Clinical trial results:
A Randomized, Double-Blind, Placebo-Controlled, Two-Period Cross-Over, Proof of Activity Study to Evaluate the Effects of TAK-041 on Motivational Anhedonia as Add-On to Antipsychotics in Subjects with Stable Schizophrenia

Summary

EudraCT number	2017-001084-20
Trial protocol	GB
Global end of trial date	06 November 2019

Results information

Result version number	v1 (current)
This version publication date	22 November 2020
First version publication date	22 November 2020

Trial information

Trial identification

Sponsor protocol code	TAK-041-2001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03319953
WHO universal trial number (UTN)	U1111-1191-6915

Notes:

Sponsors

Sponsor organisation name	Takeda
Sponsor organisation address	61 Aldwych, London, United Kingdom, WC2B 4AE
Public contact	Medical Director, Takeda, 001 +18778253327, trialdisclosures@takeda.com
Scientific contact	Medical Director, Takeda, 001 +18778253327, trialdisclosures@takeda.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	06 November 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	06 November 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of the study is to determine whether motivation/reward deficits observed in schizophrenia are attenuated and whether cognitive impairment associated with schizophrenia is improved by add-on TAK-041 administration to antipsychotics in participants with stable schizophrenia.

Protection of trial subjects:

All study participants were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	21 December 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 23
Worldwide total number of subjects	23
EEA total number of subjects	23

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	23
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants took part in the study at single investigative sites in United Kingdom from 21 December 2017 to 06 November 2019.

Pre-assignment

Screening details:

Participants with stable schizophrenia were enrolled to receive TAK-041 or placebo in this study in crossover pattern along with the add on to antipsychotics to assess the proof of activity.

Period 1

Period 1 title	Period 1 (Day 1 to 14)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Treatment Sequence 1: TAK-041 40 mg/Placebo + Antipsychotics

Arm description:

TAK-041 40 milligram (mg), suspension, orally on Day 1 of Treatment Period 1, followed by 35 days wash-out Period, followed by TAK-041 placebo-matching, suspension, orally on Day 1 of Treatment Period 2. All participants received a stable dose of antipsychotics as per standard of care throughout the duration of the Treatment Period.

Arm type	Experimental
Investigational medicinal product name	TAK-041 40 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for oral suspension
Routes of administration	Oral use

Dosage and administration details:

TAK-041 suspension

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for oral suspension
Routes of administration	Oral use

Dosage and administration details:

TAK-041 placebo-matching suspension

Arm title	Treatment Sequence 2: Placebo/TAK-041 40 mg + Antipsychotics

Arm description:

TAK-041 placebo-matching, suspension, orally on Day 1 of Treatment Period 1, followed by 35 days Wash-out Period, followed by TAK-041 40 mg, suspension, orally on Day 1 of Treatment Period 2. All participants received a stable dose of antipsychotics as per standard of care throughout the duration of the Treatment Period.

Arm type	Experimental

Investigational medicinal product name	TAK-041 40 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for oral suspension
Routes of administration	Oral use

Dosage and administration details:

TAK-041 suspension

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for oral suspension
Routes of administration	Oral use

Dosage and administration details:

TAK-041 placebo-matching suspension

Arm title	Treatment Sequence 3: TAK-041 160 mg/Placebo + Antipsychotics

Arm description:

TAK-041 160 mg, suspension, orally on Day 1 of Treatment Period 1, followed by 35 days Wash-out Period, followed by TAK-041 placebo-matching, suspension, orally on Day 1 of Treatment Period 2. All participants received stable dose of antipsychotics as per standard of care throughout the duration of the Treatment Period.

Arm type	Experimental
Investigational medicinal product name	TAK-041 160 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for oral suspension
Routes of administration	Oral use

Dosage and administration details:

TAK-041 suspension

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for oral suspension
Routes of administration	Oral use

Dosage and administration details:

TAK-041 placebo-matching suspension

Arm title	Treatment Sequence 4: Placebo/TAK-041 160 mg + Antipsychotics

Arm description:

TAK-041 placebo-matching, suspension, orally on Day 1 of Treatment Period 1, followed by 35 days Wash-out Period, followed by TAK-041 160 mg, suspension, orally on Day 1 of Treatment Period 2. All participants received stable dose of antipsychotics as per standard of care throughout the duration of the Treatment Period.

Arm type	Experimental
Investigational medicinal product name	TAK-041 160 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for oral suspension
Routes of administration	Oral use

Dosage and administration details:

TAK-041 suspension

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	

Pharmaceutical forms	Concentrate for oral suspension
Routes of administration	Oral use

Dosage and administration details:

TAK-041 placebo-matching suspension

Number of subjects in period 1	Treatment Sequence 1: TAK-041 40 mg/Placebo + Antipsychotics	Treatment Sequence 2: Placebo/TAK-041 40 mg + Antipsychotics	Treatment Sequence 3: TAK-041 160 mg/Placebo + Antipsychotics
Started	3	4	9
Completed	3	4	9

Number of subjects in period 1	Treatment Sequence 4: Placebo/TAK-041 160 mg + Antipsychotics
Started	7
Completed	7

Period 2

Period 2 title	Washout Period (Day 15 to 49)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Treatment Sequence 1: TAK-041 40 mg/Placebo + Antipsychotics

Arm description:

TAK-041 40 milligram (mg), suspension, orally on Day 1 of Treatment Period 1, followed by 35 days wash-out Period, followed by TAK-041 placebo-matching, suspension, orally on Day 1 of Treatment Period 2. All participants received a stable dose of antipsychotics as per standard of care throughout the duration of the Treatment Period.

