Clinical trial results:
A Multinational, Multicenter, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Study with an Open-Label, Long-Term Safety Phase to Evaluate the Efficacy, Safety, and Tolerability of Olanzapine for Extended-Release Injectable Suspension (TV-44749) for Subcutaneous Use as Treatment of Adult Patients with Schizophrenia

Summary

EudraCT number	2022-001865-11
Trial protocol	BG
Global end of trial date	27 January 2025

Results information

Result version number	v1 (current)
This version publication date	08 February 2026
First version publication date	08 February 2026

Trial information

Trial identification

Sponsor protocol code	TV44749-CNS-30096

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT05693935
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Teva Branded Pharmaceutical Products R&D LLC
Sponsor organisation address	145 Brandywine Parkway, West Chester, United States, 19380
Public contact	Director, Clinical Research, Teva Branded Pharmaceutical Products R&D LLC, MedInfo@tevaeu.com
Scientific contact	Director, Clinical Research, Teva Branded Pharmaceutical Products R&D LLC, MedInfo@tevaeu.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	07 May 2025
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	27 January 2025
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to evaluate the efficacy of TV-44749 in adult participants with schizophrenia.

Protection of trial subjects:

This trial was conducted in full accordance with the International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Consolidated Guideline (E6) and any applicable national and local laws and regulations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 February 2023
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Bulgaria: 21
Country: Number of subjects enrolled	China: 8
Country: Number of subjects enrolled	Romania: 1
Country: Number of subjects enrolled	Türkiye: 1
Country: Number of subjects enrolled	United States: 644
Worldwide total number of subjects	675
EEA total number of subjects	22

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)	675

From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study comprised 2 periods: Period 1 (double-blind, placebo-controlled, efficacy and safety period [acute treatment phase]) and Period 2 (open-label safety period [long-term safety phase]).

Pre-assignment

Screening details:

Per planned analysis, the safety analysis was performed separately for Period 1 and for the integrated trial period. Integrated trial period included all participants who received 1 of the 3 TV-44749 treatments in Period 1 and all randomized participants to Period 2 who received at least 1 dose of TV-44749.

Period 1

Period 1 title	Double-blind Period (8 Weeks)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Carer, Assessor, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Participants received placebo matched to TV-44749 subcutaneously (SC) once monthly over 8 weeks in double-blind period.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Placebo matched to TV-44749 was administered per schedule specified in the arm description.

Arm title	TV-44749 318 mg

Arm description:

Participants received TV-44749 extended-release injectable suspension at a dose of 318 milligrams (mg) SC once monthly over 8 weeks in double-blind period and up to an additional 48 weeks in open-label period, for a total of 56 weeks.

Arm type	Experimental
Investigational medicinal product name	TV-44749
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

TV-44749 was administered per schedule specified in the arm description.

Arm title	TV-44749 425 mg

Arm description:

Participants received TV-44749 extended-release injectable suspension at a dose of 425 mg SC once monthly over 8 weeks in double-blind period and up to an additional 48 weeks in open-label period, for a total of 56 weeks.

Arm type	Experimental

Investigational medicinal product name	TV-44749
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

TV-44749 was administered per schedule specified in the arm description.

Arm title	TV-44749 531 mg

Arm description:

Participants received TV-44749 extended-release injectable suspension at a dose of 531 mg SC once monthly over 8 weeks in double-blind period and up to an additional 48 weeks in open-label period, for a total of 56 weeks.

Arm type	Experimental
Investigational medicinal product name	TV-44749
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

TV-44749 was administered per schedule specified in the arm description.

Number of subjects in period 1	Placebo	TV-44749 318 mg	TV-44749 425 mg
Started	168	169	169
Received at Least 1 Dose of Study Drug	167	164	168
Safety Analysis Set for Period 1	167	163	168
Completed	119	115	121
Not completed	49	54	48
Consent withdrawn by subject	26	35	31
Other Than Specified	11	5	8
Adverse event, non-fatal	5	4	2
Randomized But Not Treated	1	5	1
Lost to follow-up	5	4	6
Lack of efficacy	1	1	-

Number of subjects in period 1	TV-44749 531 mg
Started	169
Received at Least 1 Dose of Study Drug	168
Safety Analysis Set for Period 1	169
Completed	121
Not completed	48
Consent withdrawn by subject	33
Other Than Specified	7
Adverse event, non-fatal	3

Randomized But Not Treated	1
Lost to follow-up	4
Lack of efficacy	-

Period 2

Period 2 title	Open-label Period (48 Weeks)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	TV-44749 318 mg

Arm description:

Participants received TV-44749 extended-release injectable suspension at a dose of 318 mg SC once monthly over 8 weeks in double-blind period and up to an additional 48 weeks in open-label period, for a total of 56 weeks.

Arm type	Experimental
Investigational medicinal product name	TV-44749
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

TV-44749 was administered per schedule specified in the arm description.

Arm title	TV-44749 425 mg

Arm description:

Participants received TV-44749 extended-release injectable suspension at a dose of 425 mg SC once monthly over 8 weeks in double-blind period and up to an additional 48 weeks in open-label period, for a total of 56 weeks.

Arm type	Experimental
Investigational medicinal product name	TV-44749
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

TV-44749 was administered per schedule specified in the arm description.

Arm title	TV-44749 531 mg

Arm description:

Participants received TV-44749 extended-release injectable suspension at a dose of 531 mg SC once monthly over 8 weeks in double-blind period and up to an additional 48 weeks in open-label period, for a total of 56 weeks.

Arm type	Experimental

Investigational medicinal product name	TV-44749
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

TV-44749 was administered per schedule specified in the arm description.

Arm title	Placebo to TV-44749 318 mg

Arm description:

Participants who received placebo during the double-blind period, received TV-44749 extended-release injectable suspension at a dose of 318 mg SC once monthly for up to 48 weeks in open-label period.

Arm type	Experimental
Investigational medicinal product name	TV-44749
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

TV-44749 was administered per schedule specified in the arm description.

Arm title	Placebo to TV-44749 425 mg

Arm description:

Participants who received placebo during the double-blind period, received TV-44749 extended-release injectable suspension at a dose of 425 mg SC once monthly for up to 48 weeks in open-label period.

Arm type	Experimental
Investigational medicinal product name	TV-44749
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

TV-44749 was administered per schedule specified in the arm description.

Arm title	Placebo to TV-44749 531 mg

Arm description:

Participants who received placebo during the double-blind period, received TV-44749 extended-release injectable suspension at a dose of 531 mg SC once monthly for up to 48 weeks in open-label period.

Arm type	Experimental
Investigational medicinal product name	TV-44749
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

TV-44749 was administered per schedule specified in the arm description.

Number of subjects in period 2[1]	TV-44749 318 mg	TV-44749 425 mg	TV-44749 531 mg
Started	100	107	112
Received at Least 1 Dose of Study Drug	100	106	112
Completed	32	40	30
Not completed	68	67	82
Consent withdrawn by subject	32	29	39
Other Than Specified	12	9	10
Adverse event, non-fatal	5	6	14
Randomized But Not Treated	-	1	-
Lost to follow-up	17	19	17
Lack of efficacy	1	2	1
Protocol deviation	1	1	1

Number of subjects in period 2[1]	Placebo to TV-44749 318 mg	Placebo to TV-44749 425 mg	Placebo to TV-44749 531 mg
Started	40	35	29
Received at Least 1 Dose of Study Drug	40	35	29
Completed	15	10	8
Not completed	25	25	21
Consent withdrawn by subject	14	15	8
Other Than Specified	4	3	4
Adverse event, non-fatal	4	1	3
Randomized But Not Treated	-	-	-
Lost to follow-up	3	5	4
Lack of efficacy	-	1	2
Protocol deviation	-	-	-

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: Not all participants who completed Period 1, continued to Period 2.

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Participants received placebo matched to TV-44749 subcutaneously (SC) once monthly over 8 weeks in double-blind period.	
Reporting group title	TV-44749 318 mg
Reporting group description:	
Participants received TV-44749 extended-release injectable suspension at a dose of 318 milligrams (mg) SC once monthly over 8 weeks in double-blind period and up to an additional 48 weeks in open-label period, for a total of 56 weeks.	
Reporting group title	TV-44749 425 mg
Reporting group description:	
Participants received TV-44749 extended-release injectable suspension at a dose of 425 mg SC once monthly over 8 weeks in double-blind period and up to an additional 48 weeks in open-label period, for a total of 56 weeks.	
Reporting group title	TV-44749 531 mg
Reporting group description:	
Participants received TV-44749 extended-release injectable suspension at a dose of 531 mg SC once monthly over 8 weeks in double-blind period and up to an additional 48 weeks in open-label period, for a total of 56 weeks.	

