BITOPERTIN (RG1678), A NOVEL GLYCINE REUPTAKE INHIBITOR, DOES NOT CAUSE QTcF PROLONGATION IN HEALTHY MALE VOLUNTEERS AT THERAPEUTIC AND SUPRATHERAPEUTIC EXPOSURE

Carsten Hofmann[1], Ludger Banken[1], Michael Hahn[2], Dennis Swearingen[3], Sandra Nagel[4], Meret Martin-Facklam[1]

[1]F. Hoffmann-La Roche Ltd., Basel, Switzerland, [2]Roche Products Ltd., Welwyn Garden City, United Kingdom, [3]Celerion, Phoenix, Arizona, USA, [4]Roche Ltd., Strasbourg, France

Background

- Bitopertin (RG1678) selectively inhibits glycine transporter type 1 (GlyT1), thereby increasing the synaptic concentration of glycine and facilitating NMDA receptor function which is postulated to play an important role in the pathophysiology of schizophrenia. [1-3]
- In an 8-week phase 2 study, 10 and 30 mg of bitopertin demonstrated consistent reductions of negative symptoms in patients with schizophrenia, reaching statistical significance in those who completed the trial. [4]
- A thorough QT study was conducted where the primary objective was to evaluate whether bitopertin had a threshold pharmacological effect on cardiac repolarization, as detected by changes in the QTcF interval at steady-state, when administered at a predicted therapeutic and supra-therapeutic dose.

Methods

Study Design

- The study was a multiple-dose, randomized, placebo-controlled, double-blind, double-dummy, parallel-group design conducted in male healthy volunteers at two clinical research centers.
- The estimated sample size was 52 and 26 in treatment groups A/B and C/D, respectively based on a standard deviation of 11 ms in time-matched QTcF changes in baseline and a prolongation of no more than 1 ms and 2 ms for 30 mg and 175 mg bitopertin, respectively. This sample size was estimated to provide 80% probability to demonstrate non-inferiority (one-sided upper 95% CI < 10 ms) compared to placebo at up to 16 time points.
- Subjects were randomized to receive one of four treatments (Table 1). The therapeutic dose in this study, 30 mg, was selected based on changes in cerebrospinal fluid (CSF) glycine observed in healthy volunteers. [5] The supra-therapeutic dose of 175 mg corresponded to the maximum tolerated dose in males. [6] Moxifloxacin 400 mg was used as the active comparator. All treatments were given orally under fasted conditions.

Table 1: Study design

ECG assessments / Treatment Group	Number of Subjects	Day -1	Day 1	Day 2 to Day 9	Day 10	Day 11
Holter ECG assessments		✔	✔		✔	✔
A Bitopertin 30 mg	56		○ ■	■	■	○
B Bitopertin 175 mg	56		○ ■	■	■	○
C Moxifloxacin / Placebo	28		● □	□	□	○
D Placebo / Moxifloxacin	28		○ □	□	□	●

■ Bitopertin active, □ Bitopertin placebo, ● Moxifloxacin active, ○ Moxifloxacin placebo

- Triplicate ECGs were obtained from Holter electrocardiogram (ECG) monitors (Spiderview, Ela Medical, Le Plessis, France) at 1, 2, 3, 4, 6, 8, 12, and 24 hours after bitopertin administration on day 10, and on the day prior to randomization based on predicted time of first dose. In addition, ECGs were extracted 1, 2, 3, 4, 6, and 12 hours after dosing on days 1 and 11. Subjects remained supine for at least 15 minutes before, to 5 minutes after each scheduled ECG extraction period.
- Blood samples for pharmacokinetic analysis of bitopertin were collected pre-dose on Days 1, 4, 8, 9 and day 10, and 1, 2, 3, 4, 6, 8, 12, 24, 48, 96, 144 and 216 hours after dosing on Day 10. Moxifloxacin plasma concentrations were measured pre-dose, 1, 2, 3, 4, 6, and 12 hours after dosing on Days 1 or 11, depending on when moxifloxacin was administered.

Volunteers

- Male volunteers aged between 18 and 65 years were eligible for inclusion in the study if they had a body mass index between 18 and 30 kg m^{-2} and were healthy on the basis of physical and medical examinations. Volunteers had normal blood pressure (systolic blood pressure [SBP] ≥ 90 and ≤ 140 mmHg, diastolic blood pressure [DBP] ≥ 50 and ≤ 90 mmHg) and triplicate ECG parameters at screening and Day -1 (heart rate between 45 and 90 bpm, QTc ≥300 ms and ≤ 450 ms and < 30 ms difference in two extremes of any QTc).

