of QTcF on RR intervals over the whole range of observed RR intervals; however, as most of the ECGs were within a much narrower window and no consistent effect of sevabertinib on heart rate was observed, the use of the Fridericia's formula was considered reasonable
- Scatterplots of ΔQTcF *vs* plasma concentration showed no signs of systematic counterclockwise loops, indicating no delayed effect between exposure and ΔQTcF (Figure 3)

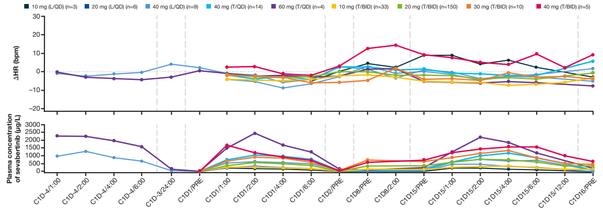
Results of the LME model

- Linear regression analysis estimated a statistically significant ($p>0.0055$) concentration–effect slope of 0.00186 ms/(µg/L). At the maximum observed drug concentration (C_{max}) after nominal dosing of 20 mg BID (874 µg/L), the upper limit of the 90% CI of predicted ΔQTcF was well below the threshold of regulatory concern of 20 ms for oncology drugs.[6] This threshold was also not reached at the highest observed concentration of 3519 µg/L, which was 4 times the geometric mean C_{max} after 20 mg BID (Figure 4 and Table 3)
- The predicted C_{max} after nominal dosing of the recommended dose of 20 mg BID for 21 days is considerably lower than the highest plasma concentration observed in the initial first-in-human study

Model qualification

- All of the 90% CIs at each of the deciles (except for the first decile) showed an overlap with the linear model with no trending towards lower or higher values in different sevabertinib plasma concentration sections (Figure 4); therefore, it was concluded that the data can be represented using a linear model

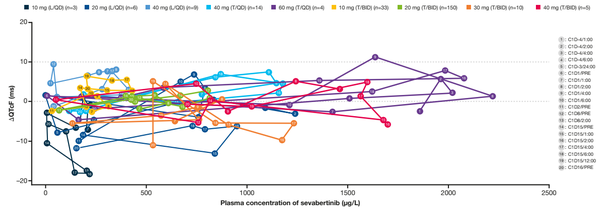
Figure 2. Mean changes from baseline in heart rate by dose group (all patients treated in cycle 1)



Upper panel: connected colored dots indicate mean change in heart rate from baseline (ΔHR) at each time point after dosing during cycle 1. Lower panel: median plasma concentrations for each dose group

bpm, beats per minute; C1, cycle 1; D, day; HR, heart rate; L, liquid service formulation; PRE, before dosing; T, tablet formulation

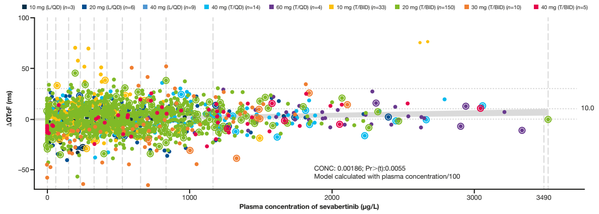
Figure 3. Scatterplot of mean placebo-corrected changes in QTcF *vs* mean plasma concentration



Colored dots indicate mean ΔQTcF at each time point after dosing *vs* mean plasma concentration connected according to time, separately for each dose group

C1, cycle 1; D, day; L, liquid service formulation; ms, milliseconds; PRE, before dosing; T, tablet formulation

Figure 4. ΔQTcF *vs* sevabertinib plasma concentration and LME model result



Colored dots: all observations of patients with respective dose of sevabertinib; open colored circles: observations at maximum plasma concentration of participants treated with sevabertinib; dotted lines, horizontal: ΔQTcF = 0 or +10 ms; dotted lines, vertical: decile limits of the plasma concentration; black vertical lines with whiskers: decile values (± 90% CI) of the ΔQTcF plotted at mean plasma concentration of the respective decile; solid black line and gray shaded area: model estimated ΔQTcF with 90% CI

CONC, slope of the linear C-QTcF relationship; L, liquid service formulation; ms, milliseconds; Pr>|t|, *p* value for the calculated slope; T, tablet formulation

Table 3. Results of the LME model

Effect	Estimate	Standard error	DF	Pr>|t|	Lower 90% CI	Upper 90% CI
Intercept	0.1899	0.6643	201	0.7752	−0.9078	1.2876
Slope/100	0.1858 (0.001858)[a]	0.063	37.5	0.0055	0.07959	0.2921

[a]Actual slope with original scaling

DF, degrees of freedom according to Kenward-Roger method; Pr>|t|, *p* value for the calculated slope

CONCLUSIONS

- Sevabertinib caused no clinically relevant QTc interval prolongation, with a ΔQTcF well below the threshold of regulatory concern of 20 ms at the recommended dose of 20 mg BID or the highest observed concentration
- Therefore, the risk of cardiovascular events due to sevabertinib treatment, as observable from ECGs, is considered low

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