Arm type	Experimental
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for oral suspension
Routes of administration	Oral use

Dosage and administration details:

TAK-041 placebo-matching suspension

Investigational medicinal product name	TAK-041 40 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for oral suspension
Routes of administration	Oral use

Dosage and administration details:

TAK-041 suspension

Arm title	Treatment Sequence 2: Placebo/TAK-041 40 mg + Antipsychotics

Arm description:

TAK-041 placebo-matching, suspension, orally on Day 1 of Treatment Period 1, followed by 35 days Wash-out Period, followed by TAK-041 40 mg, suspension, orally on Day 1 of Treatment Period 2. All participants received a stable dose of antipsychotics as per standard of care throughout the duration of the Treatment Period.

Arm type	Experimental
Investigational medicinal product name	TAK-041 40 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for oral suspension
Routes of administration	Oral use

Dosage and administration details:

TAK-041 suspension

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for oral suspension
Routes of administration	Oral use

Dosage and administration details:

TAK-041 placebo-matching suspension

Arm title	Treatment Sequence 3: TAK-041 160 mg/Placebo + Antipsychotics

Arm description:

TAK-041 160 mg, suspension, orally on Day 1 of Treatment Period 1, followed by 35 days Wash-out Period, followed by TAK-041 placebo-matching, suspension, orally on Day 1 of Treatment Period 2. All participants received stable dose of antipsychotics as per standard of care throughout the duration of the Treatment Period.

Arm type	Experimental
Investigational medicinal product name	TAK-041 160 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for oral suspension
Routes of administration	Oral use

Dosage and administration details:

TAK-041 suspension

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for oral suspension
Routes of administration	Oral use

Dosage and administration details:

TAK-041 placebo-matching suspension

Arm title	Treatment Sequence 4: Placebo/TAK-041 160 mg + Antipsychotics

Arm description:

TAK-041 placebo-matching, suspension, orally on Day 1 of Treatment Period 1, followed by 35 days Wash-out Period, followed by TAK-041 160 mg, suspension, orally on Day 1 of Treatment Period 2. All participants received stable dose of antipsychotics as per standard of care throughout the duration of the Treatment Period.

Arm type	Experimental
Investigational medicinal product name	TAK-041 160 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for oral suspension
Routes of administration	Oral use

Dosage and administration details:

TAK-041 suspension

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for oral suspension
Routes of administration	Oral use

Dosage and administration details:

TAK-041 placebo-matching suspension

Number of subjects in period 2	Treatment Sequence 1: TAK-041 40 mg/Placebo + Antipsychotics	Treatment Sequence 2: Placebo/TAK-041 40 mg + Antipsychotics	Treatment Sequence 3: TAK-041 160 mg/Placebo + Antipsychotics
Started	3	4	9
Completed	3	4	9

Number of subjects in period 2	Treatment Sequence 4: Placebo/TAK-041 160 mg + Antipsychotics
Started	7
Completed	7

Period 3

Period 3 title	Period 2
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes

Arm title	Treatment Sequence 1: TAK-041 40 mg/Placebo + Antipsychotics

Arm description:

TAK-041 40 milligram (mg), suspension, orally on Day 1 of Treatment Period 1, followed by 35 days wash-out Period, followed by TAK-041 placebo-matching, suspension, orally on Day 1 of Treatment Period 2. All participants received a stable dose of antipsychotics as per standard of care throughout the duration of the Treatment Period.

Arm type	Experimental
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for oral suspension
Routes of administration	Oral use

Dosage and administration details:

TAK-041 placebo-matching suspension

Investigational medicinal product name	TAK-041 40 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for oral suspension
Routes of administration	Oral use

Dosage and administration details:

TAK-041 suspension

Arm title	Treatment Sequence 2: Placebo/TAK-041 40 mg + Antipsychotics

Arm description:

TAK-041 placebo-matching, suspension, orally on Day 1 of Treatment Period 1, followed by 35 days Wash-out Period, followed by TAK-041 40 mg, suspension, orally on Day 1 of Treatment Period 2. All participants received a stable dose of antipsychotics as per standard of care throughout the duration of the Treatment Period.

Arm type	Experimental
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for oral suspension
Routes of administration	Oral use

Dosage and administration details:

TAK-041 placebo-matching suspension

Investigational medicinal product name	TAK-041 40 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for oral suspension
Routes of administration	Oral use

Dosage and administration details:

TAK-041 suspension

Arm title	Treatment Sequence 3: TAK-041 160 mg/Placebo + Antipsychotics

Arm description:

TAK-041 160 mg, suspension, orally on Day 1 of Treatment Period 1, followed by 35 days Wash-out Period, followed by TAK-041 placebo-matching, suspension, orally on Day 1 of Treatment Period 2. All participants received stable dose of antipsychotics as per standard of care throughout the duration of the Treatment Period.

Arm type	Experimental

Investigational medicinal product name	TAK-041 160 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for oral suspension
Routes of administration	Oral use

Dosage and administration details:

TAK-041 suspension

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for oral suspension
Routes of administration	Oral use

Dosage and administration details:

TAK-041 placebo-matching suspension

Arm title	Treatment Sequence 4: Placebo/TAK-041 160 mg + Antipsychotics

Arm description:

TAK-041 placebo-matching, suspension, orally on Day 1 of Treatment Period 1, followed by 35 days Wash-out Period, followed by TAK-041 160 mg, suspension, orally on Day 1 of Treatment Period 2. All participants received stable dose of antipsychotics as per standard of care throughout the duration of the Treatment Period.

