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An open-label study on ulotaront's effects on insulin-glucose regulation in schizophrenia patients with metabolic syndrome and prediabetes: Part I

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Abstract

Aims: Ulotaront is an investigational trace amine-associated receptor 1 (TAAR1) agonist demonstrated to slow gastric emptying in schizophrenia patients with metabolic syndrome (MetSyn) and prediabetes type 2. Here we evaluate the effects of ulotaront on glucose-insulin dynamics in schizophrenia patients with MetSyn and prediabetes.

Methods and Methods: NCT05463770 was a Phase 1b clinical trial, with an open-label, multi-dose design comparing ulotaront's metabolic effects to each participant's baseline of prior antipsychotic treatment. Oral glucose tolerance test (oGTT), a mixed meal tolerance test (MMTT) and a spirulina breath test (GEBT) were conducted at a baseline of prior antipsychotic medication and repeated after up to 3 weeks of twice-a-day dosing of ulotaront.

Results: In oGTT and MMTT, mean changes from baseline AUCs for glucose, c-peptide and insulin were -19.7 h×mg/dL, -269 h×pg/mL, -41.0 h×uIU/mL, and -10.8 h×mg/dL, -2860 h×pg/mL, -132 h×mg/dL, respectively. Insulin response during the MMTT reached nominal statistical significance ($p = 0.021$, effect size $= -0.7$). The mean change from baseline gastric emptying time was -0.60 min.

Conclusions: Despite limited sample size, primary endpoints favoured ulotaront over prior antipsychotics with respect to a reduction trend in glucose, c-peptide and insulin. The insulin response after a solid meal was nominally significant, suggesting that semi-chronic twice-a-day dosing of ulotaront might improve insulin dynamics in schizophrenia patients at high diabetes risk.

KEYWORDS
drug development, glycaemic control, insulin resistance, phase I–II study

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1 | INTRODUCTION

Mendelian studies indicate a potential causal link between insulin-related traits, characterized by a genetic predisposition to high insulin secretion and insulin resistance and an increased risk of schizophrenia.[1] This risk is further heightened with standard (typical or atypical)[2,3] antipsychotic treatment for schizophrenia and triples compared to those untreated patients.[4] Notably, atypical antipsychotics can cause worsening in glucose tolerance within just 6 months of treatment in medication-naïve patients with schizophrenia.[5] Additionally, these drugs affect insulin secretion and resistance, whether by long-term exposure in schizophrenia patients[6,7] or short-term exposure in healthy volunteers.[8,9] Evidence also suggests that psychiatric patients, regardless of the diagnosis, when on atypical antipsychotics may exhibit alterations in insulin secretion, indicative of pancreatic β-cell dysfunction,[10] and revealing potential metabolic effect across various diagnostic categories.

The investigational agent ulotaront, a trace amine-associated receptor 1 (TAAR1) agonist, is currently being studied for the treatment of schizophrenia,[11] generalized anxiety disorder (NCT05729373), and as an adjunctive treatment for major depressive disorder (NCT05593029). In line with preclinical rodent studies,[12] a recent clinical study showed that an acute dose of ulotaront (150 mg) delayed gastric emptying of solids in high-risk schizophrenia patients with comorbid metabolic syndrome and prediabetes type 2.[13] In a ulotaront thorough QT (TQT) study,[14] following a standardized meal challenge in patients with chronic schizophrenia, exploratory analyses demonstrated that ulotaront reduced circulating insulin and c-peptide concentrations and attenuated the postprandial glucose response compared with placebo. These findings suggest that ulotaront may exert a modulatory effect on glycaemic control in the post-prandial state, with large effect sizes on insulin and c-peptide levels.[15]

This paper presents findings from an open-label, fixed-sequence, multiple-dose study that evaluates the metabolic changes in subjects diagnosed with schizophrenia, concurrent metabolic syndrome and prediabetes. At baseline, participants maintained their regular outpatient antipsychotic treatments, followed by the washout and twice a day (bid) administration of ulotaront for up to 3 weeks. Well-established physiological and metabolic tests, including the gastric emptying breath test (GEBT) to evaluate gastric emptying, the oral glucose tolerance test (oGTT) to assess glucose processing efficiency and the mixed meal tolerance test (MMTT) to probe insulin secretion in response to a complex meal, were utilized at baseline (while patients were on their outpatient antipsychotics) and after semi-chronic dosing of ulotaront. The study concluded after enrolling 15 participants for reasons unrelated to the drug's safety or efficacy. However, collected data from 12 subjects who completed the study revealed valuable insights into the potential metabolic effects of ulotaront bid dosing in this high-risk patient group.