Reporting group values	Placebo	TV-44749 318 mg	TV-44749 425 mg
Number of subjects	168	169	169
Age Categorical Units: participants			
18 - 30 years	16	28	22
>30 - 45 years	86	59	65
>45 - 65 years	66	82	82
Sex: Female, Male Units: participants			
Female	42	42	42
Male	126	127	127
Race/Ethnicity, Customized Units: Subjects			
White	36	51	56
Black or African American	121	116	106
Asian	3	2	4
American Indian or Alaska Native	2	0	1
Native Hawaiian or Other Pacific Islander	1	0	1
Not reported	0	0	0
Other	5	0	1
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	28	38	34
Not Hispanic or Latino	139	130	135
Unknown or Not Reported	1	1	0

Reporting group values	TV-44749 531 mg	Total	

Number of subjects	169	675	
Age Categorical Units: participants			
18 - 30 years	24	90	
>30 - 45 years	64	274	
>45 - 65 years	81	311	
Sex: Female, Male Units: participants			
Female	42	168	
Male	127	507	
Race/Ethnicity, Customized Units: Subjects			
White	44	187	
Black or African American	119	462	
Asian	3	12	
American Indian or Alaska Native	1	4	
Native Hawaiian or Other Pacific Islander	0	2	
Not reported	2	2	
Other	0	6	
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	32	132	
Not Hispanic or Latino	135	539	
Unknown or Not Reported	2	4	

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Participants received placebo matched to TV-44749 subcutaneously (SC) once monthly over 8 weeks in double-blind period.	
Reporting group title	TV-44749 318 mg
Reporting group description:	
Participants received TV-44749 extended-release injectable suspension at a dose of 318 milligrams (mg) SC once monthly over 8 weeks in double-blind period and up to an additional 48 weeks in open-label period, for a total of 56 weeks.	
Reporting group title	TV-44749 425 mg
Reporting group description:	
Participants received TV-44749 extended-release injectable suspension at a dose of 425 mg SC once monthly over 8 weeks in double-blind period and up to an additional 48 weeks in open-label period, for a total of 56 weeks.	
Reporting group title	TV-44749 531 mg
Reporting group description:	
Participants received TV-44749 extended-release injectable suspension at a dose of 531 mg SC once monthly over 8 weeks in double-blind period and up to an additional 48 weeks in open-label period, for a total of 56 weeks.	
Reporting group title	TV-44749 318 mg
Reporting group description:	
Participants received TV-44749 extended-release injectable suspension at a dose of 318 mg SC once monthly over 8 weeks in double-blind period and up to an additional 48 weeks in open-label period, for a total of 56 weeks.	
Reporting group title	TV-44749 425 mg
Reporting group description:	
Participants received TV-44749 extended-release injectable suspension at a dose of 425 mg SC once monthly over 8 weeks in double-blind period and up to an additional 48 weeks in open-label period, for a total of 56 weeks.	
Reporting group title	TV-44749 531 mg
Reporting group description:	
Participants received TV-44749 extended-release injectable suspension at a dose of 531 mg SC once monthly over 8 weeks in double-blind period and up to an additional 48 weeks in open-label period, for a total of 56 weeks.	
Reporting group title	Placebo to TV-44749 318 mg
Reporting group description:	
Participants who received placebo during the double-blind period, received TV-44749 extended-release injectable suspension at a dose of 318 mg SC once monthly for up to 48 weeks in open-label period.	
Reporting group title	Placebo to TV-44749 425 mg
Reporting group description:	
Participants who received placebo during the double-blind period, received TV-44749 extended-release injectable suspension at a dose of 425 mg SC once monthly for up to 48 weeks in open-label period.	
Reporting group title	Placebo to TV-44749 531 mg
Reporting group description:	
Participants who received placebo during the double-blind period, received TV-44749 extended-release injectable suspension at a dose of 531 mg SC once monthly for up to 48 weeks in open-label period.	
Subject analysis set title	Double-blind: Placebo
Subject analysis set type	Full analysis
Subject analysis set description:	
Participants received placebo matched to TV-44749 SC once monthly over 8 weeks in double-blind period.	
Subject analysis set title	Double-blind: TV-44749 318 mg
Subject analysis set type	Full analysis

Subject analysis set description:

Participants received TV-44749 extended-release injectable suspension at a dose of 318 mg SC once monthly over 8 weeks in double-blind period.

Subject analysis set title	Double-blind: TV-44749 425 mg
Subject analysis set type	Full analysis

Subject analysis set description:

Participants received TV-44749 extended-release injectable suspension at a dose of 425 mg SC once monthly over 8 weeks in double-blind period.

Subject analysis set title	Double-blind: TV-44749 531 mg
Subject analysis set type	Full analysis

Subject analysis set description:

Participants received TV-44749 extended-release injectable suspension at a dose of 531 mg SC once monthly over 8 weeks in double-blind period.

Subject analysis set title	Double-blind: Placebo
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants received placebo matched to TV-44749 SC once monthly over 8 weeks in double-blind period.

Subject analysis set title	Double-blind: TV-44749 318 mg
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants received TV-44749 extended-release injectable suspension at a dose of 318 mg SC once monthly over 8 weeks in double-blind period.

Subject analysis set title	Double-blind: TV-44749 425 mg
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants received TV-44749 extended-release injectable suspension at a dose of 425 mg SC once monthly over 8 weeks in double-blind period.

Subject analysis set title	Double-blind: TV-44749 531 mg
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants received TV-44749 extended-release injectable suspension at a dose of 531 mg SC once monthly over 8 weeks in double-blind period.

Subject analysis set title	Integrated Study Period: TV-44749 318 mg
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants received TV-44749 extended-release injectable suspension at a dose of 318 mg SC once monthly over 8 weeks in double-blind period and up to an additional 48 weeks in open-label period, for a total of 56 weeks.

Subject analysis set title	Integrated Study Period: TV-44749 425 mg
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants received TV-44749 extended-release injectable suspension at a dose of 425 mg SC once monthly over 8 weeks in double-blind period and up to an additional 48 weeks in open-label period, for a total of 56 weeks.

Subject analysis set title	Integrated Study Period: TV-44749 531 mg
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants received TV-44749 extended-release injectable suspension at a dose of 531 mg SC once monthly over 8 weeks in double-blind period and up to an additional 48 weeks in open-label period, for a total of 56 weeks.

Primary: Double-blind Period: Change in the Positive and Negative Syndrome Scale (PANSS) Total Score From Baseline to Week 8

End point title	Double-blind Period: Change in the Positive and Negative Syndrome Scale (PANSS) Total Score From Baseline to Week 8

End point description:

PANSS is a 30-item scale used to evaluate positive and negative symptoms of schizophrenia. Each item was scored on a 7-point scale ranging from 1 (absent) to 7 (extreme). Positive symptom scale includes 7 items with a maximum score of 49; negative symptom scale includes 7 items with a maximum score of 49; and general psychopathology scale includes 16 items with a maximum score of 112. Total score was sum of 30-item scale, ranging from 30 (absent) to 210 (extreme), with a higher score indicating greater severity of symptoms. Least square (LS) mean was calculated using a repeated measures model with treatment, study visit, treatment visit interaction, stratification variables (sex and geographic region), age, and PANSS total score at baseline as covariates. Full Analysis Set included all participants randomized to study arms in Period 1 regardless of actual treatment the participant received. 'Number of participants analyzed' = participants evaluable for this endpoint.

End point type	Primary

End point timeframe:

Baseline, Week 8

End point values	Double-blind: Placebo	Double-blind: TV-44749 318 mg	Double-blind: TV-44749 425 mg	Double-blind: TV-44749 531 mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	165	163	166	165
Units: units on a scale				
least squares mean (confidence interval 95%)	-12.17 (-15.34 to -8.99)	-21.91 (-25.13 to -18.70)	-23.44 (-26.52 to -20.36)	-21.93 (-25.01 to -18.85)

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Mixed model for repeated measures fitted to 200 multiply imputed datasets generated in accordance with the estimand. Treatment group LS mean, 95% confidence intervals, and two-sided p values were pooled across imputations using Rubin's rules.

Comparison groups	Double-blind: Placebo v Double-blind: TV-44749 318 mg
Number of subjects included in analysis	328
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001 [1]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-9.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.6
upper limit	-5.89

Notes:

[1] - p-value was adjusted for multiple comparisons (using Truncated Hochberg).

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Mixed model for repeated measures fitted to 200 multiply imputed datasets generated in accordance with the estimand. Treatment group LS mean, 95% confidence intervals, and two-sided p values were pooled across imputations using Rubin's rules.

Comparison groups	Double-blind: Placebo v Double-blind: TV-44749 425 mg
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001 [2]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-11.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	-15.01
upper limit	-7.53

Notes:

[2] - p-value was adjusted for multiple comparisons (using Truncated Hochberg).

Statistical analysis title	Statistical Analysis 3

Statistical analysis description:

Mixed model for repeated measures fitted to 200 multiply imputed datasets generated in accordance with the estimand. Treatment group LS mean, 95% confidence intervals, and two-sided p values were pooled across imputations using Rubin's rules.

Comparison groups	Double-blind: Placebo v Double-blind: TV-44749 531 mg
Number of subjects included in analysis	330
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001 [3]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-9.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.5
upper limit	-6.02

Notes:

[3] - p-value was adjusted for multiple comparisons (using Truncated Hochberg).

Secondary: Double-blind Period: Change in Clinical Global Impression-Severity (CGI-S) Scale Score From Baseline to Week 8

End point title	Double-blind Period: Change in Clinical Global Impression-Severity (CGI-S) Scale Score From Baseline to Week 8

End point description:

The CGI-S is a 7-point scale that assess the participant’s current severity of illness on a scale of 1 to 7, where 1=normal/not at all ill, 2=borderline mentally ill, 3=mildly ill, 4=moderately ill, 5=markedly ill,

6=severely ill, and 7=among the most extremely ill patients. LS mean was calculated using a repeated measures model with treatment, study visit, treatment visit interaction, stratification variables (sex and geographic region), age, and CGI-S score at baseline as covariates. Full Analysis Set included all participants randomized to study arms in Period 1 regardless of the actual treatment the participants received. 'Number of participants analyzed' = participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 8

End point values	Double-blind: Placebo	Double-blind: TV-44749 318 mg	Double-blind: TV-44749 425 mg	Double-blind: TV-44749 531 mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	165	163	166	165
Units: units on a scale				
least squares mean (confidence interval 95%)	-0.72 (-0.90 to -0.54)	-1.25 (-1.43 to -1.07)	-1.33 (-1.51 to -1.15)	-1.19 (-1.36 to -1.01)

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Mixed model for repeated measures fitted to 200 multiply imputed datasets generated in accordance with the estimand. Treatment group LS mean, 95% confidence intervals, and two-sided p values were pooled across imputations using Rubin's rules.

Comparison groups	Double-blind: Placebo v Double-blind: TV-44749 318 mg
Number of subjects included in analysis	328
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001 [4]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-0.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.75
upper limit	-0.31

Notes:

[4] - p-value was adjusted for multiple comparisons (using Truncated Hochberg).

Statistical analysis title	Statistical Analysis 3

Statistical analysis description:

Mixed model for repeated measures fitted to 200 multiply imputed datasets generated in accordance with the estimand. Treatment group LS mean, 95% confidence intervals, and two-sided p values were pooled across imputations using Rubin's rules.

Comparison groups	Double-blind: Placebo v Double-blind: TV-44749 531 mg

Number of subjects included in analysis	330
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001 [5]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-0.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.68
upper limit	-0.25

Notes:

[5] - p-value was adjusted for multiple comparisons (using Truncated Hochberg).

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Mixed model for repeated measures fitted to 200 multiply imputed datasets generated in accordance with the estimand. Treatment group LS mean, 95% confidence intervals, and two-sided p values were pooled across imputations using Rubin's rules.

Comparison groups	Double-blind: Placebo v Double-blind: TV-44749 425 mg
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001 [6]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-0.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.82
upper limit	-0.39

Notes:

[6] - p-value was adjusted for multiple comparisons (using Truncated Hochberg).

Secondary: Double-blind Period: Number of Participants With Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point title	Double-blind Period: Number of Participants With Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point description:

An AE was defined as any untoward medical occurrence in a participant who received the study drug without regard to possibility of causal relationship. The SAEs were defined as death, a life-threatening AE, inpatient hospitalization or prolongation of existing hospitalization, persistent or significant disability or incapacity, a congenital anomaly or birth defect, or an important medical event that jeopardized participant and required medical intervention to prevent 1 of the outcomes listed in this definition. A summary of other non-serious AEs and all serious AEs, regardless of causality is located in the Reported AE section. Safety Analysis Set for Period 1 included all randomized participants who received at least 1 dose of TV-44749 or placebo. Participants were included in the treatment group corresponding to what they actually received.

End point type	Secondary

End point timeframe:

Baseline up to Week 8

End point values	Double-blind: TV-44749 318 mg	Double-blind: Placebo	Double-blind: TV-44749 425 mg	Double-blind: TV-44749 531 mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	163	167	168	169
Units: participants				
Any TEAE	112	84	117	126
SAE	4	3	1	2

Statistical analyses

No statistical analyses for this end point

Secondary: Double-blind Period: Change in Personal and Social Performance Scale (PSP) Score From Baseline to Week 8

End point title	Double-blind Period: Change in Personal and Social Performance Scale (PSP) Score From Baseline to Week 8

End point description:

PSP is a 100-point single-item rating scale, divided into 10 equal intervals, where 0 (grossly impaired functioning) to 100 (excellent functioning). Score was based on assessment of participant's functioning in 4 categories: 1) socially useful activities, including work and study; 2) personal and social relationships; 3) self-care; and 4) disturbing and aggressive behaviors. Higher scores represented better personal and social functioning, with ratings from 91 to 100 indicating more than adequate functioning, while scores under 30 indicating poor functioning that required intensive supervision. LS mean was calculated using a repeated measures model with treatment, study visit, treatment visit interaction, stratification variables (sex and geographic region), age, and PSP score at baseline as covariates. Full Analysis Set: all participants randomized to study arms in Period 1 regardless of the actual treatment received. 'Number analyzed' = participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 8

End point values	Double-blind: Placebo	Double-blind: TV-44749 318 mg	Double-blind: TV-44749 425 mg	Double-blind: TV-44749 531 mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	165	163	166	165
Units: units on a scale				
least squares mean (confidence interval 95%)	5.59 (3.14 to 8.04)	10.31 (7.91 to 12.72)	8.83 (6.44 to 11.22)	10.59 (8.17 to 13.02)

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Mixed model for repeated measures fitted to 200 multiply imputed datasets generated in accordance with the estimand. Treatment group LS mean, 95% confidence intervals, and two-sided p values were pooled across imputations using Rubin's rules.

Comparison groups	Double-blind: Placebo v Double-blind: TV-44749 318 mg
Number of subjects included in analysis	328
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0011 [7]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	4.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.05
upper limit	7.4

Notes:

[7] - p-value was adjusted for multiple comparisons (using Truncated Hochberg).

Statistical analysis title	Statistical Analysis 3

Statistical analysis description:

Mixed model for repeated measures fitted to 200 multiply imputed datasets generated in accordance with the estimand. Treatment group LS mean, 95% confidence intervals, and two-sided p values were pooled across imputations using Rubin's rules.

Comparison groups	Double-blind: Placebo v Double-blind: TV-44749 531 mg
Number of subjects included in analysis	330
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0007 [8]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	5.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.35
upper limit	7.66

Notes:

[8] - p-value was adjusted for multiple comparisons (using Truncated Hochberg).

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Mixed model for repeated measures fitted to 200 multiply imputed datasets generated in accordance with the estimand. Treatment group LS mean, 95% confidence intervals, and two-sided p values were pooled across imputations using Rubin's rules.

Comparison groups	Double-blind: Placebo v Double-blind: TV-44749 425 mg

Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0167 [9]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	3.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.59
upper limit	5.89

Notes:

[9] - p-value was adjusted for multiple comparisons (using Truncated Hochberg).

Secondary: Integrated Study Period: Number of Participants With AEs and SAEs

End point title	Integrated Study Period: Number of Participants With AEs and SAEs

End point description:

AE was defined as any untoward medical occurrence in a participant who received study drug without regard to possibility of causal relationship. SAEs: death, life-threatening AE, inpatient hospitalization or prolongation of existing hospitalization, persistent or significant disability/incapacity, a congenital anomaly or birth defect, or an important medical event that jeopardized participant and required medical intervention to prevent 1 of the outcomes listed in this definition. A summary of other non-serious AEs and all SAEs regardless of causality is located in Reported AE section. Safety Analysis Set for integrated study period: all participants in safety analysis set of period 1 that received 1 of the 3 TV-44749 treatments and all randomized participants to Period 2 who received at least 1 dose of TV-44749. Participants were included in their randomized groups regardless of actual treatment received.

End point type	Secondary

End point timeframe:

Baseline up to Week 60

End point values	Integrated Study Period: TV-44749 318 mg	Integrated Study Period: TV-44749 425 mg	Integrated Study Period: TV-44749 531 mg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	204	203	197	
Units: participants				
Any TEAEs	149	147	153	
SAEs	15	8	13	

Statistical analyses

No statistical analyses for this end point

Secondary: Double-blind Period: Clinical Global Impression-Improvement (CGI-I) Scale Score at Weeks 4 and 8

End point title	Double-blind Period: Clinical Global Impression-Improvement

	(CGI-I) Scale Score at Weeks 4 and 8

End point description:

The CGI-I is a 7-point scale that permits a global evaluation of the participant’s overall improvement in symptoms on a scale of 1 to 7, where 1=very much improved, 2=much improved, 3=minimally improved, 4=no change, 5=minimally worse, 6=much worse, 7=very much worse. LS mean was calculated using a repeated measures model with treatment, study visit, treatment visit interaction, stratification variables (sex and geographic region), age, and CGI-I score at baseline as covariates. Full Analysis Set included all participants randomized to study arms in Period 1 regardless of the actual treatment the participants received. 'Number of participants analyzed' = participants evaluable for this endpoint. 'n' = participants evaluable at specified timepoint.

End point type	Secondary

End point timeframe:

Weeks 4 and 8

End point values	Double-blind: Placebo	Double-blind: TV-44749 318 mg	Double-blind: TV-44749 425 mg	Double-blind: TV-44749 531 mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	146	131	152	150
Units: units on a scale				
least squares mean (standard error)				
Week 4 (n = 146,131,152,150)	3.42 (± 0.09)	2.97 (± 0.09)	3.00 (± 0.08)	2.97 (± 0.08)
Week 8 (n = 115,112,121,119)	3.31 (± 0.10)	2.64 (± 0.10)	2.51 (± 0.10)	2.56 (± 0.10)

Statistical analyses

No statistical analyses for this end point

Secondary: Double-blind Period: Change in PANSS Total Score From Baseline to Weeks 1, 2, and 4

End point title	Double-blind Period: Change in PANSS Total Score From Baseline to Weeks 1, 2, and 4

End point description:

PANSS is a 30-item scale used to evaluate positive and negative symptoms of schizophrenia. Each item was scored on a 7-point scale ranging from 1 (absent) to 7 (extreme). Positive symptom scale includes 7 items with a maximum score of 49; Negative symptom scale includes 7 items with a maximum score of 49; and the general psychopathology scale includes 16 items with a maximum score of 112. Total score was sum of 30-item scale, ranging from 30 (absent) to 210 (extreme), with a higher score indicating greater severity of symptoms. LS mean was calculated using a repeated measures model with treatment, study visit, treatment visit interaction, stratification variables (sex and geographic region), age, and PANSS total score at baseline as covariates. Full Analysis Set included all participants randomized to study arms in Period 1 regardless of the actual treatment the participants received. 'Number of participants analyzed' = participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Weeks 1, 2, and 4

End point values	Double-blind: Placebo	Double-blind: TV-44749 318 mg	Double-blind: TV-44749 425 mg	Double-blind: TV-44749 531 mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	165	163	166	165
Units: units on a scale				
least squares mean (confidence interval 95%)				
Change at Week 1	-5.74 (-8.09 to -3.39)	-7.54 (-9.86 to -5.21)	-7.29 (-9.61 to -4.96)	-6.22 (-8.53 to -3.91)
Change at Week 2	-7.95 (-10.50 to -5.40)	-11.02 (-13.54 to -8.50)	-11.25 (-13.75 to -8.75)	-10.05 (-12.54 to -7.55)
Change at Week 4	-9.40 (-12.16 to -6.65)	-15.27 (-18.03 to -12.51)	-15.91 (-18.61 to -13.21)	-14.74 (-17.43 to -12.05)

Statistical analyses

No statistical analyses for this end point

Secondary: Double-blind Period: Change in CGI-S Scale Score From Baseline to Weeks 1, 2, and 4

End point title	Double-blind Period: Change in CGI-S Scale Score From Baseline to Weeks 1, 2, and 4

End point description:

The CGI-S is a 7-point scale that assess the participant’s current severity of illness on a scale of 1 to 7, where 1=normal/not at all ill, 2=borderline mentally ill, 3=mildly ill, 4=moderately ill, 5=markedly ill, 6=severely ill, and 7=among the most extremely ill patients. LS mean was calculated using a repeated measures model with treatment, study visit, treatment visit interaction, stratification variables (sex and geographic region), age, and CGI-S score at baseline as covariates. Full Analysis Set included all participants randomized to Period 1 regardless of the actual treatment the participants received. 'Number of participants analyzed' = participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Weeks 1, 2, and 4

End point values	Double-blind: Placebo	Double-blind: TV-44749 318 mg	Double-blind: TV-44749 425 mg	Double-blind: TV-44749 531 mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	165	163	166	165
Units: units on a scale				
least squares mean (confidence interval 95%)				
Change at Week 1	-0.27 (-0.41 to -0.13)	-0.33 (-0.47 to -0.19)	-0.33 (-0.47 to -0.19)	-0.23 (-0.37 to -0.10)
Change at Week 2	-0.42 (-0.57 to -0.27)	-0.56 (-0.72 to -0.41)	-0.59 (-0.74 to -0.44)	-0.48 (-0.63 to -.033)
Change at Week 4	-0.54 (-0.70 to -0.37)	-0.86 (-1.02 to -0.69)	-0.79 (-0.95 to -0.63)	-0.76 (-0.92 to -0.60)

Statistical analyses

No statistical analyses for this end point

Secondary: Double-blind Period: Patient Global Impression-Improvement (PGI-I) Scale Score at Weeks 2, 4, and 8

End point title	Double-blind Period: Patient Global Impression-Improvement (PGI-I) Scale Score at Weeks 2, 4, and 8

End point description:

The PGI-I scale is a 1-item participant-rated instrument that measures improvement of the participant's disease. The participant rated the perceived change in his/her condition in response to therapy on a scale of 1 to 7, where 1=very much better, 2=much better, 3=a little better, 4=no change, 5=a little worse, 6=much worse, 7=very much worse. LS mean was calculated using a repeated measures model with treatment, study visit, treatment visit interaction, stratification variables (sex and geographic region), age, and PGI-I score at baseline as covariates. Full Analysis Set included all participants randomized to Period 1 regardless of the actual treatment the participants received. 'Number of participants analyzed' = participants evaluable for this endpoint. 'n' = participants evaluable at specified timepoint.

End point type	Secondary

End point timeframe:

Weeks 2, 4, and 8

End point values	Double-blind: Placebo	Double-blind: TV-44749 318 mg	Double-blind: TV-44749 425 mg	Double-blind: TV-44749 531 mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	154	143	157	154
Units: units on a scale				
least squares mean (standard error)				
Week 2 (n = 154,143,157,154)	3.30 (± 0.11)	2.95 (± 0.11)	2.92 (± 0.11)	3.16 (± 0.11)
Week 4 (n = 143,131,149,147)	3.24 (± 0.12)	2.79 (± 0.12)	2.92 (± 0.12)	2.81 (± 0.12)
Week 8 (n = 115,110,121,119)	2.99 (± 0.13)	2.46 (± 0.13)	2.49 (± 0.12)	2.43 (± 0.12)

Statistical analyses

No statistical analyses for this end point

Secondary: Double-blind Period: Change in Schizophrenia Quality of Life Scale (SQLS) Total Score From Baseline to Weeks 4 and 8

End point title	Double-blind Period: Change in Schizophrenia Quality of Life Scale (SQLS) Total Score From Baseline to Weeks 4 and 8

End point description:

The SQLS Revision 4 was administered to capture quality of life. The 33-item measure yields subscales pertaining to psychosocial (20 items) and cognition/vitality factors (13 items). Each item was scored on a 5-point scale (1 - never, 2 - rarely, 3 - sometimes, 4 - often, 5 - always). Individual domain and total scores were standardized by scoring algorithm from 0 (best health status) to 100 (worst health status) scale, with higher scores indicating comparatively lower quality of life. Full Analysis Set included all participants randomized to Period 1 regardless of the actual treatment the participants received. 'Number of participants analyzed' = participants evaluable for this endpoint. 'n' = participants evaluable at specified timepoint.