Arm type	Experimental
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for oral suspension
Routes of administration	Oral use

Dosage and administration details:

TAK-041 placebo-matching suspension

Investigational medicinal product name	TAK-041 160 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for oral suspension
Routes of administration	Oral use

Dosage and administration details:

TAK-041 suspension

Number of subjects in period 3	Treatment Sequence 1: TAK-041 40 mg/Placebo + Antipsychotics	Treatment Sequence 2: Placebo/TAK-041 40 mg + Antipsychotics	Treatment Sequence 3: TAK-041 160 mg/Placebo + Antipsychotics
Started	3	4	9
Completed	2	4	8
Not completed	1	0	1
Consent withdrawn by subject	1	-	-
Reason not Specified	-	-	1

Number of subjects in period 3	Treatment Sequence 4: Placebo/TAK-041 160 mg + Antipsychotics

Started	7
Completed	6
Not completed	1
Consent withdrawn by subject	-
Reason not Specified	1

Baseline characteristics

Reporting groups	
Reporting group title	Treatment Sequence 1: TAK-041 40 mg/Placebo + Antipsychotics

Reporting group description:

TAK-041 40 milligram (mg), suspension, orally on Day 1 of Treatment Period 1, followed by 35 days wash-out Period, followed by TAK-041 placebo-matching, suspension, orally on Day 1 of Treatment Period 2. All participants received a stable dose of antipsychotics as per standard of care throughout the duration of the Treatment Period.

Reporting group title	Treatment Sequence 2: Placebo/TAK-041 40 mg + Antipsychotics

Reporting group description:

TAK-041 placebo-matching, suspension, orally on Day 1 of Treatment Period 1, followed by 35 days Wash-out Period, followed by TAK-041 40 mg, suspension, orally on Day 1 of Treatment Period 2. All participants received a stable dose of antipsychotics as per standard of care throughout the duration of the Treatment Period.

Reporting group title	Treatment Sequence 3: TAK-041 160 mg/Placebo + Antipsychotics

Reporting group description:

TAK-041 160 mg, suspension, orally on Day 1 of Treatment Period 1, followed by 35 days Wash-out Period, followed by TAK-041 placebo-matching, suspension, orally on Day 1 of Treatment Period 2. All participants received stable dose of antipsychotics as per standard of care throughout the duration of the Treatment Period.

Reporting group title	Treatment Sequence 4: Placebo/TAK-041 160 mg + Antipsychotics

Reporting group description:

TAK-041 placebo-matching, suspension, orally on Day 1 of Treatment Period 1, followed by 35 days Wash-out Period, followed by TAK-041 160 mg, suspension, orally on Day 1 of Treatment Period 2. All participants received stable dose of antipsychotics as per standard of care throughout the duration of the Treatment Period.

Reporting group values	Treatment Sequence 1: TAK-041 40 mg/Placebo + Antipsychotics	Treatment Sequence 2: Placebo/TAK-041 40 mg + Antipsychotics	Treatment Sequence 3: TAK-041 160 mg/Placebo + Antipsychotics
Number of subjects	3	4	9
Age categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	42.0	39.3	46.8
standard deviation	± 16.5	± 16.1	± 12.1
Sex: Female, Male Units: participants			
Female	0	2	2
Male	3	2	7
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	3	4	9
Unknown or Not Reported	0	0	0
Race (NIH/OMB) Units: Subjects			

American Indian or Alaska Native	0	0	0
Asian	0	0	1
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	3	3	4
White	0	1	4
More than one race	0	0	0
Unknown or Not Reported	0	0	0
Region of Enrollment Units: Subjects			
United Kingdom	3	4	9
Body Mass Index (BMI)			
Body Mass Index (BMI) was calculated as weight (kg)/[height (m)^2].			
Units: kg/m^2			
arithmetic mean	30.7	26.3	32.3
standard deviation	± 3.1	± 3.8	± 7.1

Reporting group values	Treatment Sequence 4: Placebo/TAK-041 160 mg + Antipsychotics	Total	
Number of subjects	7	23	
Age categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	43.4		
standard deviation	± 9.6	-	
Sex: Female, Male Units: participants			
Female	2	6	
Male	5	17	
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	0	0	
Not Hispanic or Latino	7	23	
Unknown or Not Reported	0	0	
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	0	1	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	6	16	
White	0	5	
More than one race	1	1	
Unknown or Not Reported	0	0	
Region of Enrollment Units: Subjects			
United Kingdom	7	23	

Body Mass Index (BMI)			
Body Mass Index (BMI) was calculated as weight (kg)/[height (m)^2].			
Units: kg/m^2			
arithmetic mean	30.0		
standard deviation	± 4.7	-	

Subject analysis sets

Subject analysis set title	Placebo
Subject analysis set type	Sub-group analysis

Subject analysis set description:

TAK-041 placebo-matching, suspension, orally on Day 1 of Treatment Period 1 or 2. All participants took a stable dose of antipsychotics as per standard of care throughout the duration of the Treatment Period.

Subject analysis set title	TAK-041 40 mg
Subject analysis set type	Sub-group analysis

Subject analysis set description:

TAK-041 40 mg, suspension, orally on Day 1 of Treatment Period 1 or 2. All participants took a stable dose of antipsychotics as per standard of care throughout the duration of the Treatment Period.

