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ORIGINAL ARTICLE

A phase 1 study to evaluate the safety, tolerability and pharmacokinetics of TAK-041 in healthy participants and patients with stable schizophrenia

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Aims: TAK-041 (NBI-1065846), an orally available, investigational, small molecule agonist of GPR139, an orphan G-protein-coupled receptor, has shown promise in preclinical studies for the treatment of symptoms associated with schizophrenia. Here, we report the results from a phase 1 study to evaluate the safety, tolerability and pharmacokinetics of TAK-041 in healthy adults and exploratory efficacy assessment of TAK-041 as adjunctive therapy to antipsychotics in adults with stable schizophrenia (ClinicalTrials.gov: NCT02748694).

Methods: The study comprised 4 parts: parts 1–3 were undertaken in healthy adults and part 4 in patients with stable schizophrenia. Part 1 was a single-rising-dose study, part 2 was a multiple-rising-dose study that assessed plasma exposure and accumulation, part 3 evaluated the bioavailability of tablet formulation versus oral suspension, and part 4 was a repeat multiple-dose study in patients with stable schizophrenia.

Results: No serious adverse events were reported. TAK-041 had a nearly linear pharmacokinetics profile, with rapid absorption and long half-life of 170–302 hours across all doses tested. Bioavailability was similar between the tablet formulation and oral suspension, and no meaningful food effect was detected. Systemic exposure was 22–30% lower for patients with schizophrenia than for healthy volunteers. A potential signal of improvement was detected in the anxiety–depression scale of the Positive and Negative Syndrome Scale ($P = .0002$, not corrected for multiplicity) and the Temporal Experience of Pleasure Scale in patients with schizophrenia.

Conclusion: TAK-041 was generally well tolerated in healthy volunteers and adults with schizophrenia. Further investigation of TAK-041 in individuals with schizophrenia is supported.

KEYWORDS
pharmacokinetics, safety, schizophrenia, TAK-041

Wei Yin and David Han contributed equally to this work

The authors confirm that the principal investigator for this paper is Dr David Han and that he had direct clinical responsibility for patients.

1 | INTRODUCTION

Schizophrenia is a severe, chronic mental disorder associated with psychosis, cognitive impairment, and social and motivational deficits.[1,2] Approximately 7 individuals in 1000 will be affected by the disorder, with a median lifetime prevalence of 7.2 per 1000 persons and a mean lifetime prevalence of 11.9 per 1000.[3] The disorder is characterized by core features of positive symptoms (such as hallucinations or delusions), negative symptoms (impaired motivation, reduced spontaneous speech and social withdrawal) and cognitive impairment. Commonly affected cognitive domains include attention, working memory and executive functions.[4]

Whereas positive symptoms of schizophrenia tend to relapse and remit, negative symptoms and cognitive impairments are usually chronic and associated with long-term effects on social function.[4] Two studies of individuals with schizophrenia ($n = 821$ and $n = 1427$) found that negative symptoms correlated with worse functional impairment, with even modest negative symptoms being associated with social deficits.[5,6] Moreover, despite some successes with pharmacotherapy for positive symptoms, effective treatment for negative symptoms and cognitive impairment remains an unmet medical need. Indeed, antipsychotics, the cornerstone of treatment for positive symptoms, can exacerbate negative symptoms.[7]

Schizophrenia, among other psychiatric disorders, has been shown to be associated with dysfunctional habenula activity.[8] The habenula mediates midbrain monoaminergic systems, notably **dopamine** and **serotonin**, and integrates cognitive with emotional and sensory processing. In mammals, the orphan G-protein-coupled receptor **GPR139** is predominantly expressed in the central nervous system, with the highest expression observed in the habenula, as well as in the striatum, pituitary, thalamus and hypothalamus.[8,9] In rodents, the habenula has been shown to be densely populated with GPR139-expressing neurons.[10]

TAK-041 (NBI-1065846), an investigational, orally available, small molecule, GPR139 agonist, has shown positive results in preclinical studies.[11] In vivo, TAK-041 has been shown to elevate levels of c-fos (the product of an immediate early gene downstream of GPR139 activation), with increased expression in the habenula of wild-type mice but not GPR139-knockout mice. In addition, chronic dosing with TAK-041 did not result in desensitization of c-fos in the habenula.[11] Moreover, in 2 different mouse models exhibiting social interaction deficits, TAK-041 mitigated the social deficits, reversing anhedonia, anxiety-like behaviour and depressive-like behaviour.[11] These findings suggest that TAK-041 has the potential to provide treatment for individuals with schizophrenia, particularly for negative symptoms and cognitive impairments.

Here, we report the results from a phase 1 study to evaluate the safety, tolerability and pharmacokinetics (PK) of TAK-041 following a single-rising dose (SRD) and multiple-rising doses (MRD) in healthy adults, and as an add-on therapy to antipsychotics in patients with stable schizophrenia (ClinicalTrials.gov identifier: NCT02748694). Exploratory efficacy analysis was also undertaken in patients with stable schizophrenia to inform future studies.

What is already known about this subject

- Schizophrenia is associated with chronic cognitive impairments that affect social functioning.
- TAK-041 (NBI-1065846) is an orally available, small molecule agonist of GPR139, an orphan G-protein-coupled receptor. GPR139 is almost exclusively expressed in the central nervous system.
- TAK-041 has been shown to improve cognitive function and social interaction in animal models.

What this study adds

- This paper describes the first-in-human study to assess the safety, tolerability and pharmacokinetics of TAK-041 in healthy participants and patients with stable schizophrenia as an add-on treatment to antipsychotics.
- Exploratory efficacy analysis was also undertaken in patients with stable schizophrenia to inform future studies.
- Findings support further investigation of TAK-041, including efficacy assessments, in patients with schizophrenia.