End point type	Secondary

End point timeframe:

Baseline, Weeks 4 and 8

End point values	Double-blind: Placebo	Double-blind: TV-44749 318 mg	Double-blind: TV-44749 425 mg	Double-blind: TV-44749 531 mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	146	131	151	150
Units: units on a scale				
least squares mean (standard error)				
Change at Week 4 (n = 146,131,151,150)	-5.63 (± 1.59)	-8.47 (± 1.62)	-7.16 (± 1.57)	-8.45 (± 1.58)
Change at Week 8 (n = 115,110,121,119)	-6.43 (± 1.79)	-10.42 (± 1.81)	-11.82 (± 1.75)	-12.08 (± 1.77)

Statistical analyses

No statistical analyses for this end point

Secondary: Double-blind Period: Number of Participants Receiving At Least 1 Concomitant Medication

End point title	Double-blind Period: Number of Participants Receiving At Least 1 Concomitant Medication

End point description:

Concomitant medications included all medications taken while the participant was treated with the study drug. Any concomitant medication received by the participant for AEs was recorded on the case report form (CRF). Concomitant medications included: zolpidem, zopiclone, zaleplon, or diphenhydramine for insomnia; benztropine, trihexyphenidyl, or diphenhydramine for parkinsonian symptoms; propranolol and benzodiazepines for akathisia; lorazepam on an as-needed basis for indications other than akathisia (for example, anxiety); and antihistamine and anticholinergic drugs for agitation and insomnia. Safety Analysis Set for Period 1 included all randomized participants who received at least 1 dose of TV-44749 or placebo. Participants were included in the treatment group corresponding to what they actually received.

End point type	Secondary

End point timeframe:

Baseline up to Week 8

End point values	Double-blind: TV-44749 318 mg	Double-blind: Placebo	Double-blind: TV-44749 425 mg	Double-blind: TV-44749 531 mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	163	167	168	169
Units: participants	128	138	128	141

Statistical analyses

No statistical analyses for this end point

Secondary: Double-blind Period: Change in PSP Score From Baseline to Week 4

End point title	Double-blind Period: Change in PSP Score From Baseline to Week 4

End point description:

PSP is a 100-point single-item rating scale, divided into 10 equal intervals, where 0 (grossly impaired functioning) to 100 (excellent functioning). Score was based on assessment of participant's functioning in 4 categories: 1) socially useful activities, including work and study; 2) personal and social relationships; 3) self-care; and 4) disturbing and aggressive behaviors. Higher scores represented better personal and social functioning, with ratings from 91 to 100 indicating more than adequate functioning, while scores under 30 indicating functioning so poor that intensive supervision was required. LS mean was calculated using repeated measures model with treatment, study visit, treatment visit interaction, stratification variables (sex and geographic region), age, and PSP score at baseline as covariates. Full Analysis Set: all participants randomized to Period 1 regardless of actual treatment received. 'Number of participants analyzed' = participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 4

End point values	Double-blind: Placebo	Double-blind: TV-44749 318 mg	Double-blind: TV-44749 425 mg	Double-blind: TV-44749 531 mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	165	163	166	165
Units: units on a scale				
least squares mean (confidence interval 95%)	3.22 (1.02 to 5.42)	6.14 (3.93 to 8.35)	4.46 (2.30 to 6.62)	4.88 (2.70 to 7.07)

Statistical analyses

No statistical analyses for this end point

Secondary: Integrated Study Period: Change From Baseline to Week 60 in AIMS Total Score

End point title	Integrated Study Period: Change From Baseline to Week 60 in AIMS Total Score

End point description:

The AIMS total score was calculated as a sum of items 1 through 7. Items 1 through 7 included facial and oral movements (Items 1-4), extremity movements (Items 5-6), and trunk movements (Item 7). Each item was rated from 0 (none) to 4 (severe) The AIMS total score for Items 1-7 ranged from 0 (no dyskinesia) to 28 (severe dyskinesia) with a higher score indicating greater severity of the condition. Safety Analysis Set for integrated study period included all participants in the safety analysis set of period 1 that received 1 of the 3 TV-44749 treatments groups and all randomized participants to Period 2 who received at least 1 dose of TV-44749. Participants were included in their randomized treatment groups regardless of the actual treatment received. 'Number of participants analyzed' = participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 60

End point values	Integrated Study Period: TV-44749 318 mg	Integrated Study Period: TV-44749 425 mg	Integrated Study Period: TV-44749 531 mg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	100	105	110	
Units: units on a scale				
arithmetic mean (standard deviation)	-0.14 (± 1.215)	-0.11 (± 0.423)	-0.08 (± 0.592)	

Statistical analyses

No statistical analyses for this end point

Secondary: Double-blind Period: Change From Baseline to Week 8 in Abnormal Involuntary Movement Scale (AIMS) Total Score

End point title	Double-blind Period: Change From Baseline to Week 8 in Abnormal Involuntary Movement Scale (AIMS) Total Score

End point description:

The AIMS is a 14-item scale that includes assessments of orofacial movements, extremity and truncal dyskinesia, examiner’s judgment of global severity, subjective measures of awareness of movements and distress, and a yes/no assessment of problems concerning teeth and/or dentures. AIMS total score was calculated as a sum of items 1 through 7. Items 1 through 7 included facial and oral movements (Items 1-4), extremity movements (Items 5-6), and trunk movements (Item 7). Each item was rated from 0 (none) to 4 (severe) The AIMS total score for Items 1-7 ranged from 0 (no dyskinesia) to 28 (severe dyskinesia) with a higher score indicating greater severity of the condition. Safety Analysis Set for Period 1 included all randomized participants who received at least 1 dose of TV-44749 or placebo. Participants were included in the treatment group corresponding to what they actually received. 'Number of participants analyzed' = participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 8

End point values	Double-blind: Placebo	Double-blind: TV-44749 318 mg	Double-blind: TV-44749 425 mg	Double-blind: TV-44749 531 mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	117	111	121	120
Units: units on a scale				
arithmetic mean (standard deviation)	-0.1 (± 0.83)	-0.1 (± 0.81)	0.0 (± 0.64)	0.0 (± 0.50)

Statistical analyses

No statistical analyses for this end point

Secondary: Integrated Study Period: Number of Participants Receiving At Least 1 Concomitant Medication

End point title	Integrated Study Period: Number of Participants Receiving At Least 1 Concomitant Medication

End point description:

Concomitant medications included all medications taken while the participant was treated with the study drug. Any concomitant medication received by the participant for AEs was recorded on the CRF. Concomitant medications included: zolpidem, zopiclone, zaleplon, or diphenhydramine for insomnia; benztropine, trihexyphenidyl, or diphenhydramine for parkinsonian symptoms; propranolol and benzodiazepines for akathisia; lorazepam on an as-needed basis for indications other than akathisia (for example, anxiety); and antihistamine and anticholinergic drugs for agitation and insomnia. Safety Analysis Set for integrated study period included all participants in the safety analysis set of period 1 that received 1 of the 3 TV-44749 treatments groups and all randomized participants to Period 2 who received at least 1 dose of TV-44749. Participants were included in their randomized treatment groups regardless of the actual treatment received.

End point type	Secondary

End point timeframe:

Baseline up to Week 60

End point values	Integrated Study Period: TV-44749 318 mg	Integrated Study Period: TV-44749 425 mg	Integrated Study Period: TV-44749 531 mg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	204	203	197	
Units: participants	148	142	156	

Statistical analyses

No statistical analyses for this end point

Secondary: Double-blind Period: Change From Baseline to Week 8 in Barnes Akathisia Rating Scale (BARS) Total Score

End point title	Double-blind Period: Change From Baseline to Week 8 in Barnes Akathisia Rating Scale (BARS) Total Score

End point description:

The BARS is an instrument that assesses the severity of drug-induced akathisia. The BARS included 3 items for rating objective restless movements, subjective restlessness, and any subjective distress associated with akathisia that were scored on a 4-point scale of 0 (normal) to 3 (most severe) and summed up yielding a total score ranging from 0 (normal) to 9 (most severe). Higher scores indicated greater severity of akathisia. Safety Analysis Set for Period 1 included all randomized participants who received at least 1 dose of TV-44749 or placebo. Participants were included in the treatment group corresponding to what they actually received. 'Number of participants analyzed' = participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 8

End point values	Double-blind: Placebo	Double-blind: TV-44749 318 mg	Double-blind: TV-44749 425 mg	Double-blind: TV-44749 531 mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	117	111	121	120
Units: units on a scale				
arithmetic mean (standard deviation)	-0.1 (± 0.56)	-0.1 (± 0.66)	0.0 (± 0.48)	-0.1 (± 0.50)

Statistical analyses

No statistical analyses for this end point

Secondary: Integrated Study Period: Change From Baseline to Week 60 in SAS Mean Score

End point title	Integrated Study Period: Change From Baseline to Week 60 in SAS Mean Score

