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A study to evaluate the effect of JNJ-63623872 on cardiac repolarization interval in healthy subjects

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Background: JNJ-63623872 is a novel non-nucleotide inhibitor of the influenza A virus PB2 protein currently in Phase 2b clinical development. This two-part Phase 1 study evaluated the effect of JNJ-63623872 on cardiac repolarization interval in healthy adults 18–50 years of age.

Material/methods: In order to confirm safety and adequate systemic drug exposure at the intended supratherapeutic dose, the “thorough QT” (TQT) study part was preceded by a randomized, double-blind, placebo-controlled, dose escalation part (Panel 1). JNJ-63623872 was administered orally as a single-dose of 2,400 mg and 3,000 mg (n=12 at each dose level; 8 active, 4 placebo) under fasted conditions. Based on an interim safety and pharmacokinetic analysis from Panel 1, a supratherapeutic dose of JNJ-63623872 was selected for the actual TQT study part, a randomized, double-blind, double-dummy, placebo- and positive-controlled (moxifloxacin 400 mg) 3-period crossover study (Panel 2, n=42). The effect of single-dose JNJ-63623872 was assessed on the QT/QTc interval. Continuous 12-lead digital ECGs were obtained using Mortara H12+ Holter monitors with ECGs extracted in triplicate at predose and at 11 postdose timepoints over 24 hours and analyzed by a central ECG laboratory using blinded readers.

Results: Administration of a single dose of JNJ-63623872 2,400 or 3,000 mg was generally safe and well tolerated. No deaths or other serious adverse events (AEs) were reported during the study. None of the subjects discontinued the study due to a treatment-emergent AE. Based on the systemic JNJ-63623872 exposure data of Panel 1, the supratherapeutic dose of JNJ-63623872 2,400 mg was selected for Panel 2 as this dose exceeded the targeted 2.4- to 3-fold C_{max} above the therapeutic dose. For Panel 2, all time-matched least square (LS) mean changes from baseline in QTcF between JNJ-63623872 2,400 mg and placebo ($\Delta\Delta$QTcF) had an upper 90% confidence limit that was below the regulatory limit of 10 milliseconds (ms), with the largest $\Delta\Delta$QTcF being 2.8 ms (90% CI 0.9 to 4.7

ms) observed at 8 hours postdose. The lower limit of the 1-sided 97.5% CI for the difference in time-matched LS mean changes from baseline in QTcF between moxifloxacin and placebo (ΔΔQTcF) was greater than 5 ms at 3 of the 4 pre-selected time points, demonstrating assay sensitivity.

Conclusions: JNJ-63623872 induces no QT/QTc prolongation of clinical or regulatory concern.