Statistical Analysis

- The primary study variable was the time-matched change in QTcF interval at steady-state. It was derived by subtracting the mean of the triplicate measurements at each time point on Day -1 from the corresponding mean value on Day 10.
- Data were analyzed on a per protocol basis, including all subjects who were randomized and fully adherent to study procedures. The safety analysis population included all subjects who received at least one dose.
- One-sided upper 95% confidence intervals (CI) for the mean difference in time-matched change in QTcF between each of the bitopertin dose levels and placebo were estimated for all eight time-points using the respective contrasts from an analysis of variance (ANOVA) model. The placebo groups C and D were combined for this analysis.
- Lower one-sided 98.3% CI between moxifloxacin and placebo were estimated at three consecutive time points (starting at the mean T_{max} of moxifloxacin). ANOVA was applied to the difference calculated by subtracting the difference of Day 10 minus Day -1 from the difference of Day 11 minus day 1 [8]. Relationships between plasma concentrations of bitopertin and changes in QTc were investigated by visual inspection of plots of changes in QTc against plasma concentrations.

Safety Assessments

- Safety was assessed by monitoring adverse events, clinical laboratory evaluations, ECGs, and vital signs.

Results

Subject Disposition and Demographics

- 162 subjects (~96%) completed the treatment period and were included in the analysis. Demographic characteristics were comparable across treatment groups (Table 2).

Table 2. Subject demographics

All subjects were healthy male volunteers. Data are presented as mean ± SD (range).

	Bitopertin 30 mg *n* = 56	Bitopertin 175 mg *n* = 56	Moxifloxacin / placebo *n* = 57
Age (years)	32.5 ± 8.9 (19–59)	31.1 ± 8.0 (19–52)	31.8 ± 9.3 (19–56)
Weight (kg)	73.1 ± 10.0 (50.8–95.5)	76.0 ± 10.5 (57.2–98.8)	75.9 ± 10.1 (51.6–101.1)
Body mass index (kg m^{-2})	24.7 ± 2.8 (18.5–29.6)	25.7 ± 2.7 (20.5–29.9)	26.0 ± 2.8 (18.1–30.0)
Race (n[%])			
American Indian or Alaskan Native	1 (2)	-	-
Asian	-	-	2 (4)
Black	2 (4)	1 (2)	4 (7)
White	53 (95)	55 (98)	51 (89)

- Six subjects were withdrawn from the study because of adverse events and one subject was withdrawn because of a faulty Holter ECG flash card.

Effect of Bitopertin on QTc Intervals

- At all time-points after administration of both the therapeutic and supra-therapeutic doses of bitopertin on Day 10, the upper one-sided 95% CI for the placebo-subtracted change from time-matched baseline in QTcF was < 10 ms and the mean difference from placebo was < 5 ms (Figure 1). The lower one-sided 98.3% CI for placebo-corrected mean changes from baseline with moxifloxacin was > 5 ms at 4 hours post dose, thus establishing the assay sensitivity (Figure 2). [7]

Figure 1: Placebo-corrected estimates and upper one-sided 95% confidence intervals for QTcF changes from time-matched baseline (ms) on Day 10 in bitopertin-treated subjects

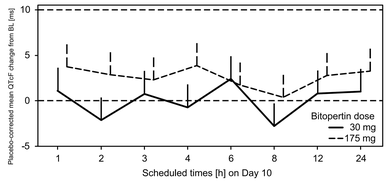
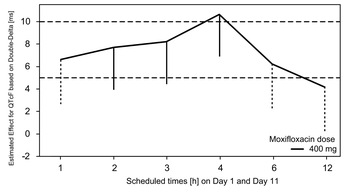


Figure 2: Estimated baseline and placebo corrected effect of moxifloxacin on QTcF with lower 98.3% confidence intervals



- No QTcF or QTcB (QT interval corrected with Bazett's formula) values greater than 450 ms were observed and no subject had a maximum change from time-matched baseline above 60 ms. One subject exceeded the QTcF change from baseline threshold of 30 ms (bitopertin 175 mg) and two subjects exceeded the QTcB change from baseline threshold of 30 ms (placebo).

Effect on other ECG parameters

- There were no differences in PR, QRS, heart rate or RR among treatment groups and no relationships between these parameters and plasma concentrations of bitopertin were observed.
- In one subject receiving bitopertin 175 mg, asymptomatic nodal rhythm was observed in predose safety ECGs on Day 10, which disappeared several days after drug discontinuation. A dedicated analysis of the Holter ECG recordings revealed frequent premature ventricular extrasystoles, which were not of supra-ventricular origin.

Pharmacokinetic Assessments

- The pharmacokinetic parameters $C_{max,ss}$ and AUC_t exhibited slightly less than dose proportional increases after once daily administration of 30 mg and 175 mg bitopertin (Figure 3a and b, Table 3).

