Results of a Thorough QT/QTc (TQT) Study of Orally Administered RPC1063, a Novel, Selective S1P1 Receptor Agonist, in Healthy Adult Volunteers

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INTRODUCTION

- RPC1063 is a potent, selective, orally available sphingosine 1-phosphate 1 receptor (SIPIR) agonist.
- Stimulation of this receptor results in biological activities that are likely to improve pathological processes in relapsing multiple sclerosis (MS).
- S1P1R stimulation is also associated with a decrease in heart rate (HR) with diminished effect and tachyphylaxis upon repeat dosing.
- Fingolimod, a non-selective S1PR agonist, has also demonstrated prolongation of QTc. S1P3R, expressed on mouse heart conduction tissue, may be responsible for this QTc prolongation (unpublished observations).
- A thorough QT/QTc (TQT) study of RPC1063 was recently completed to examine the effects of RPC1063 on HR and on cardiac repolarisation/QT prolongation.

OBJECTIVES

Primary Objective

- To assess whether exposure to therapeutic (1 mg) or supratherapeutic (2 mg) doses of RPC1063 in healthy male and female subjects increased the corrected QT (QTc) interval compared to Placebo (PBO)

Secondary Objectives

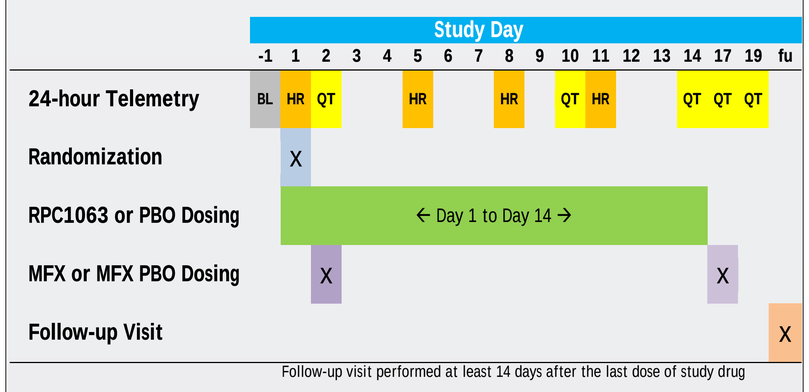
- To demonstrate assay sensitivity by showing that the positive control (moxifloxacin [MXF] 400 mg) treatment, corrected for PBO, produced a QTc change >5 msec
- To evaluate the pharmacokinetics (PK) of RPC1063 and its metabolites
- To assess the safety and tolerability of RPC1063

METHODS

Study Design

- This was a single-centre, double-blind, randomized, placebo- and positive-controlled, parallel-group, nested crossover for positive control, thorough QT/QTc study in healthy male and female subjects.
- Subjects were 124 healthy male and female subjects, aged 18-45 years, with approximately 1:1 male to female ratio.
- Subjects were randomized in a 1:1 ratio to RPC1063 (0.25 to 2 mg) in a 14-day dose titration regimen or matching PBO.
- The RPC1063 dose titration regimen is the same regimen that is used in on-going Phase 2 studies.
- Subjects in the PBO group received MXF as the positive control for QT effects on Day 2 or Day 17.

Figure 1: Study Design



Follow-up visit performed at least 14 days after the last dose of study drug

Table 1: RPC1063 Dose Titration Schedule

	RPC1063 Dose (mg)													
Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Dose	0.25	0.25	0.25	0.25	0.5	0.5	0.5	1.0	1.0	1.0	2.0	2.0	2.0	2.0

Assessments

- The effect of RPC1063 on QTcF was compared to PBO by measuring time-matched differences between the mean changes from baseline in QTcF.
- Safety and tolerability were assessed by collection and analysis of adverse events (AEs), vital signs, clinical laboratory tests, electrocardiogram (ECG), and continuous 24-hour cardiac monitoring (telemetry).
- 24-hour telemetry monitoring for the TQT analysis was performed on Day 2, Day 10, Day 14, and Day 17.
- 24-hour telemetry monitoring for HR characterization was performed on each day when the RPC1063 dose was increased, on Day 1, Day 5, Day 8 and Day 11.
- Robust PK sampling was also performed on Days 2, 10, 14, and 17.

