Reversal of Antipsychotic-Induced Weight Gain in Rats with Miricorilant, a Selective Glucocorticoid Receptor (GR) Modulator

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The following poster describes a use that has not been approved by the U.S. Food and Drug Administration.

ABSTRACT

Background: Antipsychotic-induced weight gain is a significant problem for patients taking second generation antipsychotic medications. Management strategies such as switching medications, lifestyle modifications, and the use of metformin have had modest and mixed results on these patients' weight. Mifepristone, a glucocorticoid and progesterone antagonist, prevents and reverses weight gain in rats administered olanzapine. In healthy male subjects, mifepristone attenuated weight gain associated with olanzapine or risperidone. Miricorilant, a glucocorticoid receptor modulator without affinity for the progesterone receptor, has previously been reported to prevent olanzapine-induced weight gain in rats. We now report the ability of miricorilant to reverse olanzapine-induced weight gain in rats.

Methods: Forty-eight female Sprague-Dawley rats received 2.4 mg/kg/day olanzapine (OLZ) for 34 days while on a normal diet. On day 35, the rats were randomized to 4 different interventions and remained on study until day 57:

1) OLZ + vehicle daily by oral gavage
2) OLZ + 2 mg/kg/day miricorilant once daily
3) OLZ + 1 mg/kg miricorilant twice daily
4) OLZ + 10 mg/kg/day miricorilant once daily

A vehicle only group (n=12) for the entirety of the 57 days was included as a control.

Results: By day 34, the olanzapine treated groups had a higher mean body weight compared to the vehicle only control group (298.2 g vs 270 g, $P<0.01$). From days 35–57, the OLZ + vehicle group continued to gain weight. However, rats randomized to receive OLZ + miricorilant all had statistically significant ($P<0.01$) decreases in their weight by 12%–17% compared to the OLZ + vehicle group. Weight loss in the miricorilant treated rats was immediate and sustained until the end of the study. All rats remained healthy and active during the interventional phase with miricorilant or vehicle.

Conclusion: Miricorilant was effective in reversing the weight gain associated with olanzapine in rats despite the continuation of olanzapine. These findings merit validation in a clinical trial. A phase 2, double-blind, placebo-controlled, clinical study (GRATITUDE, NCT03818256) is actively enrolling in the US to evaluate the safety, efficacy, and pharmacokinetics of miricorilant in reversing recent antipsychotic-induced weight gain in obese patients with schizophrenia.

INTRODUCTION

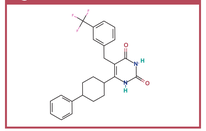
CARDIOMETABOLIC SIDE EFFECTS OF ANTIPSYCHOTIC MEDICATIONS: DRIVERS OF MORBIDITY AND MORTALITY

- Schizophrenia, which has a lifetime prevalence of about 1% [1], is associated with a 2-fold higher prevalence of metabolic syndrome [2] and a 3.5-fold increase in mortality [3] compared with the general population.
- Second-generation antipsychotic medications, eg, olanzapine, are the first-line treatment for patients with schizophrenia.
  - However, these medications are associated with cardiometabolic side effects, including weight gain, type 2 diabetes mellitus, and dyslipidemia, that contribute significantly to the observed elevated morbidity and mortality [4].
  - In the CATIE study [5], patients taking olanzapine gained an average of 2 pounds per month, with 30% of patients gaining more than 7% of baseline body weight.

COUNTERACTING ANTIPSYCHOTIC-INDUCED WEIGHT GAIN: ROLE OF GLUCOCORTICOID RECEPTOR MODULATION

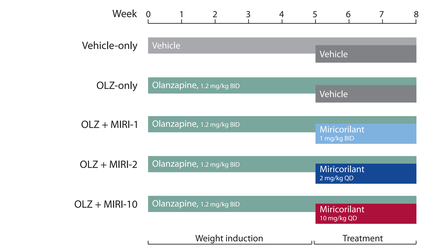
- Lifestyle changes, switching or reducing the dose of antipsychotics, and existing pharmacological therapies have shown modest results in controlling antipsychotic-induced weight gain (AIWG) [6].
- While currently no medications are approved for the management of AIWG, glucocorticoid receptor (GR) modulators have demonstrated their potential to control AIWG in preclinical and clinical studies.
  - Mifepristone, a GR antagonist, has been shown to prevent and reverse weight gain in rats administered olanzapine [7].
  - In healthy male subjects, mifepristone attenuated weight gain associated with olanzapine or risperidone [8, 9]. However, due to antiprogesterone effects, mifepristone is associated with side effects such as endometrial hypertrophy, irregular vaginal bleeding, and termination of pregnancy, which limit its use in the general population.
  - Miricorilant (CORT118335, Corcept Therapeutics, **Figure 1**), an investigational new drug that modulates GR without affinity for the progesterone receptor, has previously been reported to prevent olanzapine-induced weight gain in rats [10].
- Here, we report the ability of miricorilant to reverse olanzapine-induced weight gain in rats and introduce GRATITUDE, a phase 2, double-blind, placebo-controlled, clinical study to evaluate the safety, efficacy, and pharmacokinetics of miricorilant in reversing recent AIWG in obese patients with schizophrenia.

Figure 1. Miricorilant Structure



REVERSAL OF AIWG IN RODENTS

Figure 2. Design of the Rodent Study



n=12 for each group. All compounds were dosed by oral gavage.
MIRI, miricorilant; OLZ, olanzapine.