Figure 3: Plasma concentration-time profiles for bitopertin on Day 10. (a) steady-state concentrations (b) time course of concentrations following the final dose

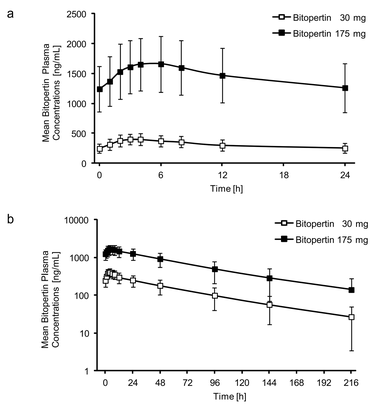


Table 3: Pharmacokinetic parameters of bitopertin on Day 10. Results are presented as geometric means with CVs except for T_{max}, where medians and ranges are shown

	Bitopertin 30 mg *n* = 56	Bitopertin 175 mg *n* = 52
C_{max} (ng mL^{-1})	408 (24%)	1690 (28%)
T_{max} (h)	3.3 (1.1–8.2)	4.3 (2.2–12.4)
AUC_t (h ng mL^{-1})	7180 (30%)	33400 (30%)
$t_{½}$ (h)	53.5 (34.4%)	53.0 (37.8%)

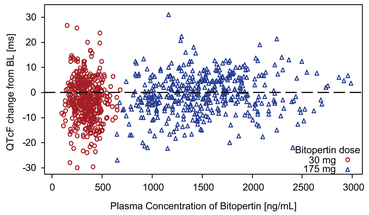
CV: coefficients of variation

- Following administration of 400 mg moxifloxacin, mean C_{max} was 1750 ng mL-1 and median T_{max} was 2.2 hours (range 1.1–4.3 hours).

Pharmacokinetic/Pharmacodynamic Relationship Assessment

- Individual concentrations ranged from 93 to 2980 ng/mL on Day 10.
- There was no apparent effect of bitopertin concentrations on the magnitude of changes in QTcF on Day 10 (Figure 4).

Figure 4: Relationship between changes in QTcF on Day 10 and plasma concentrations of bitopertin



Safety Assessments: Adverse Events

- The proportion of subjects with adverse events was higher in the bitopertin 175 mg treatment group (64%) than in the bitopertin 30 mg (39%) and placebo/moxifloxacin (37%) groups (Table 4).

Table 4: Adverse events (AEs) occurring in ≥5% of subjects in any group

	Bitopertin 30 mg *n* = 56	Bitopertin 175 mg *n* = 56	Moxifloxacin / placebo *n* = 57
Subjects with AEs	22 (39)*	36 (64)	21 (37)
Total number of AEs	66	123	44
Dizziness	7 (13)	22 (39)	3 (5)
Headache	7 (13)	9 (16)	6 (11)
Somnolence	1 (2)	3 (5)	1 (2)
Nausea	0 (0)	8 (14)	1 (2)
Diarrhoea	3 (5)	3 (5)	0 (0)
Back pain	5 (9)	2 (4)	0 (0)
Blurred vision	0 (0)	6 (11)	0 (0)
Insomnia	1 (2)	4 (7)	2 (4)
Sleep disorders	1 (2)	4 (7)	0 (0)
Pruritus	2 (4)	3 (5)	0 (0)
Decreased appetite	0 (0)	4 (7)	1 (2)
Palpitations	0 (0)	3 (5)	0 (0)

* n (%)

- Six subjects withdrew from the study because of adverse events. Two subjects in the placebo/moxifloxacin groups (moderate acute tonsillitis, moderate cellulitis) and four in the bitopertin 175 mg group (severe bronchitis, moderate dizziness, nodal rhythm, mild tremor). No serious adverse events were reported during the study.

Safety Assessments: Others

- There were no relevant differences in heart rate, body temperature, and diastolic and systolic blood pressure between treatment groups.
- A trend for dose-related changes in some hematological parameters (decrease in mean corpuscular hemoglobin [MCH], mean corpuscular volume [MCV], hemoglobin and reticulocytes, and increase in iron and ferritin) were observed after multiple doses of bitopertin, but values mostly remained within the normal range and all changes were reversible.
- No relevant differences in laboratory parameters (including liver transaminases) were observed. One subject in the bitopertin 30 mg dose group presented with clinically significant aspartate aminotransferase (AST; 2.1x ULN [upper limit of normal]) and alanine aminotransferase (ALT; 3.9x ULN) increases on Day 20 which returned back to the normal range on Day 36. No other clinically relevant values outside the normal range were reported.

Conclusion

- Multiple dosing of bitopertin had no clinically relevant effect on QTcF up to the supra-therapeutic dose of 175 mg, which is 6-18 fold higher than the effective doses in a phase 2 study. [4]
- Ten days of dosing of 30 mg of bitopertin was well-tolerated and 175 mg of bitopertin was reasonably well-tolerated given that it is a supra-therapeutic dose.

References:

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