2 | METHODS

2.1 | Study objectives

The objective of the study was to evaluate the safety, tolerability and PK of TAK-041 following oral single and multiple doses in healthy participants and as an add-on therapy to antipsychotics in patients with stable schizophrenia. Additional exploratory efficacy assessments were undertaken in patients with stable schizophrenia to inform future studies.

2.2 | Ethics

This study complied with the Institutional Review Board regulations, the Good Clinical Practice regulations and guidelines, and all applicable local regulations. The study was conducted according to the ethical principles from the Declaration of Helsinki, the requirements and definitions of the ICH Harmonised Tripartite Guideline for Good Clinical Practice and all applicable local regulations. All participants gave informed consent before any protocol-specific screening procedures.

2.3 | Study design

This phase 1, first-in-human study was conducted at a single site in the USA and consisted of 4 parts. Parts 1–3 were conducted in healthy adults and part 4 was conducted in adults with stable schizophrenia (Figure S1).

Part 1 was a double-blind, SRD study to evaluate dose escalation, utilizing an alternating-panel design (cohorts 1 and 2) and sequential-panel design (cohorts 3, 4 and 5). Cohorts were randomized in a 6:2 ratio to receive either TAK-041 or placebo. In the alternating-panel design, TAK-041 was administered as an oral suspension (5, 10, 20 and 40 mg) or matched placebo, with a washout period of at least 7 days between treatment periods. In the sequential-panel design (cohorts 3, 4 and 5), TAK-041 oral suspension was evaluated at 80, 120 and 160 mg, respectively. The higher doses following the dose of 80 mg were determined based on emerging safety, tolerability and PK data from the preceding cohorts. To assess preliminary safety and tolerability before dosing, a sentinel group was used for cohort 1, period 1, in which the initial 2 participants were allocated 1:1 to receive either TAK-041 or placebo. The remaining 6 participants were dosed following a review of safety and tolerability data 24 hours postdose. Subsequent cohorts were dosed based on a minimum of 21 days of emerging safety, tolerability and available PK data from the previous cohorts.

Part 2 was an MRD study to assess plasma exposure and accumulation of TAK-041, and it consisted of 4 cohorts (1–4) randomized in a 6:2 ratio to receive either TAK-041 or placebo. Part 2 was initiated after 21 days of safety, tolerability and PK data had been obtained from cohort 3 in part 1. Placebo was administered daily, whereas participants in the TAK-041 arm received a loading dose on day 1 and maintenance doses of half the initial dose on days 8, 15 and 22, administered as an oral suspension. Baseline measurements were obtained on day −2, and study-specific measurements were obtained following oral dose administrations on days 1, 8, 15 and 22. Participants in part 2 of the study were required to stay in the study unit for 5 days for each cycle of TAK-041 administration. For the loading dose administration, participants were required to remain in the study unit from day −2 to day 3 and, for the maintenance doses, they were required to stay in the unit on days 7–10, 14–17 and 21–24. Study-specific measurements were conducted in the 48-hour period postdose, before participants were discharged. After discharge on day 24, participants returned for follow-up on days 26, 29, 36, 43, 50, 57 and 64. A final visit occurred 12–16 days following the final safety and PK follow-up.

Part 3 was a randomized, open-label, single-dose, parallel-design study to evaluate the bioavailability of the TAK-041 tablet formulation relative to the oral suspension administered in parts 1 and 2, and the effect of food on the PK in healthy participants. Participants were randomized in a 1:1 ratio to receive a single TAK-041 40 mg dose as a tablet after either a 10-hour overnight fast or 30 minutes after beginning ingestion of a high-fat, high-calorie breakfast. Following dosing, participants remained in the study unit for an additional 48 hours for safety and PK assessments. Follow-up visits took place on days 4–5 and on days 17–21.

Part 4 was a double-blind, weekly single-dose, parallel-design study in patients with stable schizophrenia. Participants were randomized in a 2:1 ratio to receive either TAK-041 oral suspension or placebo. For study participants in the TAK-041 arm, a loading dose was administered on day 1 and maintenance doses, at half the initial dose, were administered on days 8, 15 and 22. Study participants in the placebo arm received placebo on all study dosing days. Part 4 was initiated after 21 days of safety, tolerability and PK data had been obtained in part 2. Participants in part 4 were required to stay in the study unit for 5 days for each cycle of TAK-041 administration. For the loading-dose administration, participants were required to remain in the study unit from day −2 to day 3, and for the maintenance doses, they were required to remain in the unit on days 7–10, 14–17 and 21–24. Study-specific measurements were conducted in the 48-hour period postdose before participants were discharged. After discharge on day 24, participants returned for follow-up on days 26, 29, 36, 43, 50, 57 and 64. A final visit that completed the study occurred 12–16 days following the final safety and PK follow-up.

2.4 | Key inclusion criteria

Eligible participants were men and women aged 18–55 years at the time of informed consent, with a body mass index of 18–32 kg/m^2 for healthy participants or 18–40.5 kg/m^2 for patients with schizophrenia. In part 4, participants were eligible if they met schizophrenia criteria as defined by the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition, and the Mini International Neuropsychiatric Interview, and if they had a Positive and Negative Syndrome Scale (PANSS) total score of 90 or less, and a sum of PANSS N1, N2, N3, N4, N6, G7 and G16 scores of 15 or more at screening and baseline. In addition, participants had to be on a stable dose of antipsychotic medication for at least 2 months preceding randomization.