RESULTS

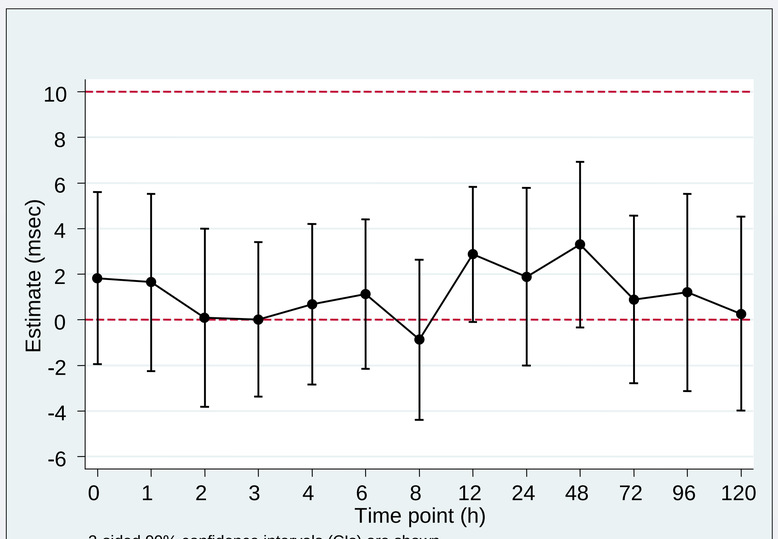
Subject Disposition

- A total of 124 subjects were enrolled in the study, with 62 subjects randomized to RPC1063 and to PBO, respectively.
- In the RPC1063 group, 56 patients completed the study, and in the PBO group, 57 patients completed the study.

Effects on QT Interval

- This was a negative TQT study. A clinically relevant effect for RPC1063 on cardiac repolarization was ruled out.
- The upper 95% one-sided (90% two-sided) confidence limit was always below the threshold value of regulatory concern (10 msec) (**Figure 2**)
- Assay sensitivity was demonstrated with the positive control agent MXF.
- In addition, RPC1063 caused no remarkable changes in waveform morphology.

Figure 2: Estimates and 90% (2-sided) CIs for the Effect of a Supratherapeutic 2 mg Dose of RPC1063 (relative to Placebo) on QTcF

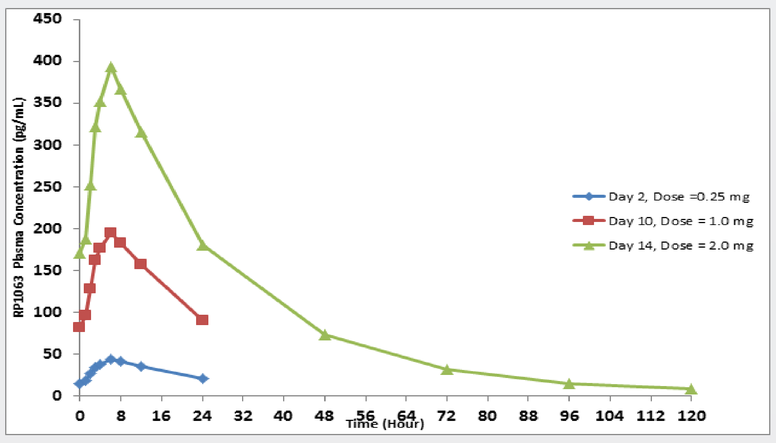


2-sided 90% confidence intervals (CIs) are shown

Pharmacokinetics

- The RPC1063 plasma concentration profile (**Figure 3**) and PK parameters were consistent with the results from a prior Phase 1 study.
- The mean terminal elimination half-life (t1/2) was 20.1 hr on Day 14 (following a 2 mg dose).
- The mean apparent volume of distribution associated with the terminal elimination phase (Vz/F) was large (ranging from 7,447 to 8,826 L on Days 2, 10, and 14).
- The mean T_{max} ranged from 5.9 to 6.7 hr on Days 2, 10, and 14.
- The mean C_{max} increased from 44.9 pg/mL on Day 2 to 406.3 pg/mL on Day 14.
- Both the therapeutic (1 mg) and supratherapeutic (2 mg) RPC1063 dosing regimens appeared to achieve steady state (based upon a t1/2 of 20 hr).

Figure 3: Mean RPC1063 Plasma Concentration (pg/mL) vs. Time (Hour)



Laboratory Tests

- No clinically notable liver function test (LFT) elevations occurred during dosing through discharge and follow-up.
- Transient and asymptomatic increases in LFTs occurred in four RPC1063 and two PBO subjects. The increases occurred at follow-up visits ≥14 days after their last dose of study drug, and all were considered unrelated to the study drug.
- There were no other hematology, chemistry or urinalysis changes of note.

DISCLOSURES

J. Hartung, R. Peach, M. Boehm, H. Smith, K. Cremer, G. Timony, A. Olson and S. Gujrathi are employees of Receptos, Inc.;

B. Mendzelevski is an employee of Bioclinica, Inc.

D. Chanter is an employee of Statisfaction Statistical Consultancy Ltd.

C. Pan is an employee of CPAN Statistical Consulting.

RESULTS (Continued)