Subject analysis set title	TAK-041 160 mg
Subject analysis set type	Sub-group analysis

Subject analysis set description:

TAK-041 160 mg, suspension, orally on Day 1 of Treatment Period 1 or 2. All participants took a stable dose of antipsychotics as per standard of care throughout the duration of the Treatment Period.

Subject analysis set title	Placebo
Subject analysis set type	Sub-group analysis

Subject analysis set description:

TAK-041 placebo-matching, suspension, orally on Day 1 of Treatment Period 1 or 2. All participants took a stable dose of antipsychotics as per standard of care throughout the duration of the Treatment Period.

Subject analysis set title	TAK-041 40 mg
Subject analysis set type	Sub-group analysis

Subject analysis set description:

TAK-041 40 mg, suspension, orally on Day 1 of Treatment Period 1 or 2. All participants took a stable dose of antipsychotics as per standard of care throughout the duration of the Treatment Period.

Subject analysis set title	TAK-041 160 mg
Subject analysis set type	Sub-group analysis

Subject analysis set description:

TAK-041 160 mg, suspension, orally on Day 1 of Treatment Period 1 or 2. All participants took a stable dose of antipsychotics as per standard of care throughout the duration of the Treatment Period.

Reporting group values	Placebo	TAK-041 40 mg	TAK-041 160 mg
Number of subjects	21	7	15
Age categorical			
Units: Subjects			

Age Continuous			
Units: years			
arithmetic mean			
standard deviation	±	±	±
Sex: Female, Male			
Units: participants			
Female			
Male			

Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino Not Hispanic or Latino Unknown or Not Reported			
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native Asian Native Hawaiian or Other Pacific Islander Black or African American White More than one race Unknown or Not Reported			
Region of Enrollment Units: Subjects			
United Kingdom			
Body Mass Index (BMI)			
Body Mass Index (BMI) was calculated as weight (kg)/[height (m)^2].			
Units: kg/m^2 arithmetic mean standard deviation	±	±	±

Reporting group values	Placebo	TAK-041 40 mg	TAK-041 160 mg
Number of subjects	20	6	13
Age categorical Units: Subjects			
Age Continuous Units: years arithmetic mean standard deviation	0.23 ± 0.396	0.23 ± 0.202	0.03 ± 0.458
Sex: Female, Male Units: participants			
Female Male			
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino Not Hispanic or Latino Unknown or Not Reported			
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native Asian Native Hawaiian or Other Pacific Islander Black or African American White More than one race Unknown or Not Reported			

Region of Enrollment Units: Subjects			
United Kingdom			

Body Mass Index (BMI)			
Body Mass Index (BMI) was calculated as weight (kg)/[height (m)^2].			
Units: kg/m^2 arithmetic mean standard deviation	±	±	±

End points

End points reporting groups

Reporting group title	Treatment Sequence 1: TAK-041 40 mg/Placebo + Antipsychotics

Reporting group description:

TAK-041 40 milligram (mg), suspension, orally on Day 1 of Treatment Period 1, followed by 35 days wash-out Period, followed by TAK-041 placebo-matching, suspension, orally on Day 1 of Treatment Period 2. All participants received a stable dose of antipsychotics as per standard of care throughout the duration of the Treatment Period.

Reporting group title	Treatment Sequence 2: Placebo/TAK-041 40 mg + Antipsychotics

Reporting group description:

TAK-041 placebo-matching, suspension, orally on Day 1 of Treatment Period 1, followed by 35 days Wash-out Period, followed by TAK-041 40 mg, suspension, orally on Day 1 of Treatment Period 2. All participants received a stable dose of antipsychotics as per standard of care throughout the duration of the Treatment Period.

Reporting group title	Treatment Sequence 3: TAK-041 160 mg/Placebo + Antipsychotics

Reporting group description:

TAK-041 160 mg, suspension, orally on Day 1 of Treatment Period 1, followed by 35 days Wash-out Period, followed by TAK-041 placebo-matching, suspension, orally on Day 1 of Treatment Period 2. All participants received stable dose of antipsychotics as per standard of care throughout the duration of the Treatment Period.

Reporting group title	Treatment Sequence 4: Placebo/TAK-041 160 mg + Antipsychotics

Reporting group description:

TAK-041 placebo-matching, suspension, orally on Day 1 of Treatment Period 1, followed by 35 days Wash-out Period, followed by TAK-041 160 mg, suspension, orally on Day 1 of Treatment Period 2. All participants received stable dose of antipsychotics as per standard of care throughout the duration of the Treatment Period.

Reporting group title	Treatment Sequence 1: TAK-041 40 mg/Placebo + Antipsychotics

Reporting group description:

TAK-041 40 milligram (mg), suspension, orally on Day 1 of Treatment Period 1, followed by 35 days wash-out Period, followed by TAK-041 placebo-matching, suspension, orally on Day 1 of Treatment Period 2. All participants received a stable dose of antipsychotics as per standard of care throughout the duration of the Treatment Period.

Reporting group title	Treatment Sequence 2: Placebo/TAK-041 40 mg + Antipsychotics

Reporting group description:

TAK-041 placebo-matching, suspension, orally on Day 1 of Treatment Period 1, followed by 35 days Wash-out Period, followed by TAK-041 40 mg, suspension, orally on Day 1 of Treatment Period 2. All participants received a stable dose of antipsychotics as per standard of care throughout the duration of the Treatment Period.

Reporting group title	Treatment Sequence 3: TAK-041 160 mg/Placebo + Antipsychotics

Reporting group description:

TAK-041 160 mg, suspension, orally on Day 1 of Treatment Period 1, followed by 35 days Wash-out Period, followed by TAK-041 placebo-matching, suspension, orally on Day 1 of Treatment Period 2. All participants received stable dose of antipsychotics as per standard of care throughout the duration of the Treatment Period.

Reporting group title	Treatment Sequence 4: Placebo/TAK-041 160 mg + Antipsychotics

Reporting group description:

TAK-041 placebo-matching, suspension, orally on Day 1 of Treatment Period 1, followed by 35 days Wash-out Period, followed by TAK-041 160 mg, suspension, orally on Day 1 of Treatment Period 2. All participants received stable dose of antipsychotics as per standard of care throughout the duration of the Treatment Period.

Reporting group title	Treatment Sequence 1: TAK-041 40 mg/Placebo +

	Antipsychotics

Reporting group description:

TAK-041 40 milligram (mg), suspension, orally on Day 1 of Treatment Period 1, followed by 35 days wash-out Period, followed by TAK-041 placebo-matching, suspension, orally on Day 1 of Treatment Period 2. All participants received a stable dose of antipsychotics as per standard of care throughout the duration of the Treatment Period.

Reporting group title	Treatment Sequence 2: Placebo/TAK-041 40 mg + Antipsychotics

Reporting group description:

TAK-041 placebo-matching, suspension, orally on Day 1 of Treatment Period 1, followed by 35 days Wash-out Period, followed by TAK-041 40 mg, suspension, orally on Day 1 of Treatment Period 2. All participants received a stable dose of antipsychotics as per standard of care throughout the duration of the Treatment Period.

Reporting group title	Treatment Sequence 3: TAK-041 160 mg/Placebo + Antipsychotics

Reporting group description:

TAK-041 160 mg, suspension, orally on Day 1 of Treatment Period 1, followed by 35 days Wash-out Period, followed by TAK-041 placebo-matching, suspension, orally on Day 1 of Treatment Period 2. All participants received stable dose of antipsychotics as per standard of care throughout the duration of the Treatment Period.

Reporting group title	Treatment Sequence 4: Placebo/TAK-041 160 mg + Antipsychotics

Reporting group description:

TAK-041 placebo-matching, suspension, orally on Day 1 of Treatment Period 1, followed by 35 days Wash-out Period, followed by TAK-041 160 mg, suspension, orally on Day 1 of Treatment Period 2. All participants received stable dose of antipsychotics as per standard of care throughout the duration of the Treatment Period.

Subject analysis set title	Placebo
Subject analysis set type	Sub-group analysis

Subject analysis set description:

TAK-041 placebo-matching, suspension, orally on Day 1 of Treatment Period 1 or 2. All participants took a stable dose of antipsychotics as per standard of care throughout the duration of the Treatment Period.

Subject analysis set title	TAK-041 40 mg
Subject analysis set type	Sub-group analysis

Subject analysis set description:

TAK-041 40 mg, suspension, orally on Day 1 of Treatment Period 1 or 2. All participants took a stable dose of antipsychotics as per standard of care throughout the duration of the Treatment Period.

Subject analysis set title	TAK-041 160 mg
Subject analysis set type	Sub-group analysis

Subject analysis set description:

TAK-041 160 mg, suspension, orally on Day 1 of Treatment Period 1 or 2. All participants took a stable dose of antipsychotics as per standard of care throughout the duration of the Treatment Period.

Subject analysis set title	Placebo
Subject analysis set type	Sub-group analysis

Subject analysis set description:

TAK-041 placebo-matching, suspension, orally on Day 1 of Treatment Period 1 or 2. All participants took a stable dose of antipsychotics as per standard of care throughout the duration of the Treatment Period.

Subject analysis set title	TAK-041 40 mg
Subject analysis set type	Sub-group analysis

Subject analysis set description:

TAK-041 40 mg, suspension, orally on Day 1 of Treatment Period 1 or 2. All participants took a stable dose of antipsychotics as per standard of care throughout the duration of the Treatment Period.

Subject analysis set title	TAK-041 160 mg
Subject analysis set type	Sub-group analysis

Subject analysis set description:

TAK-041 160 mg, suspension, orally on Day 1 of Treatment Period 1 or 2. All participants took a stable dose of antipsychotics as per standard of care throughout the duration of the Treatment Period.

Primary: Change from Placebo in the Brief Assessment of Cognition in Schizophrenia (BACS) Composite Score at Second Testing After TAK-041 Administration

End point title	Change from Placebo in the Brief Assessment of Cognition in Schizophrenia (BACS) Composite Score at Second Testing After TAK-041 Administration

End point description:

BACS is a reliable and sensitive measure of cognitive function in schizophrenia. The BACS consisted of items across 6 subtests: Verbal Memory, Digit Sequencing, Token Motor, Verbal Fluency, Symbol Coding, and Tower of London. A BACS composite score ranges up to maximum of 50 with a standard deviation of 20. Higher values (positive changes from placebo) indicate better performance. Bayesian normal linear model was used for analysis. Pharmacodynamic (PD) Analysis Set included all participants who received at least 1 dose of study drug and had at least 1 evaluable primary or exploratory PD measurement. Number analyzed is the number of participants with data available for analyses.

End point type	Primary

End point timeframe:

Baseline (Day -1) and Day 14

End point values	Placebo	TAK-041 40 mg	TAK-041 160 mg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	21	7	15	
Units: score on a scale				
arithmetic mean (standard deviation)				
Baseline (n=21,7,15)	29.72 (± 12.867)	27.35 (± 12.753)	27.89 (± 8.214)	
Day 14 (n=21,7,14)	2.28 (± 6.963)	5.35 (± 6.944)	1.31 (± 5.618)	

Statistical analyses

Statistical analysis title	TAK-041 160 mg Vs Placebo
Comparison groups	Placebo v TAK-041 40 mg
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.2079 [1]
Method	Bayesian Normal Linear Model

Notes:

[1] - Bayesian method was used to calculate the posterior probability. High posterior probability of a difference between TAK-041 and placebo >2.0.

Statistical analysis title	TAK-041 160 mg Vs Placebo
Comparison groups	Placebo v TAK-041 160 mg
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0633 [2]
Method	Bayesian Normal Linear Model

Notes:

[2] - Bayesian method was used to calculate the posterior probability. High posterior probability of a difference between TAK-041 and placebo >2.0.

Primary: Blood-Oxygen-Level-Dependent (BOLD) Signal in the Average Ventral Striatum (VS) Region of Interest (ROI) Activation in the Monetary Incentive Delay (MID) Reward Task at First Testing After TAK-041 Administration

End point title	Blood-Oxygen-Level-Dependent (BOLD) Signal in the Average Ventral Striatum (VS) Region of Interest (ROI) Activation in the Monetary Incentive Delay (MID) Reward Task at First Testing After TAK-041 Administration

End point description:

BOLD Functional magnetic resonance imaging (fMRI) changes in the BOLD - signal, which changes in response to neural activity. Baseline fMRI measurements will be followed by rewarded delayed response Working Memory (WM) task measurements in which participants are required to remember the spatial location of a target stimulus (a dot) relative to a fixation cross. Participants are given feedback indicating success or failure. Bayesian normal linear model was used for analysis. PD Analysis Set included all participants who received at least 1 dose of study drug and had at least 1 evaluable primary or exploratory PD measurement. Overall number of participants analyzed is the number of participants with data available for analyses.

End point type	Primary

End point timeframe:

Day 1

End point values	Placebo	TAK-041 40 mg	TAK-041 160 mg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	20	6	13	
Units: BOLD signal				
arithmetic mean (standard deviation)	0.23 (± 0.396)	0.23 (± 0.202)	0.03 (± 0.458)	

Statistical analyses

Statistical analysis title	TAK-041 40 mg Vs Placebo
Comparison groups	Placebo v TAK-041 40 mg
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1706 [3]
Method	Bayesian Normal Linear Model

Notes:

[3] - Bayesian method was used to calculate the posterior probability. High posterior probability of a difference between TAK-041 and placebo >0.09.

Statistical analysis title	TAK-041 160 mg Vs Placebo
Comparison groups	Placebo v TAK-041 160 mg

Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0373 [4]
Method	Bayesian Normal Linear Model

Notes:

[4] - Bayesian method was used to calculate the posterior probability. High posterior probability of a difference between TAK-041 and placebo >0.09.

Secondary: Percentage of Participants who Experience at least one Treatment Emergent Adverse Event (TEAE)

End point title	Percentage of Participants who Experience at least one Treatment Emergent Adverse Event (TEAE)

End point description:

An Adverse Event (AE) is defined as any untoward medical occurrence in a clinical investigation participant administered a drug; it does not necessarily have to have a causal relationship with this treatment. A TEAE is defined as an adverse event with an onset that occurs after receiving study drug. Safety Analysis Set included all participants who were enrolled and received at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

From the first dose of study drug up to 77 days after last dose of study drug (Up to Day 154)

End point values	Placebo	TAK-041 40 mg	TAK-041 160 mg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	21	7	15	
Units: percentage of participants				
number (not applicable)	57.1	71.4	53.3	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants who Meet the Markedly Abnormal Criteria for Safety Laboratory Tests at least Once Post Dose

End point title	Percentage of Participants who Meet the Markedly Abnormal Criteria for Safety Laboratory Tests at least Once Post Dose

End point description:

Clinical Laboratory parameters included tests for chemistry, hematology and urinalysis. Markedly abnormal values during treatment period were categorized as: alanine aminotransferase (ALT)>3.0 U/L*upper limit of normal(ULN),albumin<25 g/L*lower limit of normal(LLN), alkaline phosphatase >3.0 U/L*ULN, aspartate aminotransferase >3.0 U/L*ULN, bilirubin >34.2 umol/L*ULN, calcium <1.75 mmol/L, >2.88 mmol/L, chloride <75 mmol/L, >126 mmol/L, creatinine >177umol/L, gamma glutamyl transferase >3 U/L*ULN, glucose <2.8 mmol/L, >19.4 mmol/L, potassium<3 mmol/L, >6 mmol/L, sodium <130 mmol/L, >150 mmol/L,Urea <130 mmol/L, erythrocytes <0.8*LLN >1.2*ULN, hematocrit <0.8*LLN, >1.2*ULN, hemoglobin <0.8 g/L*LLN, >1.2 g/L*ULN, leukocytes <0.5 (10^9/L)*LLN, >1.5 (10^9/L)*ULN, platelets <75(10^9/L), >600(10^9/L). Safety Analysis Set included all participants who were enrolled and received at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

From the first dose of study drug up to 77 days after last dose of study drug (Up to Day 154)

End point values	Placebo	TAK-041 40 mg	TAK-041 160 mg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	21	7	15	
Units: percentage of participants	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants who Meet the Markedly Abnormal Criteria for Vital Sign Measurements At Least Once Post Dose

End point title	Percentage of Participants who Meet the Markedly Abnormal Criteria for Vital Sign Measurements At Least Once Post Dose

End point description:

Vital signs included oral body temperature measurement, supine and standing blood pressure, respiration rate, and pulse. Pulse and blood pressure were measured after 5 minutes supine and again at 1 and 3 minutes after standing. The markedly abnormal value (MAV) criteria for vital signs included systolic blood pressure < 85 mmHg, > 180 mmHg; diastolic blood pressure < 50 mmHg, > 110 mmHg; pulse < 50 beats/min, > 120 beats/min; temperature < 35.6 C > 37.7 C. Safety Analysis Set included all participants who were enrolled and received at least 1 dose of study drug. Categories with at least one participant are reported.

End point type	Secondary

End point timeframe:

From the first dose of study drug up to 77 days after last dose of study drug (Up to Day 154)

End point values	Placebo	TAK-041 40 mg	TAK-041 160 mg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	21	7	15	
Units: percentage of participants				
number (not applicable)				
<35.6 C	0	0	6.7	
>37.7 C	4.8	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants who Meet the Markedly Abnormal Criteria for Safety Electrocardiogram (ECG) at Least Once Post Dose

End point title	Percentage of Participants who Meet the Markedly Abnormal Criteria for Safety Electrocardiogram (ECG) at Least Once Post Dose

End point description:

The markedly abnormal value (MAV) criteria for 12-lead ECG parameters included ECG Mean Heart Rate < 50 beats/min, > 120 beats/min; PR Interval, Aggregate <= 80 msec, >= 200 msec; QRS Duration, Aggregate <= 80 msec, >= 180 msec; QTcB Interval, Aggregate <= 300 msec, >= 500 msec OR (>= 30 msec change from baseline and >= 450 msec); QTcF Interval, Aggregate <= 300 msec, >= 500 msec OR (>= 30 msec change from baseline and >= 450 msec). Safety analysis set included all participants who were enrolled and received at least 1 dose of study drug. Categories with at least one participant are reported. Number analyzed is the number of participants with data available for analyses.

End point type	Secondary

End point timeframe:

From the first dose of study drug up to 77 days after last dose of study drug (Up to Day 154)

End point values	Placebo	TAK-041 40 mg	TAK-041 160 mg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	21	7	15	
Units: percentage of participants				
number (not applicable)				
ECG Mean Heart Rate: <50 beats per minute	0	0	6.7	
PR Interval: >=200 milliseconds	10.5	20.0	13.3	
QRS Duration: <=80 milliseconds	36.8	20.0	33.3	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Suicidal Ideation or Suicidal Behavior as Measured Using Columbia-Suicide Severity Rating Scale (C-SSRS)

End point title	Number of Participants with Suicidal Ideation or Suicidal Behavior as Measured Using Columbia-Suicide Severity Rating Scale (C-SSRS)

End point description:

Treatment-emergent suicidal ideation (SI)/suicidal behavior (SB) compared to baseline was measured by increase in SI (1-5 on C-SSRS)/SB category (6-10 on the C-SSRS) during treatment from maximum SI/SB at baseline, or any SI/SB during treatment if there is none at baseline. C-SSRS is used to assesses if participant experienced SI (1: wish to be dead; 2: non-specific active suicidal thoughts; 3: active SI with any methods (not plan) without intent to act; 4: active SI with some intent to act, without specific plan; 5: active SI with specific plan and intent) and SB (6: actual attempt; 7: interrupted attempt; 8: aborted attempt; 9: preparatory acts or behavior; 10: suicidal behavior). Safety analysis set included all participants who were enrolled and received at least 1 dose of study drug. Only categories with at least one participant are reported. Number analyzed is the number of participants with data available for analyses.

End point type	Secondary

End point timeframe:

Baseline (Day -1) and Days 14, 35 and 77

End point values	Placebo	TAK-041 40 mg	TAK-041 160 mg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	21	7	15	
Units: participants				
SI-Wish to be Dead, Day -1	3	0	1	
SI-Wish to be Dead, Day 14	1	0	0	
SI-Wish to be Dead, Day 77	1	0	1	
SB-Non-suicidal Self-injurious Behaviour, Day 77	0	1	0	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the first dose of study drug up to 77 days after last dose of study drug (Up to Day 154)

Adverse event reporting additional description:

At each visit investigator had to document any occurrence of adverse events and abnormal laboratory findings. Any event spontaneously reported by participant or observed by investigator was recorded, irrespective of the relation to study treatment. Safety analysis set: all participants who were enrolled and received at least 1 dose of study drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	Placebo

Reporting group description:

TAK-041 placebo-matching, suspension, orally on Day 1 of Treatment Period 1 or 2. All participants took a stable dose of antipsychotics as per standard of care throughout the duration of the Treatment Period.

Reporting group title	TAK-041 40 mg

Reporting group description:

TAK-041 40 mg, suspension, orally on Day 1 of Treatment Period 1 or 2. All participants took a stable dose of antipsychotics as per standard of care throughout the duration of the Treatment Period.

Reporting group title	TAK-041 160 mg

Reporting group description:

TAK-041 160 mg, suspension, orally on Day 1 of Treatment Period 1 or 2. All participants took a stable dose of antipsychotics as per standard of care throughout the duration of the Treatment Period.

Serious adverse events	Placebo	TAK-041 40 mg	TAK-041 160 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 21 (0.00%)	0 / 7 (0.00%)	0 / 15 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Placebo	TAK-041 40 mg	TAK-041 160 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 21 (57.14%)	5 / 7 (71.43%)	8 / 15 (53.33%)
General disorders and administration site conditions			
Fatigue			

subjects affected / exposed	2 / 21 (9.52%)	0 / 7 (0.00%)	1 / 15 (6.67%)
occurrences (all)	2	0	1
Chest Pain			
subjects affected / exposed	1 / 21 (4.76%)	0 / 7 (0.00%)	1 / 15 (6.67%)
occurrences (all)	1	0	1
Catheter Site Pain			
subjects affected / exposed	1 / 21 (4.76%)	0 / 7 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Social circumstances			
Pregnancy Of Partner			
subjects affected / exposed	1 / 21 (4.76%)	0 / 7 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 21 (0.00%)	2 / 7 (28.57%)	0 / 15 (0.00%)
occurrences (all)	0	2	0
Nasal Congestion			
subjects affected / exposed	1 / 21 (4.76%)	0 / 7 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Oropharyngeal Pain			
subjects affected / exposed	1 / 21 (4.76%)	0 / 7 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Rhinorrhoea			
subjects affected / exposed	1 / 21 (4.76%)	0 / 7 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 21 (4.76%)	0 / 7 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Insomnia			
subjects affected / exposed	1 / 21 (4.76%)	0 / 7 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Panic Attack			
subjects affected / exposed	1 / 21 (4.76%)	0 / 7 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Paranoia			

subjects affected / exposed	1 / 21 (4.76%)	0 / 7 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Schizophrenia			
subjects affected / exposed	0 / 21 (0.00%)	0 / 7 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	0 / 21 (0.00%)	0 / 7 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Aspartate Aminotransferase Increased			
subjects affected / exposed	0 / 21 (0.00%)	0 / 7 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Lymphocyte Count Decreased			
subjects affected / exposed	0 / 21 (0.00%)	1 / 7 (14.29%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 21 (0.00%)	0 / 7 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Muscle Strain			
subjects affected / exposed	0 / 21 (0.00%)	0 / 7 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Procedural Headache			
subjects affected / exposed	0 / 21 (0.00%)	1 / 7 (14.29%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 21 (9.52%)	1 / 7 (14.29%)	1 / 15 (6.67%)
occurrences (all)	2	1	1
Somnolence			
subjects affected / exposed	1 / 21 (4.76%)	0 / 7 (0.00%)	1 / 15 (6.67%)
occurrences (all)	1	0	1
Syncope			
subjects affected / exposed	0 / 21 (0.00%)	0 / 7 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Blood and lymphatic system disorders			

Neutropenia			
subjects affected / exposed	2 / 21 (9.52%)	0 / 7 (0.00%)	0 / 15 (0.00%)
occurrences (all)	2	0	0
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	1 / 21 (4.76%)	0 / 7 (0.00%)	1 / 15 (6.67%)
occurrences (all)	1	0	1
Gastrooesophageal Reflux Disease			
subjects affected / exposed	0 / 21 (0.00%)	0 / 7 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Nausea			
subjects affected / exposed	1 / 21 (4.76%)	0 / 7 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			
Dry Skin			
subjects affected / exposed	1 / 21 (4.76%)	0 / 7 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 21 (4.76%)	0 / 7 (0.00%)	1 / 15 (6.67%)
occurrences (all)	1	0	1
Back Pain			
subjects affected / exposed	0 / 21 (0.00%)	1 / 7 (14.29%)	1 / 15 (6.67%)
occurrences (all)	0	1	1
Myalgia			
subjects affected / exposed	2 / 21 (9.52%)	0 / 7 (0.00%)	0 / 15 (0.00%)
occurrences (all)	2	0	0
Muscle Spasms			
subjects affected / exposed	1 / 21 (4.76%)	0 / 7 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Neck Pain			
subjects affected / exposed	0 / 21 (0.00%)	0 / 7 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Infections and infestations			
Nasopharyngitis			

subjects affected / exposed	3 / 21 (14.29%)	1 / 7 (14.29%)	0 / 15 (0.00%)
occurrences (all)	3	1	0
Upper Respiratory Tract Infection			
subjects affected / exposed	2 / 21 (9.52%)	0 / 7 (0.00%)	0 / 15 (0.00%)
occurrences (all)	2	0	0
Pharyngitis			
subjects affected / exposed	0 / 21 (0.00%)	0 / 7 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	0 / 21 (0.00%)	1 / 7 (14.29%)	0 / 15 (0.00%)
occurrences (all)	0	1	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 July 2017	Amendment 01: •Added a serum pregnancy test at Day 49 for each treatment Period.
07 September 2017	Amendment 02: • Removed 20 mg TAK-041 arm from both Periods •Added rationale for washout interval •Revised the primary hypotheses, progressive disease (PD) assessments, objectives, endpoints •Revised inclusion and exclusion criteria, and excluded medications •Revised the interim analysis (IA) plan •Revised plasma pharmacokinetic (PK) sampling times •Updated the determination of sample size.
02 April 2018	Amendment 03: •Decreased the washout period between dosing in Period 1 and Period 2 •Added a coprimary objective, hypothesis, and endpoint related to cognitive impairment associated with schizophrenia •Added participants on first generation antipsychotics, and excluded specific antipsychotics and revised inclusion criteria related to antipsychotic treatment •Added that up to 4 sites could be used •Updated laboratory assessments, inclusion and exclusion criteria •Revised criteria for discontinuation or withdrawal of a participant.
10 August 2018	Amendment 4: •Modified rationale and potential range for study drug dose level •Revised exclusion criteria for abnormal laboratory values •Revised exclusion criterion for magnetic resonance imaging (MRI) contraindication before imaging assessments •Introduced randomization stratification by site.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported