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A double-blind study on ulotaront's impact on weight-related parameters in schizophrenia patients with metabolic syndrome and prediabetes: Part II

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Abstract

Aims: Antipsychotics increase metabolic syndrome (MetSyn) and diabetes risk. Preclinical and translational research data suggest that ulotaront, an investigational trace amine-associated receptor 1 (TAAR1) agonist, may have beneficial metabolic effects. This Phase 1b study collected pilot data on 4-week ulotaront exposure and weight-associated metabolic markers.

Materials and Methods: A double-blind, randomised, multiple-dose within subject trial compared ulotaront to continued prior antipsychotic (PA) on metabolic markers in schizophrenia patients at high diabetes risk (presence of MetSyn and prediabetes). Metabolic characteristics of patients at check-in were compared to a matched historical cohort without schizophrenia or antipsychotic exposure.

Results: When compared to PA, ulotaront treatment showed improvement trends for high glucose clamp, low glucose clamp, liver fat, liver fibro-inflammation, back muscle fat infiltration, pancreas fat and pancreas volume. Visceral adipose tissue and weight changes favoured ulotaront treatment ($p < 0.001$, $p = 0.047$). Liver fibro-inflammation distinguished antipsychotic-induced metabolic changes from the historical cohort ($p = 0.002$).

Conclusions: Despite the sample size constraints due to early study termination, all key endpoint trends and statistically significant differences favoured ulotaront over previous antipsychotics, lending support that ulotaront may improve antipsychotic-induced weight-associated markers. Liver fibro-inflammation may serve as a potential marker for antipsychotic-induced MetSyn and prediabetes, and possible treatment target. Further research is needed to build on these findings.

KEYWORDS

beta cell function, drug development, drug mechanism, fatty liver disease, phases I and II study

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1 | INTRODUCTION

Atypical antipsychotics, classified as dopamine D2 receptor-serotonin 5-HT2A receptor (D_2/5-HT_2A) antagonists, are associated with an increased risk of metabolic syndrome and diabetes.[1] This association presents significant challenges for patient care and treatment adherence, requiring a comprehensive, multidisciplinary approach typically led by psychiatrists. Management includes monitoring body weight and body mass index (BMI), blood pressure and diagnostic metabolic indicators such as fasting blood glucose level, hemoglobin A1c (HbA1c) and lipid profile.[2] It also involves working towards lifestyle modifications concerning diet and exercise and assessing the need for medications to manage lipid or glucose levels and/or blood pressure. Non-pharmacological interventions like psychoeducation, behavioural modification, nutritional consultation or physical activity instruction have not shown significant influence on BMI, fasting glucose or triglycerides.[3]

Conversely, there is a pressing need for novel mechanisms of action antipsychotics, and an early evaluation of their potential metabolic impacts. Yet, clinical trials involving novel mechanism-based antipsychotics are often conducted in select patient groups, typically excluding those with comorbidities such as metabolic syndrome or prediabetes. This limitation results in lost opportunities to gather early metabolic data. Cardiovascular and metabolic health outcomes are usually identified later, through observational studies and meta-analyses, creating a notable information gap.

An alternative strategy might entail targeted Phase 1b studies that employ established physiological and/or structural metabolic markers. These could include insulin sensitivity (measured via glucose clamp), fat storage (assessed through magnetic resonance imaging [MRI]-derived proton density fat fraction, or PDFF) and liver fibro-inflammation (evaluated using iron-corrected T1 mapping, or cT1). Given that glucose clamp, PDFF and cT1 biomarkers have low variability,[4,5] studies employing these measures could be carried out in relatively small sample sizes, justifying feasible Phase 1b investment. MRI phenotyping carries additional benefit—the potential to detect subtle changes in fat composition and fibro-inflammation within a short time (6–12 weeks). Early collection of such data could pave the way for Phase 2 proof-of-concept studies for the treatment of metabolic disorders.