2 | METHODS

2.1 | Study registration and ethics

This study (NCT05463770) was conducted in accordance with the International Conference on Harmonization Good Clinical Practices guidelines, the ethical principles of the Declaration of Helsinki, and applicable local law(s) and regulation(s). The study protocol and informed consent form (ICF) were approved by the Institutional Review Boards before the enrolment of any participant.

2.2 | Study participants

Schizophrenia patients (Figure S1a, randomized [$n = 15$]) eligible for this study were individuals aged 18–65 years, either male or female, with a primary schizophrenia diagnosis as defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM-5). Key psychiatric, metabolic syndrome and prediabetes inclusion criteria are highlighted in Table S1a.

2.3 | Study design

This was a Phase 1, open-label, fixed-sequence, multiple-dose study assessing glucose and insulin-related parameters with ulotaront compared to the prior antipsychotic (PA) standard of care (Figures 1 and S1b). After initial screening, subjects were admitted to the clinical research unit. Upon meeting continuation criteria, subjects underwent an oGTT, a MMTT and a GEBT. Following these assessments, subjects had their PA or any other psychotropic medications washed out, based on the antipsychotic elimination half-life.

Subsequently, subjects followed an individualized ulotaront titration period (2–4 days per dose level) for up to 16 days, after which they underwent the oGTT, MMTT and GEBT tests again during the Stable Dose Period of ulotaront (lasting between 5 and 8 days). Afterwards, patients were reintroduced to their respective antipsychotic and, following stabilization on their PA medications, subjects were discharged from the clinical research unit and returned for a follow-up visit approximately 7 ± 2 days post-discharge.

2.4 | Oral glucose tolerance test

The 75 g oGTT is the standard reference method[16] or diagnosing specific categories of glucose intolerance and Type 2 diabetes. After an overnight fast, blood samples were collected to analyse plasma glucose, insulin, c-peptide and ulotaront pharmacokinetics (PK). Measurements of glucose, insulin and c-peptide are taken at 15 and 2 min before the oGTT and at 10, 20, 30, 60, 90 and 120 min after the standard oral glucose load (75 g).

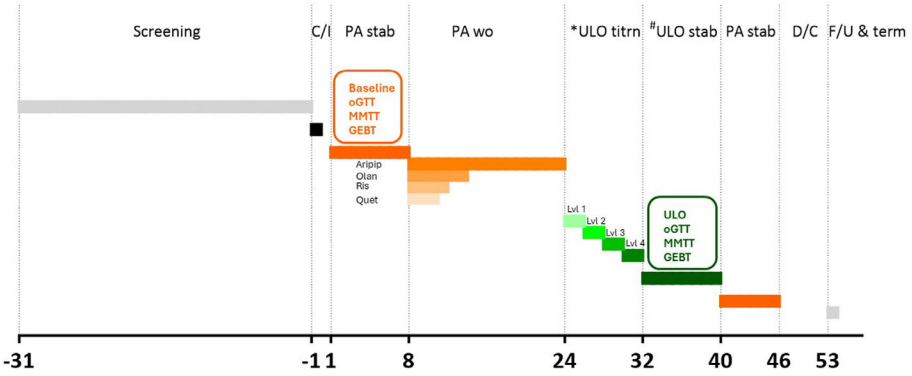

FIGURE 1 Study design. Aripip, aripiprazole; C/I, check-in on day 1; F/U and term, follow up and study termination; GEBT, ^{13}C-spirulina gastric emptying breath test; MMTT, mixed meal tolerance test; oGTT, oral glucose tolerance test; Olan, olanzapine; PA stab, prior antipsychotic stable period; Quet, quetiapine; Ris, risperidone ULO, ulotaront. *Subjects underwent a 4-step dose titration with ulotaront from 8 to 16 days except for one subject who completed two doses of the titration procedure over 16 days. #Subjects were stabilized to ulotaront 100 mg (total) from 5 to 8 days except for one subject who received 75 mg (total). An approximately 7-day window was allowed for completion of the investigations (PA: Days 1–8 and ULO: Days 32–40). The procedures (GEBT, oGTT, MMTT) were scheduled based on operational feasibility, with the order varying across participants; however, a minimum recovery period of 3 days was required between the oGTT and MMTT to avoid carryover effects. ULO titrn = ulotaront titration: (1) 50 mg in the evening and 12.5 mg in the morning for a minimum of 2 days (Dose Level 1), (2) 50 mg in the evening and 25 mg in the morning for a minimum of 2 days (Dose Level 2), (3) 50 mg in the evening and 37.5 mg in the morning for a minimum of 2 days (Dose Level 3), (4) 50 mg in the evening and 50 mg in the morning for a minimum of 2 days (Dose Level 4). ULO stab = ulotaront stable period: (1) 50 mg in the evening and 50 mg in the morning for 5–8 days.