End point description:

The SAS is a 10-item instrument for the assessment of neuroleptic-induced parkinsonism. The items on the scale include measurements of hypokinesia, rigidity, glabellar reflex, tremor, and salivation. Each item was rated on a 5-point scale (0 [normal] to 4 [severe]). The mean score was calculated by adding the individual item scores and dividing by 10, ranging from 0 (normal) to 4 (severe) with a higher score indicating greater severity of symptoms. Safety Analysis Set for integrated study period included all participants in the safety analysis set of period 1 that received 1 of the 3 TV-44749 treatments groups and all randomized participants to Period 2 who received at least 1 dose of TV-44749. Participants were included in their randomized treatment groups regardless of the actual treatment received. 'Number of participants analyzed' = participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 60

End point values	Integrated Study Period: TV-44749 318 mg	Integrated Study Period: TV-44749 425 mg	Integrated Study Period: TV-44749 531 mg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	100	105	110	
Units: units on a scale				
arithmetic mean (standard deviation)	-0.02 (± 0.135)	-0.01 (± 0.069)	-0.02 (± 0.072)	

Statistical analyses

No statistical analyses for this end point

Secondary: Double-blind Period: Change From Baseline to Week 8 in Simpson-Angus Scale (SAS) Mean Score

End point title	Double-blind Period: Change From Baseline to Week 8 in Simpson-Angus Scale (SAS) Mean Score

End point description:

The SAS is a 10-item instrument for the assessment of neuroleptic-induced parkinsonism. The items on the scale include measurements of hypokinesia, rigidity, glabellar reflex, tremor, and salivation. Each item was rated on a 5-point scale (0 [normal] to 4 [severe]). The mean score was calculated by adding the individual item scores and dividing by 10, ranging from 0 (normal) to 4 (severe) with a higher score indicating greater severity of symptoms. Safety Analysis Set for Period 1 included all randomized participants who received at least 1 dose of TV-44749 or placebo. Participants were included in the treatment group corresponding to what they actually received. 'Number of participants analyzed' = participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 8

End point values	Double-blind: Placebo	Double-blind: TV-44749 318 mg	Double-blind: TV-44749 425 mg	Double-blind: TV-44749 531 mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	116	111	121	119
Units: units on a scale				
arithmetic mean (standard deviation)	-0.02 (± 0.142)	-0.02 (± 0.107)	0.00 (± 0.065)	-0.01 (± 0.073)

Statistical analyses

No statistical analyses for this end point

Secondary: Integrated Study Period: Change From Baseline to Week 60 in BARS Total Score

End point title	Integrated Study Period: Change From Baseline to Week 60 in BARS Total Score

End point description:

The BARS is an instrument that assesses the severity of drug-induced akathisia. The BARS included 3 items for rating objective restless movements, subjective restlessness, and any subjective distress associated with akathisia that were scored on a 4-point scale of 0 (normal) to 3 (most severe) and summed up yielding a total score ranging from 0 (normal) to 9 (most severe). Higher scores indicated greater severity of akathisia. Safety Analysis Set for integrated study period included all participants in the safety analysis set of period 1 that received 1 of the 3 TV-44749 treatments groups and all randomized participants to Period 2 who received at least 1 dose of TV-44749. Participants were included in their randomized treatment groups regardless of the actual treatment received. 'Number of participants analyzed' = participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 60

End point values	Integrated Study Period: TV-44749 318 mg	Integrated Study Period: TV-44749 425 mg	Integrated Study Period: TV-44749 531 mg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	100	105	110	
Units: units on a scale				
arithmetic mean (standard deviation)	-0.1 (± 0.74)	-0.1 (± 0.48)	-0.1 (± 0.77)	

Statistical analyses

No statistical analyses for this end point

Secondary: Double-blind Period: Number of Participants With Any Suicidal Ideation or Suicidal Behavior According to the Columbia Suicide Severity Rating Scale (C-SSRS)

End point title	Double-blind Period: Number of Participants With Any Suicidal Ideation or Suicidal Behavior According to the Columbia Suicide Severity Rating Scale (C-SSRS)

End point description:

The C-SSRS is a questionnaire to assess suicidal ideation and suicidal behavior. Suicidal behavior was defined as a "yes" answer to any of 5 suicidal behavior questions: preparatory acts or behavior, aborted attempt, interrupted attempt, actual attempt, and completed suicide. Suicidal ideation was defined as a "yes" answer to any one of 5 suicidal ideation questions: wish to be dead, non-specific active suicidal thoughts, active suicidal ideation with methods without intent to act or some intent to act, without specific plan or with specific plan and intent, any self-injurious behavior with no suicidal intent. Safety Analysis Set for Period 1 included all randomized participants who received at least 1 dose of TV-44749 or placebo. Participants were included in the treatment group corresponding to what they actually received.

End point type	Secondary

End point timeframe:

Baseline up to Week 8

End point values	Double-blind: TV-44749 318 mg	Double-blind: Placebo	Double-blind: TV-44749 425 mg	Double-blind: TV-44749 531 mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	163	167	168	169
Units: participants				
No	149	154	156	165
Yes	8	9	9	4
Missing	6	4	3	0

Statistical analyses

No statistical analyses for this end point

Secondary: Integrated Study Period: Number of Participants With Any Suicidal Ideation or Suicidal Behavior According to the C-SSRS

End point title	Integrated Study Period: Number of Participants With Any Suicidal Ideation or Suicidal Behavior According to the C-SSRS

End point description:

The C-SSRS is a questionnaire to assess suicidal ideation and suicidal behavior. Suicidal behavior was defined as a "yes" answer to any of 5 suicidal behavior questions: preparatory acts or behavior, aborted attempt, interrupted attempt, actual attempt, and completed suicide. Suicidal ideation was defined as a "yes" answer to any one of 5 suicidal ideation questions: wish to be dead, non-specific active suicidal thoughts, active suicidal ideation with methods without intent to act or some intent to act, without specific plan or with specific plan and intent, any self-injurious behavior with no suicidal intent. Safety Analysis Set for integrated study period included all participants in the safety analysis set of period 1 that received 1 of the 3 TV-44749 treatments groups and all randomized participants to Period 2 who received at least 1 dose of TV-44749. Participants were included in their randomized treatment groups regardless of the actual treatment received.

End point type	Secondary

End point timeframe:

Baseline up to Week 60

End point values	Integrated Study Period: TV-44749 318 mg	Integrated Study Period: TV-44749 425 mg	Integrated Study Period: TV-44749 531 mg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	204	203	197	
Units: participants				
No	184	183	186	
Yes	14	16	11	
Missing	6	4	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Double-blind Period: Change From Baseline to Week 8 in Calgary Depression Scale for Schizophrenia (CDSS) Score

End point title	Double-blind Period: Change From Baseline to Week 8 in Calgary Depression Scale for Schizophrenia (CDSS) Score

End point description:

The CDSS is specifically designed to assess the level of depression separate from the positive, negative, and extrapyramidal symptoms in schizophrenia. This clinician-administered instrument consisted of 9 items, each rated on a 4-point scale from 0 (absent) to 3 (severe) that are added together to form the CDSS depression total score for the participant ranging from 0 (absent) to 27 (severe) with higher scores indicating a higher severity of depression. Safety Analysis Set for Period 1 included all randomized participants who received at least 1 dose of TV-44749 or placebo. Participants were included in the treatment group corresponding to what they actually received. 'Number of participants analyzed' = participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 8

End point values	Double-blind: Placebo	Double-blind: TV-44749 318 mg	Double-blind: TV-44749 425 mg	Double-blind: TV-44749 531 mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	118	116	122	123
Units: units on a scale				
arithmetic mean (standard deviation)	-1.1 (± 3.16)	-2.1 (± 3.95)	-1.7 (± 3.17)	-2.0 (± 3.77)

Statistical analyses

No statistical analyses for this end point

Secondary: Integrated Study Period: Change From Baseline to Week 60 in CDSS Score

End point title	Integrated Study Period: Change From Baseline to Week 60 in CDSS Score

End point description:

The CDSS is specifically designed to assess the level of depression separate from the positive, negative, and extrapyramidal symptoms in schizophrenia. This clinician-administered instrument consisted of 9 items, each rated on a 4-point scale from 0 (absent) to 3 (severe) that are added together to form the CDSS depression total score for the participant ranging from 0 (absent) to 27 (severe) with higher scores indicating a higher severity of depression. Safety Analysis Set for integrated study period included all participants in the safety analysis set of period 1 that received 1 of the 3 TV-44749 treatments groups and all randomized participants to Period 2 who received at least 1 dose of TV-44749. Participants were included in their randomized treatment groups regardless of the actual treatment received. 'Number of participants analyzed' = participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 60

End point values	Integrated Study Period: TV-44749 318 mg	Integrated Study Period: TV-44749 425 mg	Integrated Study Period: TV-44749 531 mg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	100	106	110	
Units: units on a scale				
arithmetic mean (standard deviation)	-2.0 (± 4.11)	-2.1 (± 3.64)	-1.9 (± 3.48)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Double-blind period: Baseline up to Week 8;
Integrated study period: Baseline up to Week 60

Adverse event reporting additional description:

All-cause mortality data were collected and reported for all enrolled participants; and Serious and Non-serious adverse events data were collected and reported for all randomized participants who received at least 1 dose of TV-44749 or placebo.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.0

Reporting groups

Reporting group title	Double blind Period: Placebo

Reporting group description:

Participants received placebo matched to TV-44749 SC once monthly over 8 weeks in double-blind period.