2.5 | Safety assessments

Safety measurements included treatment-emergent adverse events (TEAEs), physical examinations, weight, height, body mass index, vital signs, clinical laboratory evaluations and electrocardiogram procedures. Participants were also evaluated with respect to mood and alertness (Bond–Lader visual analogue scale), and suicidality (Columbia-Suicide Severity Rating Scale).

For the purposes of this study, a TEAE was defined as any adverse event that occurred or worsened after receiving the first dose and within 6 weeks of receiving the last dose of the study drug. Participants who experienced 2 or more TEAEs of the same type in any treatment group were counted only once, using the most extreme incident for the intensity. Frequent TEAEs were defined as those occurring in 2 or more participants in any treatment.

2.6 | PK assessments

In part 1 and part 3, a 4 mL blood sample was collected predose (≤60 min before dosing), and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6 (part 3 only), 8, 12, 24, 36, 48, 72 and 96 hours postdose. In part 2 and part 4, blood samples were taken predose, and at 0.5, 1, 1.5, 2, 3, 4, 8, 12, 24, 48 and 96 hours postdose on days 1 and 22. On days 8 and 15 blood was taken predose, and at 1, 2 and 4 hours postdose. Additional blood samples were collected at each weekly follow-up visit (part 1: days 8, 15, 22, 29, 36 and 43; part 2 and part 4, days 29, 36, 43, 50, 57, 64 and 70; part 3, day 19).

Urine samples were collected for all participants in part 1 and part 2, but were analysed only for participants receiving TAK-041. On day 1 in part 1 and day 14 in part 2, urine samples were collected predose (−12 to 0 hours), and between 0 and 6, 6 and 12, 12 and 24, 24 and 48, 48 and 72, and 72 and 96 hours postdose. On day 1 in part 1, samples were collected predose, and between 0 and 6, 6 and 12, and 12 and 24 hours postdose. Urine samples were collected for the determination of **cortisol** and 6β-hydroxycortisol for all participants in part 2 and all patients in part 4. Samples for participants randomized to placebo were analysed for cortisol and 6β-hydroxycortisol parameters. The ratio of urinary 6β-hydroxycortisol:cortisol is a biomarker of cytochrome P-450 (CYP) 3A4 enzyme activity and is used to evaluate the effect of TAK-041 on **CYP3A4** activity.

Plasma concentrations (validated range for TAK-041: 1–1500 ng mL^{-1}) and urine concentrations (validated range for TAK-041: 5–10 000 ng mL^{-1}) of TAK-041 and urine concentrations of cortisol and 6β-hydroxycortisol were measured by high-performance liquid chromatography with tandem mass spectrometry. The methods for measurement of plasma and urine concentrations of TAK-041 were validated successfully with respect to linearity, sensitivity, accuracy, precision, dilution, selectivity, haemolysed plasma (plasma only), lipemic plasma (plasma only), batch size, recovery, matrix effect, carryover and stability. TAK-041 in plasma was isolated through protein precipitation extraction.

PK parameters were determined from the concentration–time profiles for all evaluable participants. Actual sampling times were used in all computations and all parameters were calculated using noncompartmental analysis using Phoenix WinNonLin, version 8.0 (Certara, Princeton, NJ, USA) or SAS software, version 9.4 (SAS Institute Inc., Cary, NC, USA).

2.7 | Exploratory efficacy assessments

Exploratory efficacy assessments in part 4 included the PANSS total, subscale and factor scores; Brief Assessment of Cognition in Schizophrenia (BACS) total score; Clinical Global Impression (CGI) Severity scale score and Global Improvement scale score; Brief Negative Symptom Scale (BNSS) total score; and Temporal Experience of Pleasure Scale (TEPS) total score.

2.8 | Statistics

Three analysis sets were used for this study: the safety set (all participants who received at least 1 dose of the study drug); the PK set (all participants who received the study drug and provided sufficient data for at least a single PK parameter); and the exploratory efficacy set (used only for part 4 of the study – all participants who received the study drug and provided sufficient data for 1 baseline and 1 postbaseline scheduled exploratory efficacy parameter). PK outcomes were summarized using descriptive statistics.

A sample size of 8 participants was used in this study for part 1 cohorts 1–5 and part 2 cohorts 1–4 and was based on precedents of other first-in-human studies.

The exploratory efficacy endpoints were analysed in an exploratory manner by using Bayesian analysis and linear mixed-effects models. The Bayesian analyses have been restricted to the PANSS total score, the PANSS Negative Symptom Score and the BACS composite score. A linear mixed-effect model was used to model the trajectory of change in each of the scores associated with the PANSS, BNSS, CGI, BACS and TEPS over time. The multiplicity correction was not conducted.

2.9 | Nomenclature of targets and ligands

All molecular target nomenclature conforms to the IUPHAR/BPS guide to pharmacology nomenclature classification. Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20.[12,13]

3 | RESULTS

3.1 | Participant disposition and baseline characteristics

Of 410 individuals screened, 114 met the eligibility criteria and were randomized into the treatment period (Table 1). There were no significant differences in the demographic and baseline characteristics between the placebo and active treatment arms. All participants in parts 1, 2 and 3 completed the study. In part 4, there were no significant differences in the baseline clinical characteristics between schizophrenia patients in the placebo and active treatment arms (Table S1). The most common concurrent medications were aripiprazole, olanzapine, quetiapine, risperidone, acetaminophen and ibuprofen. All randomized patients were treated, but 2 participants voluntarily withdrew from the study: 1 discontinued after the first dose and 1 discontinued after receiving all treatments without completing the follow-up visits.