2.5 | Mixed meal tolerance test

The MMTT is a diagnostic procedure designed to evaluate the body's capability to regulate glucose levels after ingesting a meal balanced in carbohydrates, proteins and fats, thus closely mimicking normal eating conditions.[17] Standardized MMTT protocols, such as that validated by Shankar et al.,[17] demonstrate high reproducibility (intraclass correlation coefficients up to ~0.8 for key measures), operational feasibility in multicentre settings and improved tolerability relative to oGTT. Additionally, MMTT supports validated modelling approaches, including minimal model analysis of c-peptide, the insulinogenic index and the disposition index, with flexible sampling schedules such as the validated 90-min c-peptide measurement.[18] These characteristics make MMTT particularly well suited for trials targeting postprandial glucose-insulin physiology, incretin modulation, or metabolic interventions in insulin-resistant states. A standard meal consisted of: Boost Very Original Very Vanilla (calculated calories: 240; carbohydrates: 68%, fat: 15%, protein: 17%) and Power Bar Protein Plus Chocolate Peanut Butter (calculated calories: 234; carbohydrates: 56%, fat: 19%, protein: 25%). Immediately after the meal was consumed, 1500 mg of liquid acetaminophen was given for assessment of gastric emptying rate. The MMTT provides a comprehensive physiological stimulus for insulin secretion, as β-cells respond to specific amino acids and fatty acids in addition to glucose. During the test, blood samples were collected to measure plasma glucose, insulin, c-peptide, acetaminophen and ulotaront pharmacokinetics (PK). Measurements of glucose, insulin and c-peptide concentrations, along with the β-cell responsivity index, were taken at 30, 15 and 2 min before the MMTT and at 10, 15, 20, 30, 60, 90, 120, 180 and 240 min after the ingestion of a standard meal.

2.6 | Acetaminophen test

Acetaminophen is not absorbed in the stomach and begins to be absorbed only when it reaches the small intestine. As such, it is used as a marker in a gastric emptying test to assess how quickly the stomach empties its contents into the small intestine. Subjects were given 1500 mg of liquid acetaminophen at $t = 0$ min of the MMTT. Acetaminophen blood samples were collected at 10, 15, 20, 30, 60, 90, 120, 180 and 240 min.

2.7 | Gastric emptying breath test

The [^{13}C]-spirulina breath test (GEBT)[19] is a US Food and Drug Administration (FDA)-approved breath test intended to be used for measurements of the rate of solid-phase gastric emptying and as an aid in the diagnosis of gastroparesis. GEBT results are reported using kPCD, a metric which expresses a subject's $^{13}CO_2$ excretion rate.

2.8 | Data analysis

Change from baseline PA in oGTT was a primary endpoint, derived as plasma total and net incremental area under the concentration–time curve from time 0 to 120 min ($AUC_{0-120\ min}$) of glucose, insulin and c-peptide in oGTT to stable dose (ulotaront) period assessment. Change from baseline biomarker data was calculated as the difference between the post assessment data and the baseline data, where baseline was defined as the average of the 15 and 2 min preassessment data. A post hoc exploratory analysis of hepatic insulin clearance,

defined as a ratio of c-peptide AUC to insulin AUC, was conducted. The post hoc test was based on a paired *t*-test by default. If there was a violation of normality assumption (*p*-value <0.05 in Shapiro–Wilk test), the Wilcoxon signed rank test was used.