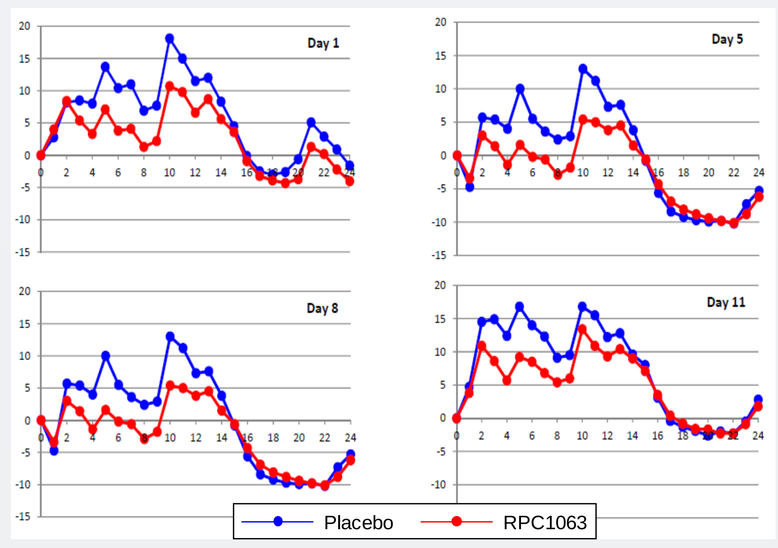
Adverse Events

- The incidence of treatment-emergent adverse events (TEAEs) was comparable for RPC1063 (48 [77.4%]) and PBO (46 [74.2%]). Most of the TEAEs were considered to be unrelated to study drug by the investigator (70/94 [74.5%]) and all were mild or moderate in severity.
- The most common TEAEs for RPC1063 and PBO, respectively, were Administration Site Reactions (39 [62.9%]; 40 [64.5%]) caused by the ECG electrodes used for continuous ECG monitoring, Headache (9 [14.5%]; 7 [11.3%]), Musculoskeletal Chest Pain (3 [4.8%], 3 [4.8%]), and Orthostatic Hypotension (5 [8.1%]; 1 [1.6%]).
- Cardiac TEAEs were comparable for RPC1063 and PBO and were limited to transient and self-limiting 1st (RPC1063 1 [1.6%]) and 2nd degree AV block (RPC1063 1 [1.6%]; PBO 1 [1.6%]) and short runs of non-sustained Ventricular Tachycardia (RPC1063 2 [3.2%]; PBO 3 [4.8%]).

Effects on Heart Rate

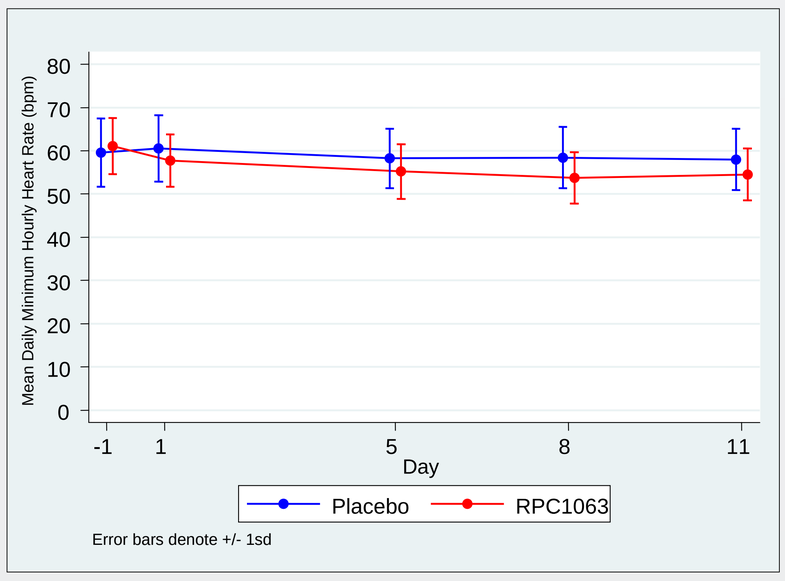
- A circadian rhythm in HR was seen in both treatment groups with an increase in HR during the day and a decrease at night when subjects were sleeping.
- During the day, mean HR increased following dosing in both groups.
- RPC1063 reduced the increase in HR during the day compared to placebo and mean HR was similar in both treatment groups at night(**Figure 4**).

Figure 4: Changes in Mean Hourly Heart Rate from Daily Baseline



- There were no clinically significant episodes of bradycardia and the Nadir HR (minimum daily HR) in both treatment groups was similar (**Figure 5, Table 2**).

Figure 5: Mean Daily Minimum Hourly Heart Rate



Error bars denote +/- 1sd

Table 2: Summary of Daily Minimum Hourly Heart Rate

Day	Placebo Mean (SD)	RPC1063 Mean (SD)	Difference
1	60.6 (7.7)	57.7 (6.1)	2.9
5	58.2 (6.8)	55.2 (6.3)	3.0
8	58.4 (7.1)	53.7 (6.0)	4.7
11	58.0 (7.1)	54.5 (6.0)	3.5

CONCLUSIONS

- The study ruled out a relevant effect of RPC1063 on cardiac repolarization and was a negative TQT study.
- RPC1063 was well tolerated and the adverse events were similar to those seen in a prior Phase 1 study.
- The dose titration regimen employed in this study starting at 0.25 mg appeared to attenuate “first dose” effects on HR on Day 1 and during the dose titration period when higher doses were administered.