Reporting group title	Double blind Period: TV-44749 318 mg

Reporting group description:

Participants received TV-44749 extended-release injectable suspension at a dose of 318 mg SC once monthly over 8 weeks in double-blind period.

Reporting group title	Double blind Period: TV-44749 425 mg

Reporting group description:

Participants received TV-44749 extended-release injectable suspension at a dose of 425 mg SC once monthly over 8 weeks in double-blind period.

Reporting group title	Integrated Study Period: TV-44749 531 mg

Reporting group description:

Participants received TV-44749 extended-release injectable suspension at a dose of 531 mg SC once monthly over 8 weeks in double-blind period and up to an additional 48 weeks in open-label period, for a total of 56 weeks.

Reporting group title	Integrated Study Period: TV-44749 318 mg

Reporting group description:

Participants received TV-44749 extended-release injectable suspension at a dose of 318 mg SC once monthly over 8 weeks in double-blind period and up to an additional 48 weeks in open-label period, for a total of 56 weeks.

Reporting group title	Integrated Study Period: TV-44749 425 mg

Reporting group description:

Participants received TV-44749 extended-release injectable suspension at a dose of 425 mg SC once monthly over 8 weeks in double-blind period and up to an additional 48 weeks in open-label period, for a total of 56 weeks.

Reporting group title	Double blind Period: TV-44749 531 mg

Reporting group description:

Participants received TV-44749 extended-release injectable suspension at a dose of 531 mg SC once monthly over 8 weeks in double-blind period.

Serious adverse events	Double blind Period: Placebo	Double blind Period: TV-44749 318 mg	Double blind Period: TV-44749 425 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 167 (1.80%)	4 / 163 (2.45%)	1 / 168 (0.60%)

number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Shoulder fracture			
subjects affected / exposed	0 / 167 (0.00%)	1 / 163 (0.61%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Toxicity to various agents			
subjects affected / exposed	0 / 167 (0.00%)	0 / 163 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 167 (0.00%)	0 / 163 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial flutter			
subjects affected / exposed	0 / 167 (0.00%)	0 / 163 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardio-respiratory arrest			
subjects affected / exposed	0 / 167 (0.00%)	0 / 163 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	0 / 167 (0.00%)	0 / 163 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Lumbar radiculopathy			
subjects affected / exposed	0 / 167 (0.00%)	0 / 163 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			

Non-cardiac chest pain			
subjects affected / exposed	0 / 167 (0.00%)	0 / 163 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug ineffective			
subjects affected / exposed	1 / 167 (0.60%)	0 / 163 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Erosive oesophagitis			
subjects affected / exposed	0 / 167 (0.00%)	1 / 163 (0.61%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia			
subjects affected / exposed	0 / 167 (0.00%)	1 / 163 (0.61%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Food poisoning			
subjects affected / exposed	0 / 167 (0.00%)	0 / 163 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain upper			
subjects affected / exposed	0 / 167 (0.00%)	1 / 163 (0.61%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 167 (0.00%)	0 / 163 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute respiratory failure			
subjects affected / exposed	0 / 167 (0.00%)	0 / 163 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Psychiatric disorders			
Alcoholic psychosis			
subjects affected / exposed	0 / 167 (0.00%)	0 / 163 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depressive symptom			
subjects affected / exposed	0 / 167 (0.00%)	0 / 163 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicidal ideation			
subjects affected / exposed	0 / 167 (0.00%)	0 / 163 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Substance-induced psychotic disorder			
subjects affected / exposed	0 / 167 (0.00%)	0 / 163 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychotic disorder			
subjects affected / exposed	1 / 167 (0.60%)	0 / 163 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychotic symptom			
subjects affected / exposed	0 / 167 (0.00%)	0 / 163 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Schizophrenia			
subjects affected / exposed	0 / 167 (0.00%)	0 / 163 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 167 (0.60%)	0 / 163 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Infections and infestations			
Sepsis			
subjects affected / exposed	0 / 167 (0.00%)	0 / 163 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 167 (0.00%)	0 / 163 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injection site abscess			
subjects affected / exposed	0 / 167 (0.00%)	0 / 163 (0.00%)	1 / 168 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	0 / 167 (0.00%)	0 / 163 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	0 / 167 (0.00%)	1 / 163 (0.61%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	0 / 167 (0.00%)	0 / 163 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Soft tissue infection			
subjects affected / exposed	0 / 167 (0.00%)	0 / 163 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Diabetic ketoacidosis			
subjects affected / exposed	0 / 167 (0.00%)	0 / 163 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Hyperglycaemia			
subjects affected / exposed	0 / 167 (0.00%)	0 / 163 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Integrated Study Period: TV-44749 531 mg	Integrated Study Period: TV-44749 318 mg	Integrated Study Period: TV-44749 425 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	13 / 197 (6.60%)	15 / 204 (7.35%)	8 / 203 (3.94%)
number of deaths (all causes)	1	2	0
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Shoulder fracture			
subjects affected / exposed	0 / 197 (0.00%)	1 / 204 (0.49%)	0 / 203 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Toxicity to various agents			
subjects affected / exposed	0 / 197 (0.00%)	1 / 204 (0.49%)	0 / 203 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 197 (0.00%)	1 / 204 (0.49%)	0 / 203 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial flutter			
subjects affected / exposed	1 / 197 (0.51%)	0 / 204 (0.00%)	0 / 203 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardio-respiratory arrest			
subjects affected / exposed	1 / 197 (0.51%)	0 / 204 (0.00%)	0 / 203 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Myocardial infarction			

subjects affected / exposed	1 / 197 (0.51%)	0 / 204 (0.00%)	0 / 203 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Lumbar radiculopathy			
subjects affected / exposed	0 / 197 (0.00%)	1 / 204 (0.49%)	0 / 203 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Non-cardiac chest pain			
subjects affected / exposed	0 / 197 (0.00%)	0 / 204 (0.00%)	1 / 203 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug ineffective			
subjects affected / exposed	0 / 197 (0.00%)	0 / 204 (0.00%)	0 / 203 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Erosive oesophagitis			
subjects affected / exposed	0 / 197 (0.00%)	1 / 204 (0.49%)	0 / 203 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia			
subjects affected / exposed	0 / 197 (0.00%)	1 / 204 (0.49%)	0 / 203 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Food poisoning			
subjects affected / exposed	0 / 197 (0.00%)	1 / 204 (0.49%)	0 / 203 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain upper			
subjects affected / exposed	0 / 197 (0.00%)	1 / 204 (0.49%)	0 / 203 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 197 (0.00%)	1 / 204 (0.49%)	0 / 203 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Acute respiratory failure			
subjects affected / exposed	0 / 197 (0.00%)	1 / 204 (0.49%)	0 / 203 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Alcoholic psychosis			
subjects affected / exposed	0 / 197 (0.00%)	0 / 204 (0.00%)	1 / 203 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depressive symptom			
subjects affected / exposed	0 / 197 (0.00%)	1 / 204 (0.49%)	0 / 203 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicidal ideation			
subjects affected / exposed	1 / 197 (0.51%)	0 / 204 (0.00%)	1 / 203 (0.49%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Substance-induced psychotic disorder			
subjects affected / exposed	0 / 197 (0.00%)	0 / 204 (0.00%)	1 / 203 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychotic disorder			
subjects affected / exposed	1 / 197 (0.51%)	1 / 204 (0.49%)	0 / 203 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychotic symptom			