Change from baseline (PA) in MMTT was a primary endpoint, derived as $AUC_{0-240\ min}$ for the glucose, insulin, c-peptide and β-cell function index to stable dose (ulotaront) period assessment. β-Cell-function index (HOMA-B) was calculated as 20× insulin (μU/mL)/[plasma glucose (mg/dL) – 63]. Change from baseline biomarker data was calculated as the difference between the postassessment data and the baseline data, where baseline was defined as the average of the 30, 15 and 2 min preassessment data for MMTT. Gastric emptying was evaluated as change from baseline (PA) in plasma $AUC_{0-240\ min}$ and maximum concentration (C_{max}) of acetaminophen levels to stable dose (ulotaront) period assessment. A post hoc exploratory analysis of hepatic insulin clearance, defined as a ratio of c-peptide AUC to insulin AUC, was conducted.

The following PK parameters were estimated for acetaminophen in plasma as a surrogate measure of gastric emptying rate: C_{max} (maximum observed concentration [ng/mL]), t_{max} (time of maximum concentration [min]), $AUC_{0-240\ min}$ calculated using the linear-log trapezoidal method. Additionally, change from baseline parameters were derived as: ΔC_{max} change from baseline C_{max}, (ULO Stable Dose Period) – C_{max} (PA Baseline period); $\Delta AUC_{0-240\ min}$ change from baseline $AUC_{0-240\ min}$ (ULO Stable Dose Period) – $AUC_{0-240\ min}$ (PA Baseline period).

Pharmacodynamic endpoints for gastric emptying were gastric emptying rate ($T_{1/2}$), lag time (i.e., times elapsed for gastric emptying by 10% denoted by t_{10}) and kPCD, a metric which expresses a subject's $^{13}CO_2$ excretion rate. kPCD was collected for measurements of the rate of solid phase gastric emptying and as an aid in the diagnosis of gastroparesis at the following nominal times during the PA Baseline period and ulotaront Stable Dose Period. Change from baseline parameters were derived as: $\Delta T_{1/2}$ ([ULO Stable Dose Period] – $T_{1/2}$ [PA Baseline Period]); Δt_{10} ([ULO Stable Dose Period] – $T_{1/2}$ [PA Baseline Period]) and ΔkPCD ([ULO Stable Dose Period] – $T_{1/2}$ [PA Baseline Period]).

For summary of change from baseline values, 95% CI and *p*-value were computed from paired *t*-test by default. If there was a violation of normality assumption (*p*-value <0.05 in Shapiro–Wilk test), Wilcoxon signed rank test was used for both 95% CI and *p*-value. Two-sided *p*-values less than 0.05 were taken to indicate nominal statistical significance. Statistical analysis was performed using SAS software v9.4 (SAS Institute, Cary, NC).

3 | RESULTS

3.1 | Demographics of participants

Table 1 is a summary of the baseline characteristics of patients; individual participant data is presented in Table S1b. The screening process involved 56 participants (Figure S1a), out of whom 15 were randomized. Fifteen participants received PA and 14 ulotaront treatment. Twelve subjects successfully completed the study, providing both PA and ulotaront data (GEBT, oGTT and MMTT).

TABLE 1 Demographics summary (safety population).

Characteristic at baseline	Mean ± SD or *N* (%), *N* = 15
Age—years	47.8 ± 10.9
Sex—*N* (%)	
Male	8 (53.3)
Female	7 (46.7)
Race—*N* (%)	
Black or African American	13 (86.7%)
White	2 (13.3%)
Ethnicity—*N* (%)	
Not Hispanic/Latino	14 (93.3%)
Hispanic/Latino	1 (6.7%)
Years since initial onset of schizophrenia	25.8 ± 12
PANSS score[a]	
Total	58.5 ± 9.9
Positive subscale	14.1 ± 3.2
Negative subscale	19.7 ± 7.8
Prior antipsychotic—*N* (%)	
Risperidone	4 (26.7)
Aripiprazole[c]	5 (33.3)
Olanzapine	1 (6.7)
Quetiapine[c]	7 (46.7)
CGI-S scale score[a]	3.1 ± 0.6
Body mass index (kg/m^2)[b]	38 ± 8.83
Metabolic syndrome criteria—*N* (%)[b]	
3/5	7 (47)
4/5	7 (47)
5/5	1 (6)
HbA1c (%)[a]	6.0 ± 0.5
HOMA-IR[a]	3.3 ± 2.5

Note: Age is relative to the date of informed consent. Baseline is defined as the last non-missing measurement prior to the first dose of study drug prior antipsychotic taken post check-in (including unscheduled assessments).
Abbreviations: HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; SD, standard deviation.
[a]Collected at screening.
[b]Collected at baseline.
[c]One subject was prescribed quetiapine + aripiprazole.