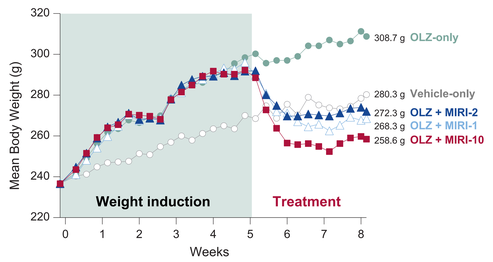
RODENT STUDY DESIGN

- To assess the effects of miricorilant on olanzapine-induced body weight gain, 60 female Sprague-Dawley rats were randomized into 5 treatment groups (**Figure 2**).
- Weight gain was induced by administration of olanzapine (OLZ) over a 5-week period ("weight-induction phase").
- Starting at week 6, either miricorilant (MIRI, 3 dosing regimens) or vehicle was administered orally. Olanzapine administration was continued during this phase ("treatment phase").
- A vehicle-only group was included as a control for the 8-week duration of the study.
- Efficacy was assessed based on body weight, food consumption, mortality, and clinical observations.

MIRICORILANT REVERSES OLANZAPINE-INDUCED WEIGHT GAIN

- As expected, administration of olanzapine significantly increased body weight compared to vehicle-only. Mean body weights at the end of the weight-induction phase (week 5) were 298.2 g vs 270.0 g ($P<0.01$, 10.4% weight gain, **Figure 3**).
- Rats in the OLZ-only group continued to gain weight for the duration of the study (308.7 g body weight at study end, 10.1% heavier than vehicle-only, $P<0.01$, **Figure 3**).
- In contrast, rats receiving olanzapine + miricorilant experienced quick, steep, and sustained weight loss during the treatment phase (weeks 6–8, **Figure 3**).
  - At study end, miricorilant-treated animals had statistically significant decreases in body weight compared to the OLZ-only group (12%–17%, $P<0.01$).
  - The 1 mg/kg BID and 2 mg/kg QD dosing regimens induced similar weight loss, resulting in body weights comparable to the vehicle-only group (268.3 g and 272.3 g, respectively, at study end, compared to 280.3 g).
  - In the 10 mg/kg miricorilant group, weight loss after the addition of miricorilant to olanzapine was greater than in the lower-dose groups (258.6 g body weight at study end).
- By all measures, rats remained healthy and active after taking miricorilant, with no mortalities or treatment-related adverse clinical signs aside from the expected reduction in body weight.

Figure 3. Changes in Mean Body Weight Over the Study Period



Treatment with miricorilant was initiated in week 6.

FOOD CONSUMPTION NORMALIZED WITH MIRICORILANT

- During the weight-induction phase (weeks 1–5), mean increase in food consumption across the groups treated with olanzapine was 13%.
- Miricorilant caused a normalization in food consumption to vehicle-only levels by study end.
  - During the first week of treatment, food consumption in miricorilant-treated animals was 13%–20% lower when compared to the vehicle-only controls ($P<0.01$) and 16%–23% lower compared to OLZ-only ($P<0.01$).
  - Food consumption returned to vehicle-only levels by study end for all 3 miricorilant dose regimens.

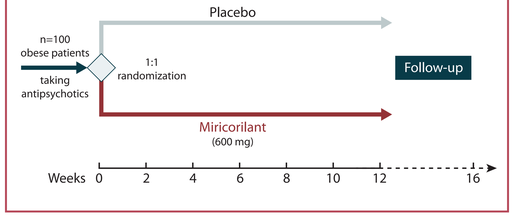
CLINICAL STUDY: THE GRATITUDE PHASE 2 TRIAL

ADDRESSING AIWG IN OBESE PATIENTS WITH SCHIZOPHRENIA

- GRATITUDE (CORT118335-876, NCT03818256) is a double-blind, placebo-controlled, randomized phase 2 study to assess the safety, efficacy, and pharmacokinetics of miricorilant in obese patients with schizophrenia and recent weight gain while taking olanzapine, risperidone, or quetiapine.
  - The study is being conducted at approximately 22 centers across the United States (**Figure 4**).
  - 100 subjects will be recruited and randomized 1:1 to receive miricorilant (600 mg) or placebo in addition to their established antipsychotic medication (**Figure 5**).

Figure 4. GRATITUDE Study Centers

Figure 5. GRATITUDE Study Design



STUDY PARTICIPANTS

Table 1. Key Inclusion and Exclusion Criteria for the GRATITUDE Study

Inclusion Criteria	Exclusion Criteria
• 18–65 years old • BMI ≥30 kg/m^2 • Diagnosis of schizophrenia • Currently taking olanzapine, risperidone, or quetiapine with documented weight gain (≥5% within 6 months of initiation) • On a stable dose of medication for 1 month prior to screening • Clinically stable and unlikely to require changes to their antipsychotic medication for the study duration	• Psychiatrically unstable • Currently taking more than one antipsychotic medication • History of medical conditions affecting body weight (eg, poorly controlled hyper- or hypothyroidism, eating disorders, polycystic ovary syndrome) • Poorly controlled diabetes mellitus or hypertension • History of orthostatic hypotension • Weight-loss treatment, surgery, or liposuction

SUMMARY

- In rodent models, the GR modulator miricorilant is effective in both preventing [10] and reversing weight gain despite continued olanzapine dosing.
- Notably, miricorilant lacks the antiprogesterone effects of mifepristone and is hence suitable for development as a drug for the management of AIWG.
- Across multiple phase 1 studies, miricorilant has been administered to more than 150 healthy volunteers.
  - Miricorilant was well tolerated, with few treatment-emergent adverse events.
  - Miricorilant has successfully attenuated olanzapine-induced weight gain in healthy male volunteers [11].
- To evaluate the safety, efficacy, and pharmacokinetics of miricorilant in obese patients with schizophrenia and recent weight gain due to antipsychotic treatment, the phase 2 study GRATITUDE (NCT03818256) is actively enrolling in the United States.

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DISCLOSURES

APL, JKB, AG, HJH: Employees, Corcept Therapeutics.

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