Full Title: Cardiac safety of ozanimod in a QT/QTc trial and a phase 2 trial in relapsing multiple sclerosis (RMS)

Short Title: Cardiac safety of ozanimod in relapsing MS

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Background: Ozanimod, an oral, once-daily immunomodulator, selectively targets sphingosine 1-phosphate (S1P) receptor 1 ($S1P_{R1}$) and 5 ($S1P_{R5}$), but not 3 ($S1P_{R3}$) which may play a role in cardiac conduction. Ozanimod's pharmacokinetic (PK) properties, eg, low systemic drug concentrations with the first dose, combined with implementation of a dose escalation regimen, may contribute to reduced first-dose cardiac rate effects.

Methods: Data from a thorough QT (TQT) study (Tran, *Clin Pharmacol Drug Dev,* 2017) and a Phase 2 RMS study (Cohen, *Lancet Neurol*, 2016) are reviewed. In the TQT study, subjects received ozanimod at an initial dose of 0.25 mg, escalated to 2 mg over 14 days. In the Phase 2 study, patients were randomized to once-daily ozanimod HCl 1 mg or 0.5 mg (initial dose 0.25 mg, escalated over 7 days) or placebo for 24 weeks.

Results: TQT study: Ozanimod 1 mg (therapeutic) and 2 mg (supratherapeutic) doses showed no evidence of QTc prolongation, and therefore no effect on cardiac repolarization. The dose escalation regimen attenuated Day 1 "first dose" effects on heart rate (HR), with no HR reduction vs pre-dose baseline. Phase 2 study: Mean HR change (Holter) during the first six hours post-dose showed reduction of <2 bpm for ozanimod versus no reduction for placebo; no ozanimod patient experienced a minimum HR <45 bpm. No Type II or 2:1 atrioventricular block or significant blood pressure changes were observed with ozanimod in either study.

Conclusion: Ozanimod had no effect on cardiac repolarization, including at a supratherapeutic dose of 2 mg in healthy subjects. Ozanimod's receptor selectivity, PK properties, and use of dose escalation potentially differentiates its cardiac profile from other S1P receptor modulators. Use of a dose

escalation regimen with an initial dose of ozanimod 0.25 mg appears to have an acceptable cardiac safety profile in patients with RMS.