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 a key role in the pathophysiology of schizophrenia (1-3). In an 8-week phase 2 study, 10 and 30 mg of bitopertin demonstrated consistent reductions in PANSS and CGI-S across the treatment period (10). One patient exceeded the QTcF change from baseline threshold of 30 ms (bitopertin 175 mg) and two patients in the placebo/moxifloxacin groups (moderate acute tonsillitis, moderate cellulitis) and four in the bitopertin 175 mg group presented with palpitations, nausea, dizziness, nasal stuffiness, and headache. No serious adverse events were reported during the study.

Methods

Study Design

The study was a multiple-dose, randomized, placebo-controlled, double-blind, double-dummy, parallel-group design conducted in multiple healthy volunteers across clinical research centers. The estimated sample size was 52 and 26 in treatment groups A/B and C/D, respectively based on the corresponding mean value on Day 10.

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 examination. Volunteers had no hypersensitivities to xerostomic drugs (chlorphenamine maleate, zanamivir) and did not exceed the age limit of 65 years.

Study Assessments

Safety Assessments: Clinical Laboratory Evaluations

Hematology: 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 mean cell hemoglobin [MCH]) were observed in bitopertin 30 mg and 175 mg groups but all changes were reversible. There were no relevant differences in laboratory parameters (including liver transaminases) between treatment groups. No relevant differences in laboratory parameters (including liver transaminases) were observed in bitopertin 30 and 175 mg groups, and there were no clinically relevant changes in liver transaminases or full blood counts. One subject in the bitopertin 30 mg dose group presented with clinically significant aspartate aminotransferase (AST) 2.1 X ULN (upper limit of normal) and alanine aminotransferase (ALT) 3.3 X ULN on Day 20 which returned back to the normal range on Day 36. No other clinically relevant values outside the normal range were reported.

Safety Assessments: Others

There were no relevant differences in heart rate, body temperature, and diastolic and systolic blood pressure between treatment groups.

Effect on other ECG parameters

An increased number of episodes of ventricular premature contraction and supraventricular extrasystoles (97%) was observed in bitopertin-treated subjects (bitopertin 175 mg) and placebo/moxifloxacin (75%) (Table 3).

Conclusion

Multiple clinical studies of bitopertin had clinically relevant effect on QTc with 50% of 10 mg, 17% of 30 mg, and 14% of 175 mg demonstrating a relevant increase in QTcF in healthy volunteers.

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 mean cell hemoglobin [MCH]) were observed in bitopertin 30 mg and 175 mg groups but all changes were reversible. There were no relevant differences in laboratory parameters (including liver transaminases) between treatment groups. No relevant differences in laboratory parameters (including liver transaminases) were observed in bitopertin 30 and 175 mg groups, and there were no clinically relevant changes in liver transaminases or full blood counts. One subject in the bitopertin 30 mg dose group presented with clinically significant aspartate aminotransferase (AST) 2.1 X ULN (upper limit of normal) and alanine aminotransferase (ALT) 3.3 X ULN on Day 20 which returned back to the normal range on Day 36. No other clinically relevant values outside the normal range were reported.

References:

[1] Carsten Hofmann, Ludger Banken, Michael Hahn, Dennis Swearingen, Sandra Nagel, Meret Martin-Facklam. BITOPERTIN (RG1678), A NOVEL GLYCINE REUPTAKE INHIBITOR, DOES NOT CAUSE QTcF PROLONGATION IN HEALTHY MALE VOLUNTEERS AT THERAPEUTIC AND SUPER-THERAPEUTIC EXPOSURE. European Neuropsychopharmacology. 2012: Poster 17. 5-9, 2011; Miami Beach, FL.

Figure 2: Estimated baseline and placebo-corrected effect of moxifloxacin on QTcF with lower 95.2% confidence intervals

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

Figure 5: Pharmacokinetic/pharmacodynamic relationship assessment

Figure 6: Effects of bitopertin on QTcF at steady-state conditions.