Exposure-Response Analyses to Assess Lack of QT Prolongation by VS-6063 in Healthy Subjects or in Patients with non-Hematologic Malignancies

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**Objectives:** Defactinib (VS-6063) is an anti-tumor agent being developed for the treatment of non-hematological cancers. The work was undertaken to evaluate the lack of QT prolongation based on exposure-response analyses utilizing data at different dose levels from a dose escalation Phase 1 oncology study and healthy subjects study evaluating food effect.

**Methods:** In Study B0761001 (n=46), the safety, pharmacokinetics (PK) and pharmacodynamics of single and multiple-doses of VS-6063 administered orally at increasing dose levels (12.5 mg to 750 mg BID) under fasted conditions (12.5 mg to 750 mg BID) and fed conditions (300 mg and 425 mg BID). Triplicate electrocardiograms (ECGs) were taken at PK-matched time points. For Study VS-6063-105, healthy subjects were given 400 mg as a single dose in a cross-over design and time-matched ECGs were collected on Day -1 and Day 1 of each period. Linear mixed-modeling was performed to analyze relationship between plasma exposure and heart-rate-corrected QT intervals.

**Results:** In the VS-6063 exposure-ddQTc model for the combined Study B0761001 and Study VS-6063-105 data the typical baseline ddQTc in the absence of drug administration was determined not to be significantly different from zero while the slope (95% CI) relating serum or plasma defactinib concentration to ddQTc was -5.43 (-9.43, -1.43) msec/μg/mL. Covariate analyses evaluating gender, age, weight or BMI and fasting/fed administration did not influence the QT interval or defactinib and exposure-QTc relationships in the exposure-QTc analysis.

**Conclusions:** As assessed in patients with advanced solid tumors and healthy subjects, VS-6063 does not affect ventricular repolarization. Early assessments of cardiac safety at ascending doses of VS-6063 suggest lack of QT prolongation and therefore, dedicated and thorough QT study may not be necessary.