Cardiac Safety of Ozanimod in a QT/QTc Trial and a Phase 2 Trial in RMS

INTRODUCTION
- Ozanimod (RPC1063) is an oral, once-daily immunomodulator selectively targeting sphingosine 1-phosphate (S1P) receptor 1 (SIP1) and 5 (SIP5) that has shown therapeutic benefit in clinical trials of relapsing multiple sclerosis (RMS) and ulcerative colitis.
- Ozanimod does not engage SIP3, which may play a role in cardiac conduction.
- The low in vivo maximum plasma concentration at steady state (Cmax) minimizes off-target effects, which, in conjunction with lower systemic drug concentrations at treatment initiation, may contribute to reduced first-dose heart-rate (HR) effects.

METHODS
Clinical data on cardiac safety of ozanimod from a thorough QT (TQT) study and a phase 2 study in RMS are reviewed.

TQT Study Design
- This was a single-center, double-blind, randomized, placebo- and positive-controlled, parallel-group, nested crossover for positive control, thorough QT-corrected QT (QTc) study in healthy male and female subjects (Figure 1).
- Healthy male and female subjects (n=124), 18–45 years of age, with approximately 70% females.
- Subjects were randomized to ozanimod (0.25 mg to 2 mg) in a 14-day dose-escalation regimen or matching placebo, in a 1:1 ratio.
- The ozanimod dose-escalation regimen was the same regimen used in all phase 2 and 3 studies.
- Subjects in the placebo group and ozanimod group received moxifloxacin (MXF) as the positive control for QT effects on day 2 or day 17.

RESULTS
- In the TQT study, multiple doses of ozanimod 1 mg (therapeutic) and 2 mg (supratherapeutic) showed no evidence of QTc prolongation, and therefore no effect on cardiac repolarization.
- The upper 95% one-sided (90%) two-sided confidence limit was always below 10 msec, and all time points except one (12-hour time point for the 1 mg/day dose) showed a point estimate of the difference between ozanimod and placebo which was not marginally larger than zero (Figure 3).

DISCUSSION
- There was no evidence of QTc prolongation, and therefore no effect on cardiac repolarization, including at a supratherapeutic dose of 2 mg in healthy subjects.
- The TQT study and the phase 2 study in RMS demonstrated that a starting dose of 0.25 mg attenuates the first-dose HR effect of ozanimod.
- Ozanimod at doses of 0.5 mg and 1 mg in patients with RMS appears to provide an acceptable cardiac safety profile.
- The receptor selectivity of ozanimod and the use of dose escalation potentially differentiates its cardiac profile from other S1P receptor modulators.

LITERATURE

Table 1. Minimum HR Within 6 Hours of Dosing on Days 1, 3, 5, and 8 (Holter Monitoring), n (%) | Table 2. Mean Hourly HR on Days 1, 3, 5, and 8 (Holter Monitoring), n (%) | Table 3. Estimates and Two-sided 90% CIs for the Effect of a Supratherapeutic Ozanimod 2 mg Dose on QTcF

DISCLOSURES
- There were no notable differences among treatment groups in baseline mean QT duration, Bazett- or Fridericia-corrected QT interval, or in mean change from baseline at any post-baseline visit.

ACKNOWLEDGMENTS
- The study starting dose of 0.25 mg attenuated first-dose effects on HR on day 1 with no reduction in HR compared with pre-dose baseline.
- A circadian rhythm in HR was seen in both treatment groups with an increase in HR during the day and a decrease at night when subjects were sleeping.
- During the day, mean HR increased following dosing in both ozanimod and placebo groups.
- Ozanimod attenuated the increase in HR during the day compared with placebo, and mean HR was similar in both treatment groups at night (Figure 2). The maximum mean HR decreased 3.6 beats per minute (bpm).

Figure 1. TQT Study Design and Dose Escalation Schedule

Figure 2. Mean Hourly HR on Days 1, 3, 5, and 11

Figure 3. Estimates and Two-sided 90% CIs for the Effect of a Supratherapeutic Ozanimod 2 mg Dose on QTcF

Figure 4. Mean Hourly HR on Day 1 (Absolute)

Figure 5. Mean Hourly HR on Day 1 (Change from Pre-dose)