Trace amine-associated receptor 1 (TAAR1) agonists, including ulotaront, have demonstrated beneficial effects on glycaemic control and weight reduction in rodent models of diet-induced obesity and iatrogenic (e.g., olanzapine-induced) weight gain.[6] In schizophrenia patients with metabolic syndrome and prediabetes, ulotaront delayed gastric emptying[7] and showed promise in improving glucose-insulin dynamics.[8] This paper presents a double-blind, randomised, multi-dose trial (NCT05542264) comparing ulotaront to conventional antipsychotics on weight-associated metabolic biomarkers (physiological and structural) in patients diagnosed with schizophrenia who also have metabolic syndrome and prediabetes. The study concluded after randomising 16 participants for reasons unrelated to the drug's safety or efficacy. However, this Phase 1b assessment of ulotaront on physiological and structural metabolic markers implements a unique approach in antipsychotic drug development, potentially yielding important insights into the potential efficacy of ulotaront (and the TAAR1 agonist class) with respect to its clinical application to disease indications and comorbidities. We also compared the baseline demographic and metabolic characteristics of schizophrenia patients with those of a matched historical cohort without psychiatric diagnoses or exposure to antipsychotics. To our knowledge, this is the first comparison of its kind, offering a unique opportunity to assess the metabolic footprint of atypical antipsychotics using high-precision and low-variability MRI metabolic markers.[5]

2 | METHODS

2.1 | Study design

This study is a double-blind, randomised, multiple-dose trial (Figure S1) that enrolled adult male and female subjects diagnosed with schizophrenia, who also exhibit metabolic syndrome and prediabetes. Following the completion of screening evaluations, subjects were admitted to the clinical research unit. Initial assessments included structural MRI scans and hyperinsulinaemic euglycaemic clamps (HEC), also known as 'glucose clamps,' before participants were randomised. Individuals assigned to ulotaront underwent a 3-day blinded washout, followed by a titration phase for ulotaront. Upon achieving a stable and well-tolerated dosage of ulotaront, participants maintained this dosage for a 16-day titration period and an additional 15 days during the Stable Dose Period. Conversely, subjects assigned to continue with their prior antipsychotic (PA) treatment received their current PA in a blinded, over-encapsulated form, following a 3-day blinded pseudo washout and a 16-day pseudo titration period, culminating in a 15-day Stable Dose Period. At the stable treatment phase's conclusion, MRI scans and glucose clamp tests were conducted again. Following assessment completion, all patients transitioned back to their PA over 3 days. Upon the Principal Investigator's stability assessment, subjects were discharged and returned to the clinic for follow-up assessments 7 ± 2 days post-discharge.

2.2 | Study participants

Schizophrenia patients (Figure S2a) 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). At screening, participants must have been receiving treatment with either risperidone, olanzapine, quetiapine or aripiprazole for schizophrenia. Metabolic eligibility at screening included meeting any three of the metabolic syndrome criteria and an increased risk for type 2 diabetes (indicative of prediabetes).

Exclusion criteria were a DSM-5 diagnosis other than schizophrenia; a history of type I or II diabetes mellitus; current or past use of

oral or injectable glucose-lowering medication; and a history of, or current treatment with, glucagon-like peptide 1 (GLP-1) receptor agonists (see Inclusion/Exclusion criteria Methods, Supporting Information S1).

2.3 | Two-dose hyperinsulinaemic euglycaemic clamp

2.3.1 | Data acquisition

Participants underwent the HEC procedure at two different insulin dosage levels: low and high. These dosages were administered in separate sessions, spaced at least 1 day apart, with each infusion lasting 180 min. Before each HEC session, participants were required to fast for a minimum of 8 h overnight, water being the only exception. The insulin titration schedule for the glucose clamp is detailed in Figure S3 and Methods, Supporting Information S1.

2.3.2 | Data analysis

During each insulin dose, the interval from $T = 120$ min to $T = 180$ min was designated as the 'steady state' (physiological steady state), a crucial phase for evaluating hepatic (low dose) and peripheral (high dose) insulin sensitivity. The Steady State Glucose Disposal Rate (ssGDR) was determined by the weighted Glucose Infusion Rate (GIR) between 120 and 180 min, based on actual time intervals, without the necessity for spatial adjustment.

A difference from the baseline ssGDR (ΔssGDR) was computed by subtracting the ssGDR during the Check-in/Baseline Period from the ssGDR during the Stable Dose Period. For the ΔssGDR outcome measures for both Low-Dose and High-Dose HEC studies, analysis was conducted using an analysis of covariance (ANCOVA). This model treated the change from baseline as the outcome, incorporating treatment (PA, ulotaront) as fixed effects, with baseline values and BMI as covariates. From this analysis, the least squares (LS) mean, standard error (SE) and two-sided 90% confidence interval (CI) were derived for the comparison of 'ulotaront versus PA' at the treatment's conclusion. The normality assumption was verified by inspecting the residuals of the model.

2.4 | Magnetic resonance imaging scan

2.4.1 | Data acquisition

MRI of the abdomen was conducted at the start (baseline) and at the end of the treatment period to accurately measure the adipose tissue in the liver, pancreas and back muscles and the degree of fibro-inflammation in the liver. The MRI scans were performed using either a 3T scanner or, if a 3T scanner was not available, a 1.5T scanner (from Siemens, Philips or GE). Liver metrics included: cT1 (ms) to measure fibro-inflammation, PDFF (%) to measure fat content and volume (mL). Pancreas metrics were PDFF (%) to measure fat content and volume (mL); fat infiltration in back muscle was measured using signal fat fraction (%). A detailed description of the determination of these parameters can be found in Methods, Supporting Information S1.

2.4.2 | Historical controls

Historical controls were selected from two sources (Figure S2b) and described in detail in the Methods, Supporting Information S1. Controls older than 45 years were selected from an imaging sub-cohort of UK Biobank[9] (UKBB) participants with a complete set of liver and pancreas imaging metrics. UKBB received ethical approval from the National Information Governance Board for Health and Social Care and the National Health Service Northwest Centre for Research Ethics Committee (Ref: 21/NW/0157). All participants provided informed consent at recruitment to the study for their data to be used for health-related research that was in the public interest. Controls aged 45 years or less were selected from participants in the COVERSCAN[10] study (clinical trial registration number: NCT04369807) examining the effects of long coronavirus disease (COVID).

3 | RESULTS

3.1 | Demographics of participants

Tables 1 and S1 display the baseline characteristics and the individual participant data, respectively. The screening process involved 44 participants (Figure S2a), out of whom 16 were randomised. The study targeted adult patients with chronic schizophrenia, as suggested by the average participant age of 45 years and a mean duration of 20 years since initial diagnosis. The proportion of female patients (31%) mirrors that found in previous clinical trials, aligning with the documented impact of sex on the illness's outcome and severity. Risperidone and quetiapine were the most administered medications among the subjects. For inclusion in the analysis of primary, secondary and exploratory endpoints, participants needed to meet a minimum of three out of five predefined criteria for metabolic syndrome and were classified as prediabetic, %HbA1c IQR: 5.9 (5.7, 6.0) and Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) IQR: 5.5 (3.8, 6.7). Additionally, a considerable number of participants were considered obese, with a median BMI of 39 and a range from 36 to 42 kg/m^2. Figure S2b shows UKBB and COVERSCAN screening and matching. Table S2 compares subjects baseline characteristics to the historical control group comprised of those taken from the UKBB and from the COVERSCAN study.

3.2 | Pharmacokinetics

The plasma pharmacokinetic parameters of ulotaront at dose levels 1 through 4 and stable exposure were determined in $N = 9$

TABLE 1 Demographics summary (safety population).

Characteristic at baseline	Median (Q1, Q3) or *N* (%)
Age—years	45 (36, 57)
Sex—*N* (%)	
Male	11 (69)
Female	5 (31)
Race—*N* (%)	
Black or African American	12 (75)
White	3 (18.75)
Hawaiian or Pacific Islander	1 (6.25)
Ethnicity—*N* (%)	
Not Hispanic/Latino	14 (87.5)
Hispanic/Latino	2 (12.5)
Years since initial onset of schizophrenia	20.6 (13.8, 26.3)
PANSS score	
Total	52 (41.5, 67.0)
Positive subscale	10.5 (8.5, 15.5)
Negative subscale	14 (12, 17.0)
Prior antipsychotic—*N* (%)	
Risperidone	6 (35)
Aripiprazole	3 (18)
Olanzapine	2 (12)
Quetiapine	6 (35)
CGI-S scale score	3.0 (2.0, 3.0)
Body mass index (kg/m^2)	39 (36, 42)
Metabolic syndrome criteria—*N* (%)	
3/5	5 (31.3)
4/5	9 (56.2)
5/5	2 (12.5)
% HbA1c	5.9 (5.6, 6)
HOMA-IR	4.3 (2.9, 6.6)

Abbreviations: CGI-S, Clinical Global Impressions-Severity; HOMA-IR, Homeostasis Model Assessment of Insulin Resistance; PANSS, Positive and Negative Syndrome Scale.

participants. The mean ± SD maximum plasma concentration (C_{max}) and area under the plasma concentration-time curve from time zero to 8 hours ($AUC_{0\text{-}8h}$) were 188 ± 117 ng/mL and 955 ± 576 ng×h/mL, respectively for dose levels 1 through 4 and stable exposure. Ulotaront had a median time to C_{max} of 3.92 h. Results are consistent with previously reported pharmacokinetic data for ulotaront.[7,11]

3.3 | Effects of treatment on insulin sensitivity

In the high-dose glucose clamp condition, the PA and ulotaront groups exhibited mean percentages of changes in ssGDR from baseline of 7.5% and 12.5%, respectively (Table 2), and the model-estimated LS mean percentages of changes from baseline were 8% and 12.3%, respectively (Table 3). Additionally, one subject in the PA group and eight subjects in the ulotaront group showed an increase in high-dose glucose clamp steady-state glucose disposal rate (ssGR) (Table 4). In the low-dose glucose clamp condition, the changes in ssGDR from baseline for the PA and ulotaront groups were −8.1% and 133%, respectively (Table 2), with model-estimated LS mean percentages of changes from baseline at −70% and 98.1%, respectively (Table 3). Moreover, one subject in the PA group and five subjects in the ulotaront group exhibited an increase in low-dose glucose clamp ssGR (Table 4). The individual subject data for both the high- and low-dose glucose clamp conditions, indicating percent changes from baseline, are presented in Figure S4.

3.4 | Effects of treatment on liver, pancreas, visceral adipose tissue, back muscle fat fraction and weight change

MRI liver outcome measures included fat (PDFF [%]), volume (mm^3) and fibro-inflammation (cT1 [ms]). The PA and ulotaront groups experienced mean percentages of changes in liver fat from baseline of +5.9% and −8.5%, in volume of +0.5% and −3.5%, and in inflammation of −0.2% and −4.7%, respectively (Table 2). Model-estimated LS mean percentages of changes from baseline for groups PA and ulotaront were +9.3% and −9.7% for liver fat, +4.7% and −4.9% for liver volume and −1.6% and −4.1% for fibro-inflammation, respectively (Table 3). No participants in the PA group saw a decrease in liver fat, whereas four in the ulotaront group did. One participant from the PA group showed a decrease in liver volume and fibro-inflammation, while seven and six participants from the ulotaront group did, respectively (Table 4). The individual participant data are presented in Figure S4.

The mean percentage of changes for infiltration of fat into back muscles in PA and ulotaront groups was −2.6% and 3.4%, respectively (Table 2). The model-estimated LS mean changes for PA and ulotaront groups were −0.1% and 2.5%, respectively (Table 3). Within the PA group, one participant showed a decrease in muscle fat infiltration and three participants in the ulotaront group (Table 4).

Outcome measures from MRI of the pancreas included fat content, quantified as the PDFF (%), and volume (mm^3). Groups PA and ulotaront observed alterations in fat content from the baseline by +5.2% and −5.6%, respectively, and in volume by +9% and −3.6%, respectively (Table 2). Model-estimated LS mean percentage of changes from baseline for groups PA and ulotaront indicated +5.8% and −5.8% changes in fat content and +13.4% and −2.2% changes in volume, respectively (Table 3). Within the PA group, one participant exhibited a decrease in fat content, in contrast to five participants in the ulotaront group. None of the subjects from the PA group demonstrated a decrease in pancreatic volume; however, five participants from the ulotaront group did (Table 4).

Visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) data were measured as cm^2. The PA and ulotaront groups experienced mean percentages of changes from baseline of 25% and

TABLE 2 Descriptive analysis (primary and other endpoints).

Parameter	PA treatment % CHG (mean CHG ± SD)	Ulotaront treatment % CHG (mean CHG ± SD)	Ulotaront-PA % CHG (mean CHG)
High-dose glu clamp—ssGDR (mg/kg/min)	7.5 (0.5 ± 1.7)	12.5 (0.3 ± 0.6)	5 (−0.2)
Low-dose glu clamp—ssGDR (mg/kg/min)	−8.1 (−0.1 ± 0.2)	133 (0.4 ± 0.6)	141 (0.5)
Liver fat—PDFF (%)	5.9 (1 ± 1.7)	−8.5 (−0.4 ± 1.1)	−14.4 (−1.4)
Liver volume (mm^3)	0.5 (13 897 ± 217 332)	−3.5 (−95 190 ± 178 504)	−4 (−109 087)
Liver inflammation (ms)	−0.2 (−1 ± 14.1)	−4.7 (−41.4 ± 49.4)	−4.5 (−40.4)
Back muscle fat infiltration (%)	−2.6 (−2.4 ± 5.8)	3.4 (0.6 ± 1.5)	6 (2.9)
Pancreas fat—PDFF (%)	5.2 (0.4 ± 1.3)	−5.6 (−0.7 ± 3.1)	−10.8 (−1.1)
Pancreas volume (mm^3)	9.0 (9293 ± 8222)	3.6 (−2608 ± 26 288)	−5.4 (−11 900)
Visceral adipose tissue (cm^2)	25.0 (48.3 ± 19.7)	−2.3 (−12.6 ± 27.6)	−27.2 (−60.9)
Abdominal subcutaneous adipose tissue (cm^2)	−8.0 (−30.7 ± NA)	−1.2 (−4 ± 31.2)	6.8 (26.7)
Weight (kg)	3.4 (3.9 ± 1.8)	−0.4 (−0.4 ± 3.9)	−3.8 (−4.3)

Abbreviations: CHG, change; PA, prior antipsychotic; PDFF, proton density fat fraction; ssGDR, Steady State Glucose Disposal Rate.

TABLE 3 Model estimate least squares mean (primary and other endpoints).

Parameter	PA treatment % CHG (mean CHG ± SD)	Ulotaront treatment % CHG (mean CHG ± SD)	Ulotaront-PA % CHG (mean CHG ± SD)	% Change *p*-value
High-dose glu clamp—ssGDR (mg/kg/min)	8 (0.5 ± 0.5)	12.3 (0.3 ± 0.4)	4.3 (−0.3 ± 0.6)	0.807
Low-dose glu clamp—ssGDR (±mg/kg/min)	70 (−0.1 ± 0.4)	98 (0.4 ± 0.2)	27.8 (0.5 ± 0.4)	0.884
Liver fat—PDFF (%)	9.3 (1.1 ± 0.8)	−9.7 (−0.5 ± 0.4)	−19 (−1.6 ± 0.9)	0.091
Liver volume (mm^3)	4.7 (70 744 ± 119 581)	−4.9 (−114 139 ± 62 748)	−9.6 (184 884 ± 143 960)	0.188
Liver inflammation (ms)	−1.6 (−15 ± 23.2)	−4.1 (−36.1 ± 13.8)	−2.5 (−21.2 ± 27.8)	0.475
Back muscle fat infiltration (%)	−0.1 (−1.7 ± 1.6)	2.5 (0.3 ± 0.9)	2.6 (2 ± 1.8)	0.789
Pancreas fat—PDFF (%)	5.8 (0.9 ± 1.7)	−5.8 (−0.9 ± 0.9)	−11.5 (−1.7 ± 1.9)	0.710
Pancreas volume (mm^3)	13.4 (13 493 ± 12 420)	2.2 (−4008 ± 7053)	−11.2 (−17 500 ± −14 457)	0.491
Visceral adipose tissue (cm^2)	24.7 (46.75 ± 10.3)	−2.2 (−12.1 ± 5.9)	−26.9 (−58.9 ± 12)	0.003
Abdominal subcutaneous adipose tissue (cm^2)	−31.5 (−143 ± 66)	3.5 (18.4 ± 16.6)	35 (161.2 ± 78)	0.182
Weight (kg)	3.3 (3.74 ± 1.45)	−0.4 (−0.37 ± 1.1)	−3.7 (−4.1 ± 1.8)	0.044

Abbreviations: CHG, change; PA, prior antipsychotic; PDFF, proton density fat fraction; ssGDR, Steady State Glucose Disposal Rate.

TABLE 4 Percent of subjects with improvement (primary and other endpoints).

Parameter	Stable dose versus baseline	PA	Ulotaront	Ulotaront-PA
High-dose glu clamp—ssGDR (mg/kg/min)	Increase	25% (1/4)	89% (8/9)	64%
Low-dose glu clamp—ssGDR (mg/kg/min)	Increase	25% (1/4)	56% (5/9)	31%
Liver fat—PDFF (%)	Decrease	0% (0/3)	44% (4/9)	44%
Liver volume (mm^3)	Decrease	33% (1/3)	78% (7/9)	44%
Liver inflammation (ms)	Decrease	33% (1/3)	75% (6/8)	42%
Back muscle fat infiltration (%)	Decrease	33% (1/3)	38% (3/8)	4%
Pancreas fat—PDFF (%)	Decrease	33% (1/3)	56% (5/9)	22%
Pancreas volume (mm^3)	Decrease	0% (0/3)	56% (5/9)	56%
Visceral adipose tissue (cm^2)	Decrease	0% (0/3)	67% (6/9)	67%
Abdominal subcutaneous adipose tissue (cm^2)	Decrease	100% (1/1)	60% (3/5)	−40%
Weight (kg)	Decrease	0% (0/5)	44% (4/9)	44%

Abbreviations: PA, prior antipsychotic; PDFF, proton density fat fraction; ssGDR, Steady State Glucose Disposal Rate.

−2.3% for VAT and −8.0% and −1.2% for SAT, respectively (Table 2). The model-estimated LS mean changes for PA and ulotaront groups were 24.7% and −2.2% for VAT and −31.5% and 3.5% for SAT (Table 3). Within the PA group, 0 and 1 participants showed a decrease in VAT and SAT, respectively, and in the ulotaront group 6 and 3 (Table 4). VAT change was statistically significant in the ulotaront group when compared to the PA group ($p = 0.003$).

The mean percent change for weight (kg) in PA and ulotaront groups was 3.4% and −0.4%, respectively (Table 2). The model-estimated LS mean changes for PA and ulotaront groups were 3.3% and −0.4% (Table 3). Within the PA group, zero participants showed a decrease in weight and four in the ulotaront group (Table 4). Weight change, last assessment day/Day 15 in stable dose period was statistically significant in the ulotaront group when compared to the PA one ($p = 0.044$).

3.5 | Demographics and imaging biomarkers results: matched historical controls and schizophrenia patients

Thirty-two matched historical controls' (UKBB and COVERSCAN) demographics and imaging baseline data were compared with our study subjects' baseline data (Table 5). There were no statistically significant differences in age, sex, BMI, liver PDFF or pancreatic volume. Half of the subjects in the historic control group had no prediabetes, as measured by HbA1c, while all schizophrenia patients had prediabetes, as confirmed by HbA1c and/or HOMA-IR. Matched controls had significantly higher standing systolic blood pressure ($p = 0.005$); however, 11 out of 16 study participants were on antihypertensive concomitant medications. Study participants had statistically significant ($p = 0.002$) and clinically meaningful higher baseline liver fibro-inflammation measured via cT1.

3.6 | Safety assessment

Adverse events are detailed in Table S4. In summary, twice-daily administration of ulotaront, at a dosage of 50 mg, was generally well received by adults with schizophrenia who were at an elevated risk for diabetes.

4 | DISCUSSION

Previous studies demonstrated that in schizophrenia patients with comorbid metabolic syndrome and prediabetes, an acute dose of ulotaront delayed gastric emptying.[7] Semi-chronic dosing (on average 2 weeks) suggested improvement in insulin sensitivity, potentially through enhanced hepatic insulin clearance or a direct effect on β-cell islets (submitted). Building on these clinically meaningful findings, the current study examined the effects of chronic ulotaront dosing in schizophrenia patients at high risk for diabetes. Our results indicate a trend towards improved insulin sensitivity in liver and peripheral tissues, consistent with the semi-chronic dosing results (submitted). Furthermore, this trend occurred concomitantly with a trend in structural changes detected at the level of liver, pancreas and muscle fat content, implying likely interrelatedness. Although no statistical difference for the primary endpoints was detected due to the small sample size,

TABLE 5 Demographics and imaging biomarkers for schizophrenia patients and matched historical controls.

Demographic	Matched controls Median (IQR)/*n*% ($N = 32$)	Schizophrenia patients Median (IQR)/*n*% $N = 16$	*p*-Value[a]
Age (years)	50 (32, 55)	43 (36, 57)	>0.9
Sex			
Female	16 (50%)	5 (31%)	0.2
Male	16 (50%)	11 (69%)	
BMI (kg/m^2)	34 (29, 41)	39 (36, 42)	0.09
Liver cT1 (ms)	721 (707, 775)	826 (781, 870)	0.002
Liver PDFF (%)	5 (3, 10)	6.0 (4, 7)	0.4
Pancreas PDFF (%)	4 (3, 6)	6 (4, 7)	0.09
Pancreas volume (mL)	80 (68, 88)	78 (70, 108)	0.4
HbA1c			
<6%	0	14 (88%)	
<6% and <6.5%	16 (50%)	2 (12%)	
Systolic BP (mmHg)	135 (125, 147)	127[b] (116, 130)	0.005

Abbreviations: BMI, body mass index; BP, blood pressure; cT1, iron-corrected T1 mapping; PDFF, proton density fat fraction.
[a]Wilcoxon rank sum test; Pearson chi-squared test; Welch two sample *t* test.
[b]Standing systolic BP (11 of 16 patients on antihypertensive con meds).

most of the measurements moved in the hypothesised direction of metabolic improvement, favouring ulotaront over PAs and their negative/deleterious effects on metabolism. Consistent with these findings are statistically significant changes in the other structural endpoints, namely a drop in VAT and a decrease in body weight in ulotaront-treated subjects. This finding aligns with a randomised, double-blind, active-comparator-controlled Phase 3 52-week study, which showed that ulotaront significantly reduced weight and waist size when compared to quetiapine.[12] An unexpected outcome of this Phase 1b study was the early onset of metabolic improvement occurring within 4 weeks of treatment of ulotaront (titration and stable exposure periods). This contrasts with previous clinical intervention studies conducted for the treatment of diabetes in which efficacy (to regulate insulin-glucose secretion or decrease fat content in liver) was generally measured over a 12-week period. Future ulotaront studies with similar duration (12 weeks) are warranted to confirm onset and persistence of efficacy. Finally, twice-a-day dosing of ulotaront was found to be safe and well tolerated.

To further understand this observation, we examined a historical cohort not exposed to antipsychotics and without schizophrenia diagnosis,[9,10] which was well matched to our schizophrenia cohort at high risk for diabetes on age, sex, BMI, liver PDFF (median values at or above the steatotic liver disease [SLD] threshold), pancreatic volume and pancreatic PDFF. While both groups displayed similar initial stages of liver steatosis, our study's schizophrenia cohort exhibited a statistically and clinically significant higher liver fibro-inflammation (cT1) value. cT1 is an MRI biomarker of chronic liver disease activity,[13] which strongly correlates with metabolic dysfunction-associated steatohepatitis (MASH) and associates with liver[14] and cardiovascular outcomes.[15] The observation of the statistically and clinically significant increase in cT1 might suggest a potentially more rapid disease progression in antipsychotic use–associated metabolic syndrome and metabolic dysfunction associated SLD (MASLD), indicative of early-stage fibrosis and steatohepatitis.

MASLD is defined as the accumulation of fat (steatosis) in more than 5% of liver cells and at least one cardiometabolic risk factor, without significant alcohol consumption. Recently, MASLD prevalence has risen, now estimated to affect 38% of the global population,[16] making it a significant public health issue. It is a primary cause of cirrhosis, hepatocellular carcinoma and liver-related mortality and a common reason for liver transplantation. Insulin resistance is a key factor in steatosis, compounded by inflammatory reactions, lipotoxicity and subsequent cell death leading to further inflammation and fibrosis.[17] Metabolic dysfunction-associated liver disease can be classified into two types depending on liver inflammation: steatosis and more advanced disease, steatohepatitis (MASH). Research suggests a link between MASLD, metabolic syndrome,[18] and type 2 diabetes.[19] The risk of developing MASLD and liver fibrosis escalates with each metabolic syndrome risk factor,[18] while patients with MASLD are at a fivefold greater risk for type 2 diabetes.[20] Consequently, MASLD is considered part of a metabolic disease continuum involving metabolic syndrome, obesity and type II diabetes.[21]