TABLE 1 Demographic and baseline characteristics

	Part 1[a] ($n = 40$)	Part 2[b] ($n = 32$)	Part 3[c] ($n = 18$)	Part 4[d] ($n = 24$)
Age, y				
Mean (SD)	39.1 (9.58)	38.5 (9.82)	34.8 (8.71)	44.8 (7.33)
Median	38.5	36.0	33.0	46.5
Range	22–54	23–55	23–54	28–55
Sex, *n* (%)				
Male	30 (75.0)	26 (81.3)	15 (83.3)	19 (79.2)
Female	10 (25.0)	6 (18.8)	3 (16.7)	5 (20.8)
Race, *n* (%)				
Asian	3 (7.5)	4 (12.5)	2 (11.1)	3 (12.5)
Black or African American	12 (30.0)	7 (21.9)	3 (16.7)	13 (54.2)
Native Hawaiian or other Pacific islander	1 (2.5)	-	-	-
White	20 (50.0)	19 (59.4)	12 (66.7)	8 (33.3)
Multiracial	4 (10.0)	2 (6.3)	1 (5.6)	0
Weight, kg				
Mean (SD)	79.68 (12.422)	79.56 (11.725)	77.74 (10.834)	96.20 (21.236)
BMI, kg m^{-2}				
Mean (SD)	26.35 (3.118)	26.32 (3.351)	25.22 (3.142)	31.47 (5.838)
Range	19.6–31.5	18.9–31.9	19.4–31.5	21.6–39.6

BMI, body mass index; SD, standard deviation.
[a]Single-rising dose in healthy participants.
[b]Multiple-rising dose in healthy participants.
[c]Food-effects cohort.
[d]Multiple-rising dose in patients with schizophrenia.

TABLE 2 Most frequently reported treatment-emergent adverse events (TEAEs)

	Part 1[a]		Part 2[b]		Part 4[c]	
	Placebo ($n = 10$)	TAK-041 ($n = 30$)	Placebo ($n = 8$)	TAK-041[d] ($n = 24$)	Placebo ($n = 8$)	TAK-041[d] ($n = 16$)
Any frequently reported TEAE[e]	2 (20.0)	4 (13.3)	1 (12.5)	5 (20.8)	5 (62.5)	7 (43.8)
Headache	0	3 (10.0)	1 (12.5)	5 (20.8)	1 (12.5)	2 (12.5)
Upper respiratory tract Infection	2 (20.0)	1 (3.3)	0	0	0	0
Somnolence	0	0	0	0	1 (12.5)	4 (25.0)
Abnormal dreams	0	0	0	0	2 (25.0)	2 (12.5)
Change in sustained attention	0	0	0	0	1 (12.5)	2 (12.5)
Nausea	0	0	0	0	2 (25.0)	0

All data are *n* (%).
[a]Single-rising dose in healthy participants.
[b]Multiple-rising dose in healthy participants.
[c]Multiple-rising dose in patients with schizophrenia.
[d]For cohorts in parts 2 and 4, a loading dose was administered on day 1, followed by a maintenance dose, which was half the loading dose, on days 8, 15 and 22.
[e]Frequently reported TEAEs are defined as those occurring in at least 2 participants. No frequently reported TEAEs were observed in Part 3.

3.2 | Safety evaluations

All randomized participants ($n = 114$) received at least 1 dose of the study drug and were included in the safety set. TEAEs experienced by participants were mild except for in 3 participants (2 in part 2 and 1 in part 3) who experienced TEAEs of moderate intensity, which were not considered to be drug-related (headache, gastroenteritis and vasovagal syncope). Headache tended to occur more frequently with

TAK-041 ($n = 10$; 12.8% for parts 1, 2 and 4) than with placebo ($n = 2$; 7.7% for parts 1, 2 and 4; Table 2). In part 4, somnolence occurred in 4 participants (25.0%) who received TAK-041 and 1 participant (12.5%) who received placebo. No deaths, serious AEs or other severe TEAEs were reported, and no clinically significant changes in baseline characteristics were observed. There were no treatment discontinuations due to TEAEs. There were no clinically relevant trends in laboratory tests, vital signs, electrocardiogram values or findings on physical examination. There were no clinically remarkable findings involving suicidal ideation.

3.2.1 | SRD in healthy participants (part 1)

Four participants (40.0%) who received placebo and 6 participants (20.0%) who received TAK-041 experienced a TEAE during the study. None of the TEAEs were considered to be related to the study drug by the investigator.

3.2.2 | MRD in healthy participants (part 2)

Three out of 8 participants (37.5%) who received placebo and 16 out of 24 participants (66.7%) who received TAK-041 experienced a TEAE during the study. One participant experienced a moderate TEAE of headache, while all the other TEAEs were mild (Table 3).

3.2.3 | Food-effects cohort (part 3)

Overall, 5 TEAEs were experienced across 3 participants (16.7%); all were mild except for a moderate event of syncope that occurred during venous blood draw and was considered to be procedure related.

Of 9 participants who were administered a single dose of TAK-041 after an overnight fast of at least 10 hours, 1 (11.1%) experienced a mild TEAE of contusion. Two participants (22.2%) who had received a single TAK-041 dose following a high-fat, high-calorie breakfast experienced TEAEs. One participant experienced a moderate TEAE of vasovagal syncope at the follow-up visit, whereas all other TEAEs observed in part 3 of the study were mild.

3.2.4 | MRD in patients with stable schizophrenia (part 4)

Six patients (75.0%) who received placebo and 9 patients (56.3%) who received TAK-041 experienced a TEAE during the study (Table 3). Drug-related TEAEs occurred in 50.0% of patients who received placebo and 56.3% of those receiving TAK-041. Somnolence was reported more frequently in patients receiving TAK-041 than in those receiving placebo (25.0% vs 12.5%).

TABLE 3 Overview of treatment-emergent adverse events (TEAEs) following multiple oral administration in healthy participants and patients with schizophrenia

	Healthy participants						Patients with schizophrenia		
	Placebo ($n = 8$)	TAK-041 40/20 mg ($n = 6$)	TAK-041 80/40 mg ($n = 6$)	TAK-041 120/60 mg ($n = 6$)	TAK-041 160/80 mg ($n = 6$)	All ($n = 32$)	Placebo ($n = 8$)	TAK-041 160/80 mg ($n = 16$)	All ($n = 24$)
Any TEAE	3 (37.5)	4 (66.7)	4 (66.7)	3 (50.0)	5 (83.3)	19 (59.4)	6 (75.0)	9 (56.3)	15 (62.5)
Related	2 (25.0)	0	1 (16.7)	0	3 (50.0)	6 (18.8)	4 (50.0)	9 (56.3)	13 (54.2)
Not related	1 (12.5)	4 (66.7)	3 (50.0)	3 (50.0)	2 (33.3)	13 (40.6)	2 (25.0)	0	2 (8.3)
Mild	3 (37.5)	4 (66.7)	4 (66.7)	2 (33.3)	5 (83.3)	18 (56.3)	6 (75.0)	9 (56.3)	15 (62.5)
Moderate	0	0	0	1 (16.7)	0	1 (3.1)	0	0	0
Serious	0	0	0	0	0	0	0	0	0
Drug discontinuation	0	0	0	0	0	0	0	0	0
Deaths	0	0	0	0	0	0	0	0	0

All data are *n* (%).

3.3 | PK of TAK-041

3.3.1 | SRD in healthy participants (part 1)

TAK-041 5–80 mg administered as an oral suspension was rapidly absorbed, with a median time of maximum concentration observed (t_{max}) of 0.99–3.00 hours. The appearance of a secondary peak in some participants for the 120- and 160-mg dose levels, possibly owing to the poor solubility of TAK-041, increased median t_{max} to 13.0 and 13.5 hours, respectively. The mean half-life ($t_{1/2z}$) fluctuated slightly and was in the range of 210–296 hours for TAK-041 20–160 mg (Figure S2). Maximum observed plasma concentration (C_{max}) and area under the plasma concentration–time curve (AUC) at 0–24 hours (AUC_{24}) and at 0–96 hours (AUC_{96}) and from time 0 to infinity (AUC_{∞}) increased less than proportionally for TAK-041 5–160 mg (Table S2). The mean C_{max} and AUC values for TAK-041 160 mg were similar or below those for TAK-041 120 mg, suggesting plasma PK saturation (Table S3).

3.3.2 | MRD in healthy participants (part 2)

TAK-041 administered as an oral suspension was rapidly absorbed, with a median t_{max} of 1.75–3.00 hours (Figure 1). Two participants (80 mg loading dose and 40 mg maintenance dose, $n = 1$; 160 mg loading dose and 80 mg maintenance dose, $n = 1$) had a t_{max} of approximately 48 hours with TAK-041, possibly owing to the poor solubility of TAK-041. Systemic exposure at steady state (day 22) increased approximately dose proportionally and mean $t_{1/2z}$ for TAK-041 was in the range of 170–302 hours (Table S4; Figure S3). All PK parameters are presented in Table 4.

3.3.3 | Food-effects cohort (part 3)

Food had little effect on TAK-041 plasma concentrations as indicated by similar mean systemic exposures for the tablet formulation between fasted and fed conditions. Median t_{max} for the TAK-041 tablet (under fasted and fed states, 2.00 hours) was similar to that for the TAK-041 oral suspension (1.82 hours). PK parameters are shown in Table S5 and the plasma concentration–time curve is plotted in Figure S4.

3.3.4 | MRD in patients with schizophrenia (part 4)

Median t_{max} for TAK-041 was 1.80 hours for patients with schizophrenia, similar to a median t_{max} of 3.00 hours for healthy participants from cohort 4 of part 2 (Figure 1). All PK parameters are shown in Table 5 and plasma concentration–time curves are shown in

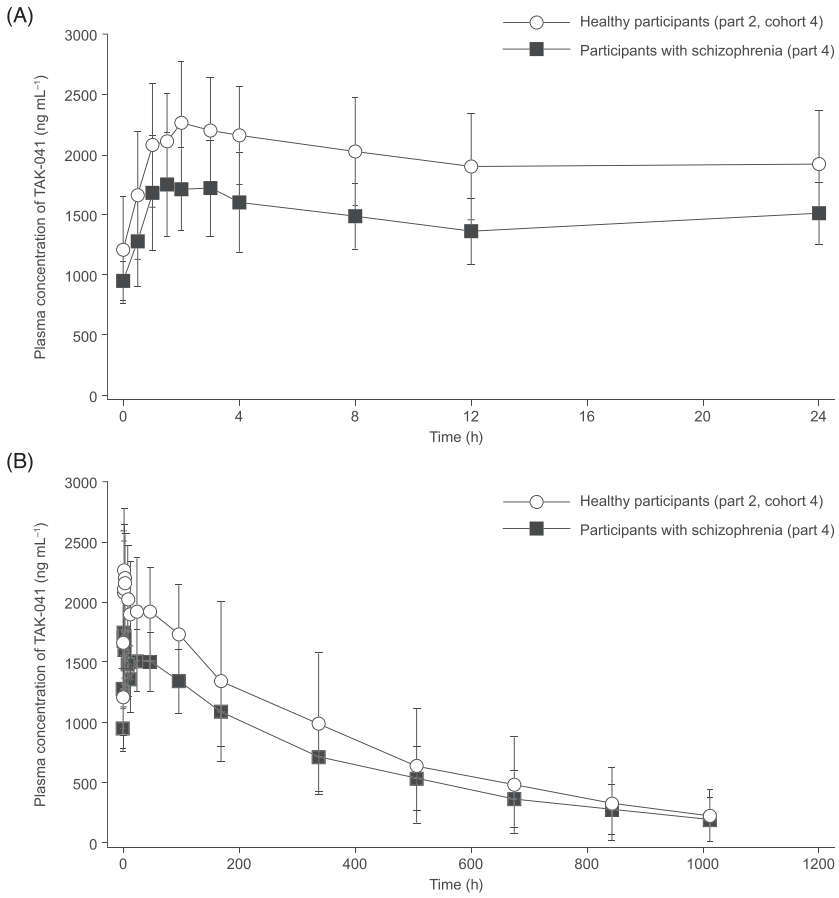

FIGURE 1 Plasma concentration–time curves of TAK-041 following multiple oral administration of TAK-041 in healthy participants and patients with stable schizophrenia, 0–24 hours postdose (A) and full profile (B). Participants were administered TAK-041 160 mg on day 1 followed by TAK-041 80 mg once-weekly oral administration. Zero is used for the below the limit of quantification values (<1.00 ng mL^{-1})

TABLE 4 Pharmacokinetic parameters in healthy participants following multiple oral administration of TAK-041

	TAK-041 40/20 mg ($n = 6$)	TAK-041 80/40 mg ($n = 6$)	TAK-041 120/60 mg ($n = 6$)	TAK-041 160/80 mg ($n = 6$)
t_{max}, median (range), h	1.750 (1.00–2.00)	2.000 (1.02–48.00)	3.000 (1.00–8.00)	3.000 (2.00–48.08)
C_{max}, mean (%CV), ng mL^{-1}	698.3 (19.3)	1251.7 (19.7)	1738.3 (9.0)	2406.7 (16.1)
AUC_{24}, mean (%CV), h*ng mL^{-1}	12 019.8 (19.6)	24 400.2 (21.8)	35 871.1 (12.0)	47 370.4 (21.3)
AUC_{96}, mean (%CV), h*ng mL^{-1}	42 174.8 (29.9)	92 680.4 (22.7)	133 990.6 (12.8)	181 257.6 (19.2)
AUC_{τ}, mean (%CV), h*ng mL^{-1}	66 160.8 (37.6)	149 396.0 (21.3)	202 713.0 (12.2)	294 190.9 (23.4)
$t_{1/2z}$, mean (%CV), h	299.5 (101.7)	301.7 (25.8)	169.7 (34.9)	270.8 (48.2)

%CV, percent coefficient of variation; AUC, area under the plasma concentration–time curve; AUC_{24}, area under the plasma concentration–time curve from 0 to 24 hours; AUC_{96}, area under the plasma concentration–time curve from 0 to 96 hours; AUC_{τ}, area under the plasma concentration–time curve during the dosing interval; C_{max}, maximum observed plasma concentration; $t_{1/2z}$, terminal half-life; t_{max}, time of first occurrence of C_{max}.

TABLE 5 Pharmacokinetic (PK) parameters in patients with schizophrenia following multiple oral administration of TAK-041

	Day 1 ($n = 15$)	Day 22 ($n = 14$)
t_{max}, median (range), h	2.000 (1.00–96.80)	1.800 (1.00–8.05)
C_{max}, mean (%CV), ng mL^{-1}	1266.5 (28.9)	1885.0 (24.3)
AUC_{24}, mean (%CV), h*ng mL^{-1}	20 400.8 (25.0)	35 523.3 (19.1)
AUC_{96}, mean (%CV), h*ng mL^{-1}	90 372.3 (25.1)	140 107.5 (17.3)
AUC_{τ}, mean (%CV), h*ng mL^{-1}	148 889.0 (27.1)	227 230.1 (18.8)[a]
$t_{1/2z}$, mean (%CV), h	–	333.8 (41.8)[a]

%CV, percent coefficient of variation; AUC, area under the plasma concentration–time curve, AUC_{24}, area under the plasma concentration–time curve from 0 to 24 hours; AUC_{48}, area under the plasma concentration–time curve from 0 to 48 hours; AUC_{96}, area under the plasma concentration–time curve from 0 to 96 hours; AUC_{τ}, area under the plasma concentration–time curve during the dosing interval; C_{max}, maximum observed plasma concentration; $t_{1/2z}$, terminal half-life; t_{max}, time of first occurrence of C_{max}.

[a]One participant missed the day 15 dose; therefore, PK concentrations for day 22 were excluded from the mean plasma concentration–time profile and PK parameters were excluded from statistical analysis. One participant terminated the study following dosing on day 1 and PK parameters were excluded from statistical analysis. Another participant terminated the study following dosing on day 22; therefore, all PK parameters with the exception of t_{max}, C_{max}, observed plasma concentration at the end of a dosing interval, AUC_{24}, AUC_{48} and AUC_{96} are excluded from summary and statistical analysis.

Figure S5. Steady state mean $t_{1/2z}$ for TAK-041 was 334 hours and 271 hours in patients with schizophrenia and healthy participants, respectively. Mean TAK-041 $t_{1/2z}$ was 334 hours in patients with schizophrenia, compared with 210–296 hours in healthy participants in part 1 and 170–302 hours in healthy participants in part 2. Peak systemic exposure of TAK-041 was 23–30% lower and total systemic exposure was 22–27% lower in patients with schizophrenia than in healthy participants.

3.4 | Urine PK

Following a single oral administration of TAK-041 5–160 mg, minimal urinary excretion was detected, with a mean total recovery of <0.12% within 96 hours. For participants in the MRD cohort, mean total recovery of TAK-041 on day 22 was <0.22% within 48 hours. Minimal recovery of TAK-041 in urine indicates that urinary excretion is not a major route of elimination for TAK-041.

The 6β-hydroxycortisol/cortisol ratios in urine, determined by the mean amount of drug excreted in the urine between 12 and 24 hours postadministration (Ae_{12-24}), demonstrated moderate variability. In participants receiving a single oral administration of TAK-041 40–160 mg, the Ae_{12-24} 6β-hydroxycortisol/cortisol ratios (6.65–12.1) were generally similar to values in participants receiving placebo (10.1). In patients with schizophrenia receiving TAK-041 160 mg, mean Ae_{12-24} 6β-hydroxycortisol/cortisol ratios were similar to those in participants receiving placebo (16.3 and 15.3, respectively). In participants receiving repeated doses of TAK-041 20–60 mg as a maintenance dose, the mean Ae_{12-24} 6β-hydroxycortisol/cortisol ratios were consistently lower than those in participants receiving placebo (7.46–7.88 and 11.9, respectively). In participants receiving a maintenance dose of 80 mg, however, the Ae_{12-24} 6β-hydroxycortisol/cortisol ratio was higher than that in participants receiving placebo (16.5 and 11.9, respectively). Similarly, in patients with schizophrenia administered TAK-041 at a maintenance dose of 160 mg, the Ae_{12-24} 6β-hydroxycortisol/

cortisol ratio was higher than that in participants receiving placebo (14.3 and 10.5, respectively).

Overall, no consistent trend was observed and urinary 6β-hydroxycortisol/cortisol ratios in healthy participants and patients with schizophrenia were not meaningfully different from placebo, possibly suggesting that CYP3A4 was not induced following TAK-041 administration. The small sample size typical for a first-in-human study may have accounted for the moderate variability in the 6β-hydroxycortisol/cortisol ratios in urine.

3.5 | Summary of PK findings

TAK-041 was rapidly absorbed following single and repeated oral administration in healthy participants and patients with schizophrenia, with a median t_{max} of 0.99–3.00 hours. At higher doses (≥120 mg), a secondary peak was sometimes observed. The ratios for TAK-041 C_{max} and AUC_{96} following single oral administration of TAK-041 tablet formulation under fasted and fed conditions were approximately 0.841 and 0.942, respectively. The median t_{max} was similar under fed and fasted conditions.

Following TAK-041 single dose (160 mg) and multiple doses (160 mg day 1, followed by once weekly doses of 80 mg for 3 wk), C_{max} and AUC_{96} were approximately 22–30% less for patients with schizophrenia than for healthy participants. Single oral doses of TAK-041 led to increases in C_{max} and AUC values that were not proportional to dose. Plasma PK saturation was observed at 160 mg, the highest dose level tested, and steady state exposure for TAK-041 was not achieved after the initial loading dose, as demonstrated by the AUC during the dosing interval (AUC_{τ}) and C_{max} values of 2.41–3.03 and 2.69–2.89, respectively. Following multiple doses of TAK-041, systemic exposure at steady state (day 22) increased approximately dose proportionally. Mean TAK-041 $t_{1/2z}$ was 334 hours in patients with schizophrenia and 170–302 hours in healthy participants, compared with 210–296 hours in healthy participants following a single dose.

3.6 | Exploratory efficacy analysis

None of the PANSS (negative symptoms; $P = .08$), BNSS ($P = .56$), BACS (composite score; $P = .25$) and TEPS ($P = .83$) scores reached statistical significance following treatment with TAK-041. Patients who received TAK-041 demonstrated a statistically significant improvement in the anxiety–depression subscale of the PANSS ($P = .0002$, not corrected for multiplicity), with a placebo-adjusted mean reduction from baseline (standard error) of 3.7 (0.83). Many participants who showed improvement in this subscale also showed improvements in the TEPS; however, the relationship between the anxiety–depression subscale and the TEPS was not linear or statistically significant for either study arm (Figure 2).

4 | DISCUSSION

In this first-in-human study that included healthy participants and patients with stable schizophrenia, TAK-041 was well tolerated, with no severe or serious TEAEs reported. TAK-041 was rapidly absorbed following single and repeated oral administration both in healthy volunteers and patients with stable schizophrenia. Preliminary findings from this study support the further investigation of TAK-041 as a potential therapy for negative symptoms and cognitive impairments in schizophrenia. Headache was the most frequently observed TEAE, occurring in 12 participants in total (11.5%), and tended to occur more frequently with TAK-041 than with placebo and appeared to be dose related. In addition, somnolence was reported by 25.0% of patients with stable schizophrenia who received TAK-041, although no patients discontinued the study because of a TEAE.

In healthy volunteers, systemic exposure generally increased less than dose proportionally following single oral doses of TAK-041, with saturation of the plasma PK observed at the highest dose level tested (160 mg). Of note, in certain participants, a secondary peak was observed at doses of 120 mg or more, possibly owing to the poor solubility of TAK-041. Although some variability was observed, a single loading dose of TAK-041 followed by weekly administrations of a maintenance dose led to approximately dose-proportional systemic exposures. For both single and multiple doses, TAK-041 systemic exposure was approximately 22–30% less for patients with schizophrenia than for healthy volunteers. Because doses of TAK-041 were not adjusted for body weight, these differences in the PK parameters of TAK-041 are likely to be a result of differences in body weight. Individuals with schizophrenia had a higher mean body weight (Table 1) and a lower body weight-adjusted dose (mg/kg) than healthy

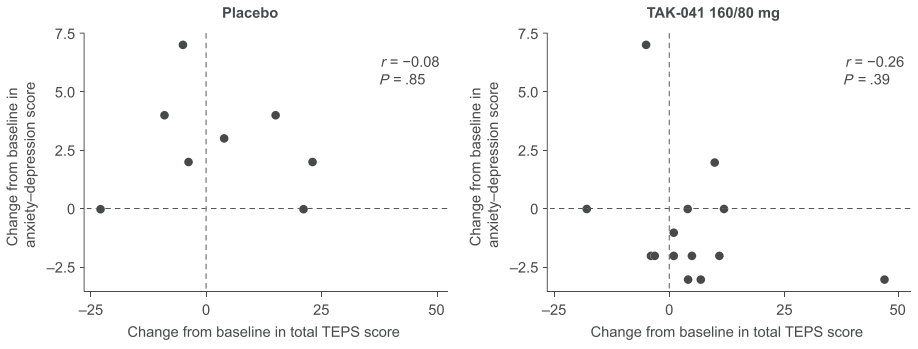

FIGURE 2 Scatter plots for change from baseline to day 29 in anxiety–depression and total TEPS scores. TEPS, Temporal Experience of Pleasure Scale; *r*, correlation coefficient

volunteers. Similar oral bioavailability of TAK-041 between the tablet and oral suspension was observed, with little food effect seen when comparing fasted and fed states. The present findings do not suggest a meaningful effect on urinary 6β-hydroxycortisol/cortisol ratios, possibly indicating that CYP3A4 was not induced following treatment with TAK-041.

In this study, the relatively long half-life of TAK-041 observed in cohorts 1 and 2 of part 1 led to a sequential design for the remaining part 1 cohorts and for part 2, with the mean half-life ($t_{1/2z}$) of TAK-041 ranging from 170 to 334 hours across all 4 parts of the study. Although most antipsychotic drugs have shorter half-lives than were observed for TAK-041 in this study, the small molecule antipsychotic aripiprazole and its active metabolite have a mean half-life of 75 hours and 94 hours, respectively, and aripiprazole is available as a long-acting formulation with a mean half-life of 29.9–46.5 days.[14] The small molecule antipsychotic olanzapine is also available as a long-acting injection with a half-life of 30 days.[14] Long-acting aripiprazole and olanzapine reach a steady-state concentration after 16 and 12 weeks, respectively.[14] In patients with schizophrenia, drugs with long half-lives may improve drug adherence and have been associated with a lower risk of hospitalizations than drugs with short half-lives.[15,16]

Given the small number of patients with schizophrenia included in this study, analysis of efficacy parameters was exploratory. However, a potential signal was observed, with patients who received TAK-041 showing a statistically significant improvement in the anxiety–depression subscale of the PANSS ($P = .0002$). Many of those who showed improvement in the anxiety–depression subscale of the PANSS also showed improvement in the TEPS, meriting further exploration in future studies.

Currently, no standards of care exist for either the treatment of negative symptoms of schizophrenia or cognitive impairments beyond nonpharmacological therapy, such as cognitive remediation training.[6] Although previous trials have suggested moderate efficacy of, for example, antidepressant medication for the treatment of negative symptoms, a large meta-analysis of 168 randomized controlled trials did not find evidence for clinically significant improvements.[17] More recent clinical studies of pharmacotherapy for negative symptoms have not yielded successful results.[18] As such, substantial unmet need remains, especially given that negative symptoms are associated with significant functional impairment.[5,6] The results presented here build on findings from preclinical models and clinical studies using positron emission tomography[19] or functional magnetic resonance imaging technology (ClinicalTrials.gov: NCT03319953). Further studies of the GPR139 agonist TAK-041 are warranted that include larger numbers of patients with schizophrenia, or other mental health disorders, than are included in the present study.

5 | CONCLUSIONS

In this first-in-human study, the GPR139 agonist TAK-041 was generally well tolerated in healthy volunteers and patients with schizophrenia. TAK-041 was rapidly absorbed following single and repeated oral administration in both healthy participants and patients with stable schizophrenia, with bioavailability being comparable between the oral suspension and the tablet formulation, and no meaningful food effect observed. In addition, a potential improvement in the anxiety–depression scale of the PANSS was detected. These results support further investigation of TAK-041 in individuals with schizophrenia.

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COMPETING INTERESTS

D.H. is an employee of Parexel. W.Y., P.K., R.B., and A.L. are employees of Takeda Pharmaceutical Company, Ltd and own stock or stock options. J.P. and D.A. are former employees of Takeda Pharmaceutical Company, Ltd.

CONTRIBUTORS

All authors contributed to the study conception and design. Data analysis was performed by Clinical Pharmacology and Biostatistics. All authors were involved in manuscript preparation and review. All authors read and approved the final manuscript.

DATA AVAILABILITY STATEMENT

The datasets, including the redacted study protocol, redacted statistical analysis plan and individual participant data supporting the results reported in this article, will be made available within 3 months from initial request, to researchers who provide a methodologically sound proposal. The data will be provided after de-identification, in compliance with applicable privacy laws, data protection and requirements for consent and anonymization.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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