The study targeted adult patients with chronic schizophrenia, with the average participant age of 48 years and a mean duration of 26 years since initial diagnosis. The proportion of female patients mirrors that found in previous clinical trials, aligning with the documented impact of sex on the illness's outcome and severity. Quetiapine was the most administered medication among the subjects. For inclusion in the analysis of primary, secondary and exploratory endpoints,

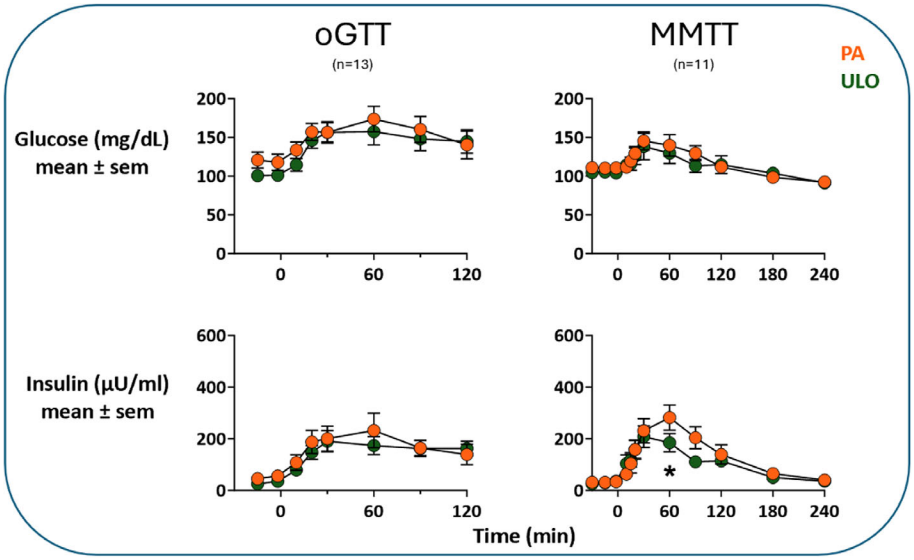

FIGURE 2 oGTT ($AUC_{0-120\ min}$) and MMTT ($AUC_{0-240\ min}$) glucose and insulin AUCs. 95% CI and *p*-value are computed from paired *t*-test by default. For insulin, there was a violation of normality (*p*-value <0.05 in Shapiro–Wilk test); Wilcoxon signed rank test was used. *The mean change from baseline (PA) to stable dose (ULO) period in $AUC_{0-240\ min}$ of insulin −132 h×uUI/mL ($p = 0.021$, 95% CI −254 to −9.9). Abbreviations: MMTT, mixed meal tolerance test; oGTT, oral glucose test; PA, prior antipsychotic; ULO, ulotaront.

participants needed to meet a minimum of three out of five predefined criteria for metabolic syndrome and were classified as prediabetic, with average HbA1c levels of 6% and HOMA-IR score of 3.3. Additionally, a considerable number of participants were considered obese, with an average body mass index of 38 ± 8.83 kg/m^2.

3.2 | Ulotaront pharmacokinetics

After administering 50 mg of ulotaront twice daily, mean plasma concentrations in 11 subjects increased from 73.3 ng/mL at 0.67 h post-dose to 183 ng/mL at 2 h post-dose during the oGTT day. On the MMTT day, levels rose from 85.0 ng/mL at 0.67 h post-dose to 194 ng/mL at 4 h post-dose.

3.3 | Effects of treatment on glucose tolerance (oGTT)

The mean change from baseline (PA) to stable dose (ulotaront) period in $AUC_{0-120\ min}$ of glucose, insulin and c-peptide was −19.7 h×mg/dL ($p = 0.542$, 95% CI −49.1 to 15.2), −41 h×uUI/mL ($p = 0.946$, 95% CI −148 to 65.8) and −269 h×pg/mL ($p = 0.859$, 95% CI −3490 to 2950), respectively (Figures 2 and S2a).

3.4 | Effects of treatment on insulin sensitivity (MMTT)

The mean change from baseline (PA) to stable dose (ulotaront) period in $AUC_{0-240\ min}$ of glucose, insulin and c-peptide was −10.8 h×mg/dL ($p = 0.588$, 95% CI −53.4 to 31.8), −132 h×uUI/mL ($p = 0.021$, 95% CI −254 to −9.9) and −2860 h×pg/mL ($p = 0.174$, 95% CI −7200 to 1475), respectively (Figures 2 and S2b). The mean change from PA baseline in pre-MMTT β-cell

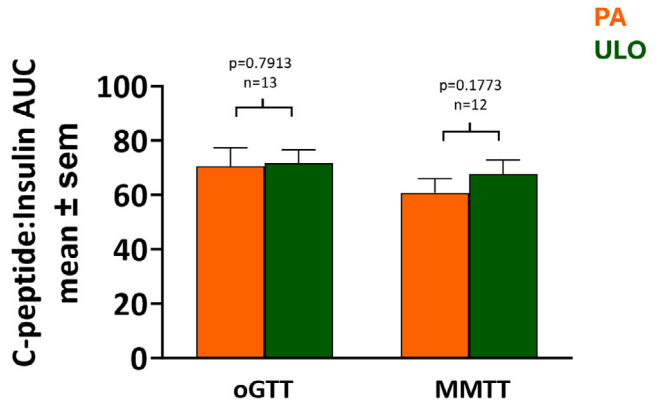

FIGURE 3 Hepatic insulin clearance estimates in oGTT and MMTT. Abbreviations: AUC, area under the curve; MMTT, mixed meal tolerance test; oGTT, oral glucose test; PA, prior antipsychotic; ULO, ulotaront.

function index (HOMA-B) was 23.1 (95% CI, −0.977 to 9.30) and a nominal *p*-value of 0.110.

3.5 | Effects of treatment on hepatic insulin clearance

Hepatic insulin clearance mean estimates, PA and ulotaront, in oGTT and MMTT, were 70.44 and 71.63 ($n = 13$, $p = 0.7913$) and 60.8 and 67.62 ($n = 12$, $p = 0.1773$), respectively (Figure 3).

3.6 | Effects of treatment on gastric emptying (GEBT)

The mean change from baseline (PA) to stable dose (ulotaront) period assessment for the time required by the stomach to empty 50% of the

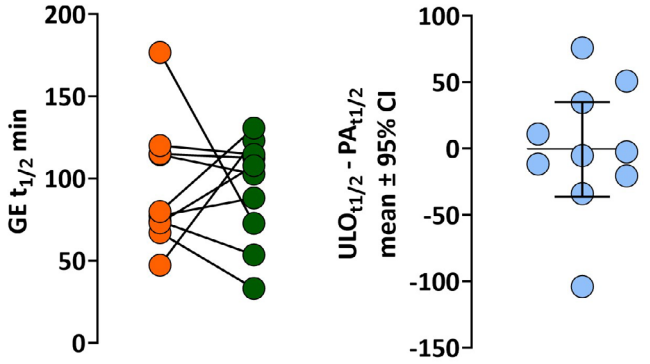

FIGURE 4 ^{13}C-spirulina breath test (GEBT); mean change gastric emptying (GE $t_{1/2}$) from baseline (PA) to stable dose (ULO) of the ingested meal. No significant changes were observed. Abbreviations: GEBT, spirulina gastric emptying breath test; GE $t_{1/2}$, time required by the stomach to empty 50% of the ingested meal; PA, prior antipsychotic, ULO, ulotaront. $n = 10$ subjects in analysis.

ingested meal (gastric emptying $T_{1/2}$) and lag time (T_{10}) and were −0.60 min ($p = 0.970$, 95% CI: −36.14 to 34.94) and −9.37 min ($p = 0.424$, 95% CI: −13.55 to 3.90), respectively. Individual subjects and mean changes from the baseline in gastric emptying $T_{1/2}$ are shown in Figure 4. kPCD mean changes from baseline for each time-point are shown in Table S3.

3.7 | Safety assessment

Adverse events are detailed in Table S2. The study reported no fatalities or serious adverse events (AEs). Consistent with the Phase 2 findings,[11] AEs such as somnolence and nausea occurred more frequently in the ulotaront-treated group. Other potential differences in reported AEs require further evaluation, considering the totality of ulotaront exposure data across all clinical stages, the twice-daily dosing regimen unique to this study and potential tachyphylaxis. In summary, twice-daily administration of 50 mg ulotaront was generally well tolerated by adults with schizophrenia who were at an elevated risk for diabetes.

4 | DISCUSSION

In this open-label, fixed-sequence study, twice-daily administration of ulotaront was generally safe and well tolerated. Assessment of glucose-insulin dynamics using the MMTT demonstrated a modest but nominally significant reduction in circulating insulin concentrations, while glucose levels remained stable. This pattern implies a possibly improved insulin handling without deterioration in glycaemic control. Complementary biomarker analyses reinforced these results, showing favourable trends in fasting β-cell function (HOMA-B) and hepatic insulin clearance, both consistent with a reduction in compensatory hyperinsulinemia. Results suggest that ulotaront may beneficially modulate insulin secretion and/or enhance hepatic insulin clearance in patients with schizophrenia who present with comorbid metabolic syndrome and prediabetes.

A 2003 FDA advisory warned of increased hyperlipidaemia and diabetes risk for patients taking second-generation (i.e., atypical) antipsychotics, requiring that class warnings be added to the labelling and that all drug manufacturers mail "Dear healthcare professional" letters to inform health care providers of the new warning.[20] Both atypical and typical antipsychotics, when administered to the first-episode, drug-naïve patients with schizophrenia and healthy volunteers were shown to increase fasting and oGTT glucose levels, and this finding reached statistical significance by week 14 of treatment.[21] Wani et al.,[21] reported that typical and atypical antipsychotics (haloperidol, risperidone, aripiprazole and olanzapine) increase plasma glucose levels compared to the healthy volunteers. Additionally, the olanzapine-treated group displayed significantly higher increase in glucose relative to risperidone-, aripiprazole- and haloperidol-exposed patients. These findings are consistent with results reported by Newcomer et al.[22] for clozapine, olanzapine and risperidone in patients with chronic schizophrenia. Moreover, Kornetova et al.[23] showed that, when stratified by the presence or absence of metabolic syndrome, patients with chronic schizophrenia had distinct metabolic and structural profiles after just 6 weeks of consistent treatment in an inpatient setting. Significant changes in glucose and lipid metabolism, and body fat composition shifts, were particularly prominent in the non-metabolic syndrome group, highlighting possible antipsychotics' role in triggering development of metabolic syndrome.[21]

Indeed, impaired glucose tolerance, compensatory hyperinsulinemia and altered lipid metabolism are observed after exposure to most atypical antipsychotics, across different ethnic and racial groups.[23–25] While the temporal association supports a causal role for these medications, the picture is complicated by the fact that antipsychotics act within an already disturbed metabolic environment. Even before the treatment, patients experiencing a first episode of schizophrenia often exhibit pretreatment insulin resistance.[26–29] Following antipsychotic exposure, however, metabolic abnormalities typically worsen, encompassing impaired glucose tolerance, hyperinsulinemia and dyslipidaemia. These changes accelerate progression toward metabolic syndrome and substantially increase the risks of type 2 diabetes[30,31] and metabolic dysfunction-associated steatotic liver disease (MASLD) or metabolic dysfunction-associated fatty liver disease (MAFLD). Prevalence rates of MASLD in schizophrenia cohorts have been reported to be as high as 64.6%.[32]

Hepatic insulin clearance is impaired in MASLD, leading to systematic hyperinsulinemia that does not necessarily reflect increased β-cell secretion but rather reduced hepatic degradation. This impairment correlates with intrahepatic fat accumulation and insulin resistance.[33,34] As hepatic steatosis progresses, insulin clearance declines further and circulating insulin levels rise disproportionately, particularly in individuals with Type 2 diabetes.[35] This phenomenon complicates the interpretation of insulin indices derived from oGTT and MMTT. Notably, reductions in insulin clearance accompanied by elevated peripheral insulin concentrations have been proposed as potential markers for identifying diabetes risk in prediabetes.[36]

In interventional trials involving patients with MASLD, the MMTT may offer a more physiological and more reproducible platform than the oGTT. Importantly, MMTT-derived insulin indices have been directly associated with MAFLD status,[37] underscoring its translational relevance in fatty liver disease. By contrast, oGTT remains indispensable for diagnostic classification but is more prone to confounding in MASLD due to accelerated gastric emptying (relative to mixed meals) and reduced hepatic insulin clearance, both of which can distort glucose and insulin readouts.[33,35,38] Accordingly, it is plausible that unrecognized comorbid MASLD/MAFLD in our high-risk schizophrenia cohort contributed to the observed discrepancy between oGTT and MMTT outcomes, where an insulin-lowering effect of ulotaront reached nominal statistical significance only with the MMTT.

An additional potential confound of this study is that in contrast to the acute daily dosing of ulotaront, which delayed gastric emptying,[13] semi-chronic, bid administration of ulotaront showed no significant effects on gastric emptying, as assessed by the GEBT or acetaminophen test. The lack of changes in gastric emptying may be due to the low number of subjects used in this study, the sensitivity/reliability of the diagnostic tests, or the confounding effect of MASLD on gastric emptying. Alternatively, tachyphylaxis may also be implicated, identifying a need for a future study incorporating gastric scintigraphy and stratification by MASLD/MAFLD status.

Reduction in insulin, nominally significant in MMTT, and no demonstrable effect on gastric emptying with semi-chronic ulotaront bid dosing suggest a possible decrease in β-cell insulin secretion or an increase in insulin clearance. Immunohistochemical evidence of TAAR1 expression in human pancreatic islets[39] and human pancreatic islets transcriptomics[40] provides plausibility of a direct effect of ulotaront on β-cell islets. In addition, TAAR1 modulation of insulin hepatic clearance could be centrally mediated through restoration of the vagal tone.[41] This could involve direct ulotaront action on the dorsal motor nucleus of the vagus nerve and its relay station, the nucleus of the solitary tract.[12] Future studies are needed to test this hypothesis.

A major limitation of this study was its premature termination, which compromised both the protocol-defined statistical power and the target sample size of 19 subjects. Nevertheless, collectively, our findings suggest that ulotaront may beneficially modulate insulin secretion and/or enhance hepatic insulin clearance in patients with schizophrenia who present with comorbid metabolic syndrome and prediabetes. The subsequent Phase 1b study, NCT05542264, examines ulotaront's effect on insulin sensitivity, liver steatosis and weight-associated structural markers in the same high-risk schizophrenia population.

In conclusion, data presented here add to the existing evidence from preclinical[12] and clinical[13,15] studies, emphasizing ulotaront's potential to positively influence glucose-insulin regulation in schizophrenia patients with comorbid prediabetes and metabolic syndrome.

AUTHOR CONTRIBUTIONS

SM: conceptualization, operationalization, methodology, data monitoring, data curation, data analysis, investigation, resources, data interpretation, writing (original draft, review and edits); **RL**: data curation, data analysis, data visualization, writing (review and edits); **KX**: data curation, data analysis, writing (review and edits); **EC**: operationalization, data monitoring; **GG**: conceptualization, dosing modelling, writing (review and edits); **Y-LC**: operationalization, data analysis; **YL**: operationalization, data analysis; **MC**: conceptualization, data interpretation, resources; **CD**: conceptualization, data monitoring, data interpretation, resources; **KK**: conceptualization, data interpretation, writing (review and edits); **SCH**: conceptualization, dosing modelling, data interpretation, writing (review and edits).

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CONFLICT OF INTEREST STATEMENT

Snezana Milanovic was an employee of Sumitomo Pharma America, Inc. (formerly Sunovion Pharmaceuticals), at the time the work was completed; received consulting fees and meeting/travel support from Sumitomo Pharma America, Inc., and holds a patent related to the work (U.S.S.N. 63/261,515). Robert Lew, Emily Casavant, Gerard Galluppi, Yongquan Lai and Kenneth Koblan were employees of Sumitomo Pharma America, Inc., at the time the work was completed. Kuangnan Xiong was an employee of Sumitomo Pharma America, Inc., at the time the work was completed and served as the study statistician and holds a patent related to the work (U.S.S.N. 63/261,515). Yu-Luan Chen is an employee of Sumitomo Pharma America, Inc. Manu Chakravarthy is an employee of Genetech, a member of the Roche Group. Clay Dehn was a consultant for and has received funding (to his institution, Evolution Research Group [ERG]) from Sunovion Pharmaceuticals, Inc. (now Sumitomo Pharma America, Inc.). Seth Hopkins was an employee of Sumitomo Pharma America, Inc., at the time the work was completed; holds a patent related to the work (U.S.S.N. 63/261,515); and is an employee of Otsuka Pharmaceuticals.

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/dom.70136.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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