Our study cohort was enriched for prediabetes, which could be a contributing factor to the observed higher incidence of MASLD. However, while prediabetes patients exhibit an increase in the liver PDFF[22] together with the change in the liver volume and shape, inflammation and fibrosis are not typically observed in prediabetes and are instead being diabetes hallmarks.[23,24]

In addition to elevating the risk of metabolic syndrome and diabetes,[1] antipsychotic medications are linked to an increased risk of MASLD, with prevalence rates estimated at 42.7%,[25] 54.84%,[26] and 64.6%[27]—all significantly higher than in the general population.[16] Factors such as antipsychotic polypharmacy, being overweight or obese and diabetes are identified as key moderators of MASLD risk.[24] Among non-obese schizophrenia patients, MASLD prevalence is 25%, with age, BMI, diabetes and triglyceride levels as notable contributing factors.[27] Interestingly, preclinical studies indicate that antipsychotic drugs can induce insulin resistance, inflammation and MASLD even before significant changes in body weight occur,[28,29] and these effects are mediated by central[30] and peripheral[31] mechanisms. Our data call for further research to understand antipsychotic associated MASLD/MASH risk in schizophrenic patients.

The current study boasts several strengths, notably its design—a double-blind, randomised, multiple-dose comparison of ulotaront, against previous antipsychotics—and its focus on unique schizophrenia patients at high risk of diabetes. Additionally, the study utilises well-established, low variability physiological[4] and structural[5] metabolic markers. However, a major limitation is the low number of completed subjects due to its premature termination for reasons unrelated to the drug's safety or efficacy. Despite this early conclusion and a shorter trial duration (4 weeks) compared to industry standards for evaluating insulin sensitivity and weight associated metabolic endpoints (6–12 weeks), a unified trend was observed across all primary endpoints. Moreover, statistically significant and clinically meaningful changes were noted in two other endpoints, VAT and body weight. These pioneering data are encouraging, demonstrating the feasibility and precision of Phase 1b psychiatric drug development for metabolic data collection, and providing solid initial translational evidence of the hypothesised structural metabolic effects of ulotaront. A proof-of-concept Phase 2 clinical trial would be a prudent next step in clinical development.

In summary, results from this Phase 1b ulotaront metabolic clinical trial are consistent with extensive preclinical,[6] Phase1[11] and Phase3[12] clinical data showing that ulotaront not only lacks adverse antipsychotic-induced metabolic changes but has the potential to improve glucose-insulin dynamics, body weight-associated markers and body weight. A study[7] in schizophrenia patients with metabolic syndrome and prediabetes translated a finding observed in preclinical models, that acute ulotaront dosing slows gastric emptying. Studies utilising semi-chronic (submitted) and chronic dosing continue to build on these findings, revealing ulotaront's potential to modulate metabolism across various organ systems in high-risk schizophrenia patients. We also demonstrate the feasibility of Phase 1b assessment of candidate antipsychotic metabolic footprint, using high-precision and low-variability metabolic markers.[4,5] Finally, we show that liver

fibro-inflammation may differentiate antipsychotic-induced metabolic syndrome and prediabetes. If replicated, this finding may bring forth ramifications regarding MASLD and MASH risk in antipsychotic-treated patients.

AUTHOR CONTRIBUTIONS

SM: conceptualisation, operationalisation, methodology, data monitoring, data curation, data analysis, investigation, resources, data interpretation, writing (original draft, review and edits); **RL**: data curation, data analysis, data visualisation, writing (review and edits); **KX**: data curation, data analysis, writing (review and edits); **EC**: operationalisation, data monitoring; **GG**: conceptualisation, dosing modelling, writing (review and edits); **Y-LC**: operationalisation, data analysis; **YL**: operationalisation, data analysis; **MC**: conceptualisation, data interpretation, resources; **CD**: conceptualisation, data monitoring, data interpretation, resources; **EJ**: data analysis (MRI), data interpretation (MRI), historic cohort data access, curation and interpretation, writing (review and edits); **KK**: conceptualisation, data interpretation, writing (review and edits); **SCH**: conceptualisation, 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 was an employee of Carmot Therapeutics, Inc., at the time the work was completed. 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.). Edward Jackson was an employee of Perspectum Ltd., the company that provided quantitative imaging biomarkers used in the study. 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.70110.

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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