subjects affected / exposed	0 / 197 (0.00%)	1 / 204 (0.49%)	0 / 203 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Schizophrenia			
subjects affected / exposed	8 / 197 (4.06%)	3 / 204 (1.47%)	3 / 203 (1.48%)
occurrences causally related to treatment / all	0 / 9	0 / 4	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 197 (0.00%)	2 / 204 (0.98%)	0 / 203 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Infections and infestations			
Sepsis			
subjects affected / exposed	1 / 197 (0.51%)	1 / 204 (0.49%)	0 / 203 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Pneumonia			
subjects affected / exposed	0 / 197 (0.00%)	1 / 204 (0.49%)	0 / 203 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Injection site abscess			
subjects affected / exposed	0 / 197 (0.00%)	0 / 204 (0.00%)	1 / 203 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	0 / 197 (0.00%)	1 / 204 (0.49%)	0 / 203 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Diverticulitis			
subjects affected / exposed	0 / 197 (0.00%)	1 / 204 (0.49%)	0 / 203 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			

subjects affected / exposed	0 / 197 (0.00%)	1 / 204 (0.49%)	0 / 203 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Soft tissue infection			
subjects affected / exposed	1 / 197 (0.51%)	0 / 204 (0.00%)	0 / 203 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Diabetic ketoacidosis			
subjects affected / exposed	0 / 197 (0.00%)	2 / 204 (0.98%)	0 / 203 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Hyperglycaemia			
subjects affected / exposed	1 / 197 (0.51%)	0 / 204 (0.00%)	0 / 203 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Double blind Period: TV-44749 531 mg		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 169 (1.18%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Shoulder fracture			
subjects affected / exposed	0 / 169 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Toxicity to various agents			
subjects affected / exposed	0 / 169 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Acute myocardial infarction			

subjects affected / exposed	0 / 169 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Atrial flutter			
subjects affected / exposed	0 / 169 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardio-respiratory arrest			
subjects affected / exposed	0 / 169 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Myocardial infarction			
subjects affected / exposed	0 / 169 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Lumbar radiculopathy			
subjects affected / exposed	0 / 169 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Non-cardiac chest pain			
subjects affected / exposed	0 / 169 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Drug ineffective			
subjects affected / exposed	0 / 169 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Erosive oesophagitis			
subjects affected / exposed	0 / 169 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Inguinal hernia			
subjects affected / exposed	0 / 169 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Food poisoning			
subjects affected / exposed	0 / 169 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Abdominal pain upper			
subjects affected / exposed	0 / 169 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 169 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Acute respiratory failure			
subjects affected / exposed	0 / 169 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Alcoholic psychosis			
subjects affected / exposed	0 / 169 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Depressive symptom			
subjects affected / exposed	0 / 169 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Suicidal ideation			
subjects affected / exposed	0 / 169 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Substance-induced psychotic disorder				
subjects affected / exposed	0 / 169 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Psychotic disorder				
subjects affected / exposed	0 / 169 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Psychotic symptom				
subjects affected / exposed	0 / 169 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Schizophrenia				
subjects affected / exposed	1 / 169 (0.59%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Acute kidney injury				
subjects affected / exposed	0 / 169 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Sepsis				
subjects affected / exposed	0 / 169 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	0 / 169 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Injection site abscess				
subjects affected / exposed	0 / 169 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Influenza			
subjects affected / exposed	0 / 169 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Diverticulitis			
subjects affected / exposed	0 / 169 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Septic shock			
subjects affected / exposed	0 / 169 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Soft tissue infection			
subjects affected / exposed	0 / 169 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Diabetic ketoacidosis			
subjects affected / exposed	0 / 169 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hyperglycaemia			
subjects affected / exposed	1 / 169 (0.59%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Double blind Period: Placebo	Double blind Period: TV-44749 318 mg	Double blind Period: TV-44749 425 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	38 / 167 (22.75%)	82 / 163 (50.31%)	99 / 168 (58.93%)
Investigations			
Weight increased			

subjects affected / exposed	13 / 167 (7.78%)	49 / 163 (30.06%)	66 / 168 (39.29%)
occurrences (all)	13	49	66
Nervous system disorders			
Headache			
subjects affected / exposed	11 / 167 (6.59%)	9 / 163 (5.52%)	14 / 168 (8.33%)
occurrences (all)	13	9	23
Somnolence			
subjects affected / exposed	3 / 167 (1.80%)	16 / 163 (9.82%)	10 / 168 (5.95%)
occurrences (all)	3	16	11
General disorders and administration site conditions			
Injection site pain			
subjects affected / exposed	7 / 167 (4.19%)	14 / 163 (8.59%)	19 / 168 (11.31%)
occurrences (all)	7	15	25
Injection site induration			
subjects affected / exposed	4 / 167 (2.40%)	18 / 163 (11.04%)	23 / 168 (13.69%)
occurrences (all)	6	23	29
Injection site erythema			
subjects affected / exposed	1 / 167 (0.60%)	12 / 163 (7.36%)	21 / 168 (12.50%)
occurrences (all)	1	14	25
Injection site swelling			
subjects affected / exposed	1 / 167 (0.60%)	9 / 163 (5.52%)	10 / 168 (5.95%)
occurrences (all)	1	12	12
Injection site pruritus			
subjects affected / exposed	1 / 167 (0.60%)	9 / 163 (5.52%)	9 / 168 (5.36%)
occurrences (all)	1	12	9
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	6 / 167 (3.59%)	4 / 163 (2.45%)	8 / 168 (4.76%)
occurrences (all)	6	4	8

Non-serious adverse events	Integrated Study Period: TV-44749 531 mg	Integrated Study Period: TV-44749 318 mg	Integrated Study Period: TV-44749 425 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	113 / 197 (57.36%)	105 / 204 (51.47%)	113 / 203 (55.67%)
Investigations			
Weight increased			

subjects affected / exposed	69 / 197 (35.03%)	73 / 204 (35.78%)	78 / 203 (38.42%)
occurrences (all)	74	74	82
Nervous system disorders			
Headache			
subjects affected / exposed	8 / 197 (4.06%)	9 / 204 (4.41%)	15 / 203 (7.39%)
occurrences (all)	10	9	25
Somnolence			
subjects affected / exposed	15 / 197 (7.61%)	17 / 204 (8.33%)	11 / 203 (5.42%)
occurrences (all)	20	18	12
General disorders and administration site conditions			
Injection site pain			
subjects affected / exposed	24 / 197 (12.18%)	25 / 204 (12.25%)	25 / 203 (12.32%)
occurrences (all)	34	26	37
Injection site induration			
subjects affected / exposed	28 / 197 (14.21%)	20 / 204 (9.80%)	27 / 203 (13.30%)
occurrences (all)	43	30	35
Injection site erythema			
subjects affected / exposed	22 / 197 (11.17%)	15 / 204 (7.35%)	24 / 203 (11.82%)
occurrences (all)	27	19	28
Injection site swelling			
subjects affected / exposed	8 / 197 (4.06%)	11 / 204 (5.39%)	11 / 203 (5.42%)
occurrences (all)	9	15	14
Injection site pruritus			
subjects affected / exposed	16 / 197 (8.12%)	13 / 204 (6.37%)	12 / 203 (5.91%)
occurrences (all)	26	35	17
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	9 / 197 (4.57%)	7 / 204 (3.43%)	12 / 203 (5.91%)
occurrences (all)	11	7	12

Non-serious adverse events	Double blind Period: TV-44749 531 mg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	98 / 169 (57.99%)		
Investigations			
Weight increased			

subjects affected / exposed	58 / 169 (34.32%)		
occurrences (all)	58		
Nervous system disorders			
Headache			
subjects affected / exposed	7 / 169 (4.14%)		
occurrences (all)	9		
Somnolence			
subjects affected / exposed	13 / 169 (7.69%)		
occurrences (all)	15		
General disorders and administration site conditions			
Injection site pain			
subjects affected / exposed	17 / 169 (10.06%)		
occurrences (all)	23		
Injection site induration			
subjects affected / exposed	23 / 169 (13.61%)		
occurrences (all)	36		
Injection site erythema			
subjects affected / exposed	15 / 169 (8.88%)		
occurrences (all)	18		
Injection site swelling			
subjects affected / exposed	6 / 169 (3.55%)		
occurrences (all)	7		
Injection site pruritus			
subjects affected / exposed	11 / 169 (6.51%)		
occurrences (all)	15		
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	8 / 169 (4.73%)		
occurrences (all)	10		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 February 2024	The primary reason for this amendment was to describe the course of action for Period 2 participants following the completion of the Period 1 efficacy analyses and the top line results availability. This amendment also provided clarity to assessments and processes in several sections. Changes to the protocol were considered to have no negative impact on the safety of participants already enrolled into the trial and to not have confounded the interpretation of safety data collected from participants currently enrolled in Period 2 of the trial following implementation of Protocol Amendment 1.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported