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

Krzysztof Selmaj[1], Ludwig Kappos[2], Hans-Peter Hartung[3], Douglas L. Arnold[4], Amit Bar-Or[5], Giancarlo Comi[6], Lawrence Steinman[7], Eva K. Havrdová[8], Bruce A.C. Cree[9], Xavier Montalbán[10], Brett E. Skolnick[11], Nataliya Agafonova[11], Jeffrey A. Cohen[12]

[1]University of Łódz, Łódz, Poland; [2]University Hospital and University of Basel, Basel, Switzerland; [3]Heinrich-Heine University Düsseldorf, Düsseldorf, Germany; [4]NeuroRx Research and Montréal Neurological Institute, McGill University, Montréal, Quebec, Canada; [5]Center for Neuroinflammation and Therapeutics, and Multiple Sclerosis Division, University of Pennsylvania, Philadelphia, Pennsylvania, United States; [6]San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Milano, Italy; [7]Beckman Center for Molecular Medicine, Leland Stanford Junior University, Stanford, California, United States; [8]First Medical Faculty, Charles University of Prague, Prague, Czech Republic; [9]UCSF Weill Institute for Neuroscience, University of California San Francisco, San Francisco, California, United States; [10]University of Toronto, St Michael's Hospital, Toronto, Canada, and Cemcat, Universitat Autonoma Barcelona, Barcelona, Spain; [11]Receptos, a wholly owned subsidiary of Celgene Corporation, San Diego, California, United States; [12]Mellen Center for MS Treatment and Research, Cleveland Clinic, Cleveland, Ohio, United States

INTRODUCTION

- Ozanimod (RPC1063) is an oral, once-daily immunomodulator selectively targeting sphingosine 1-phosphate (S1P) receptor 1 ($S1P_{R1}$) and 5 ($S1P_{R5}$) that has shown therapeutic benefit in clinical trials of relapsing multiple sclerosis (RMS) and ulcerative colitis[1,2]
- Ozanimod does not engage $S1P_{R3}$, which may play a role in cardiac conduction[3]
- The low *in vivo* maximum plasma concentration at steady state ($C_{max,ss}$) 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

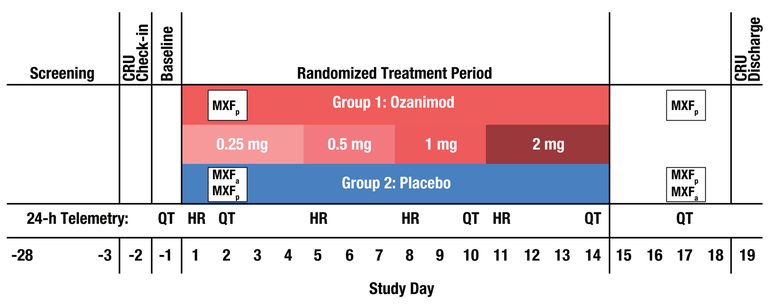
METHODS

Clinical data on cardiac safety of ozanimod from a thorough QT (TQT) study[4] and a phase 2 study in RMS[1] 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 (TQT 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 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

Figure 1. TQT Study Design and Dose Escalation Schedule



CRU, clinical research unit; HR, heart rate; MXFa, moxifloxacin active; MXFp, moxifloxacin placebo; TQT, thorough QT/QTc study.

Phase 2 Study Design

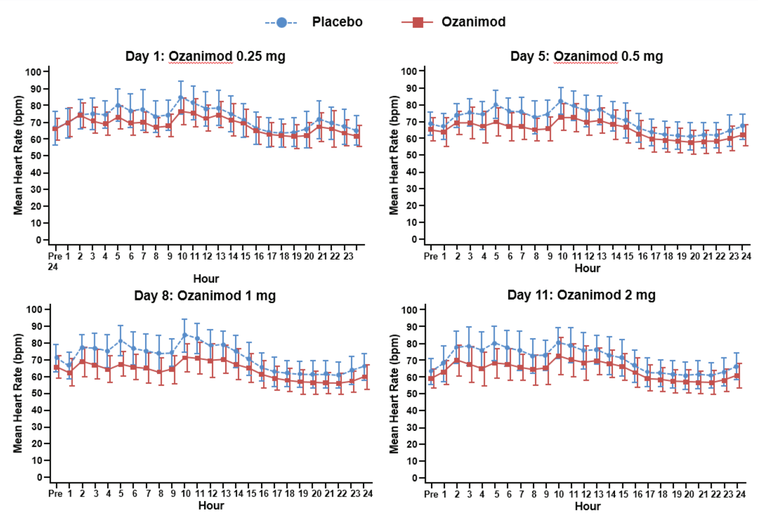
- This was a multi-center, double-blind, randomized, placebo-controlled study in patients with RMS
- A total of 258 male and female subjects, 19–55 years of age, with approximately 7:3 female-to-male ratio
- Subjects with RMS in the phase 2 study were randomized to once-daily ozanimod 1 mg or 0.5 mg or placebo for 24 weeks
- Treatment with ozanimod was initiated with a 7-day dose escalation at an initial dose of ozanimod of 0.25 mg

RESULTS

TQT Study

- 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 3–5 beats per minute (bpm)

Figure 2. Mean Hourly HR on Days 1, 5, 8, and 11

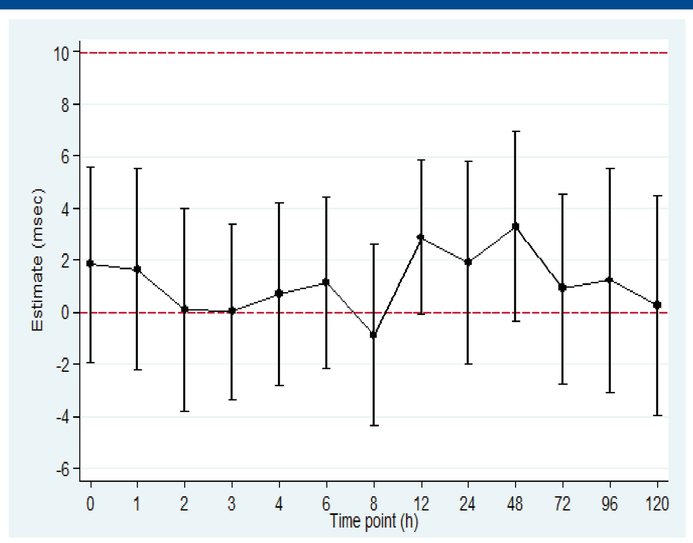


bpm, beats per minute; HR, heart rate. Error bars denote standard deviation.

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
- 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)

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



2-sided 90% confidence intervals (CIs) are shown.
QTcF, Fridericia-corrected QT.

Phase 2 Study

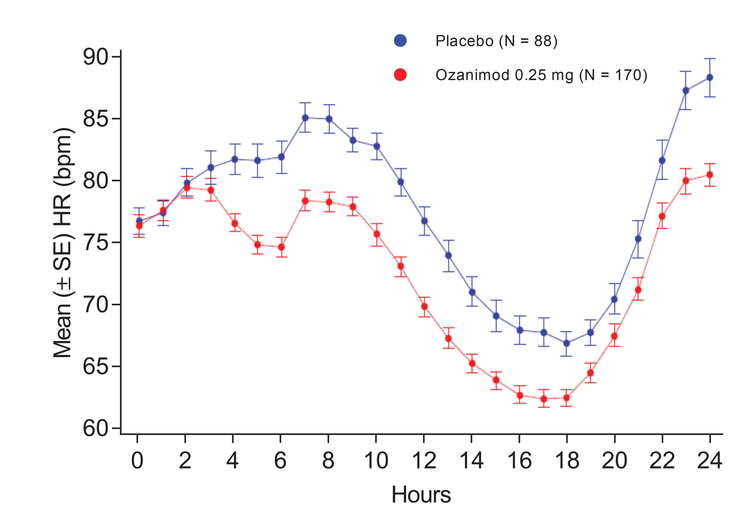
- Holter results were similar to vital signs measurements with no patients achieving a minimum hourly HR below 50 bpm on day 1 (Table 1)
- The largest mean decrease from pre-dose baseline in ozanimod-treated patients over the first 6 hours post dose was 1.9 bpm on day 1. A blunting of the normal diurnal increase in HR was observed with ozanimod after dosing on days 1, 5, and 8 (day 1 shown; Figures 4 and 5)
- No type II or higher atrioventricular (AV) block was observed with ozanimod
- The incidence of cardiac adverse events with ozanimod (two events of palpitations, one event of angina pectoris) was similar to placebo (one event of 1st degree AV block, one event of palpitations)

Table 1. Minimum HR Within 6 Hours of Dosing on Days 1, 5, and 8 (Holter Cardiac Monitoring), n (%)

	Day 1		Day 5		Day 8		
HR (bpm)	Placebo (N=88)	Ozanimod 0.25 mg (N=170)	Placebo (N=24)	Ozanimod 0.5 mg (N=53)	Placebo (N=23)	Ozanimod 0.5 mg (N=25)	Ozanimod 1 mg (N=25)
≥65	72 (81.8)	123 (72.4)	21 (87.5)	26 (49.1)	18 (78.3)	12 (48.0)	19 (76.0)
60–64	9 (10.2)	25 (14.7)	0	13 (24.5)	4 (17.4)	5 (20.0)	6 (24.0)
55–59	5 (5.7)	17 (10.0)	2 (8.3)	10 (18.9)	1 (4.3)	6 (24.0)	0
50–54	1 (1.1)	2 (1.2)	1 (4.2)	2 (3.8)	0	2 (8.0)	0
45–49	0	0	0	2 (3.8)	0	0	0
40–44	0	0	0	0	0	0	0
<40	0	0	0	0	0	0	0

bpm, beats per minute; HR, heart rate.
Note: N indicates the number of subjects who underwent Holter cardiac monitoring, conducted for all subjects on day 1, for the first 75 subjects on days 5 and 8, and on days 5 and 8 if any cardiac safety issues were observed on day 1.

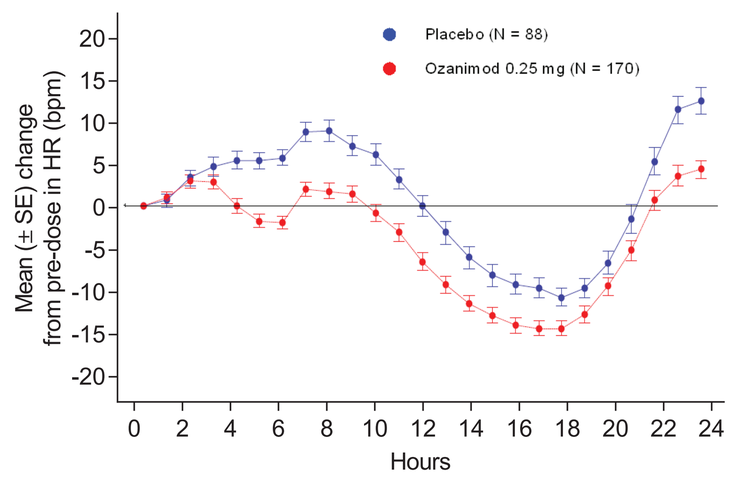
Figure 4. Mean Hourly HR on Day 1 (Absolute)



bpm, beats per minute; HR, heart rate; SE, standard error.

- 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

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



bpm, beats per minute; HR, heart rate; SE, standard error.

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LITERATURE

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DISCLOSURES

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Krzysztof Selmaj
kselmaj@gmail.com

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