



## Clinical trial results:

### A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy, Safety, and Tolerability of Risperidone Extended-Release Injectable Suspension (TV-46000) for Subcutaneous Use as Maintenance Treatment in Adult and Adolescent Patients with Schizophrenia

#### Summary

EudraCT number	2018-001619-65
Trial protocol	BG
Global end of trial date	03 December 2020

#### Results information

Result version number	v1 (current)
This version publication date	20 June 2021
First version publication date	20 June 2021

#### Trial information

##### Trial identification

Sponsor protocol code	TV46000-CNS-30072
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03503318
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	Teva Branded Pharmaceutical Products, R&D Inc.
Sponsor organisation address	145 Brandywine Parkway, West Chester, United States, 19380
Public contact	Director, Clinical Research, Teva Branded Pharmaceutical Products, R&D Inc., 001 8884838279, info.eraclinical@teva.de
Scientific contact	Director, Clinical Research, Teva Branded Pharmaceutical Products, R&D Inc., 001 8884838279, info.eraclinical@teva.de

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:

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**Results analysis stage**

Analysis stage	Final
Date of interim/final analysis	16 December 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 September 2020
Global end of trial reached?	Yes
Global end of trial date	03 December 2020
Was the trial ended prematurely?	No

Notes:

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**General information about the trial**

Main objective of the trial:

The primary objective of this study was to evaluate the efficacy of TV-46000 during maintenance treatment in adult participants with schizophrenia.

Protection of trial subjects:

This study was conducted in full accordance with the International Conference on Harmonisation 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	27 April 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

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**Population of trial subjects****Subjects enrolled per country**

Country: Number of subjects enrolled	Bulgaria: 63
Country: Number of subjects enrolled	United States: 481
Worldwide total number of subjects	544
EEA total number of subjects	63

Notes:

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**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)	1
Adults (18-64 years)	530
From 65 to 84 years	13
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

Participants were randomized to receive TV-46000 once monthly (q1m) subcutaneous (SC) injections, TV-46000 once every 2 months (q2m) SC injections, or placebo q1m SC injections in 1:1:1 ratio. Open-label oral risperidone (2 to 5 mg/day) was used to stabilize participants to the treatments (dose was based on clinical judgment) before randomization.

### Period 1

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

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Placebo

Arm description:

Participants received an SC injection of placebo matched to TV-46000 at baseline and every 4 weeks (q4w) thereafter. Participants continued treatment until they experienced a relapse event; met 1 or more of the study discontinuation or withdrawal criteria; or remained relapse-free during the double-blind phase until the study was terminated.

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

Dosage and administration details:

Placebo matched to TV-46000 was administered per dose and schedule specified in the arm description.

<b>Arm title</b>	TV-46000 q1m
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Arm description:

Participants received an SC injection of TV-46000 at baseline and q4w thereafter. The maximal dose administered to adult participants was comparable to an oral risperidone dose of 5 mg/day, and the maximal dose administered to adolescents was comparable to 4 mg/day. Participants continued treatment until they experienced a relapse event; met 1 or more of the study discontinuation or withdrawal criteria; or remained relapse-free during the double-blind phase until the study was terminated.

Arm type	Experimental
Investigational medicinal product name	TV-46000
Investigational medicinal product code	
Other name	Risperidone
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

TV-46000 was administered per dose and schedule specified in the arm description.

<b>Arm title</b>	TV-46000 q2m
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Arm description:

Participants received an SC injection of TV-46000 at baseline and every 8 weeks (q8w) thereafter, and a

placebo SC injection 4 weeks after baseline and q8w thereafter. The maximal dose administered to adult participants was comparable to an oral risperidone dose of 5 mg/day, and the maximal dose administered to adolescents was comparable to 4 mg/day. Participants continued treatment until they experienced a relapse event; met 1 or more of the study discontinuation or withdrawal criteria; or remained relapse-free during the double-blind phase until the study was terminated.

Arm type	Experimental
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Placebo matched to TV-46000 was administered per dose and schedule specified in the arm description.

Investigational medicinal product name	TV-46000
Investigational medicinal product code	
Other name	Risperidone
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

TV-46000 was administered per dose and schedule specified in the arm description.

<b>Number of subjects in period 1</b>	Placebo	TV-46000 q1m	TV-46000 q2m
Started	181	183	180
Received at least 1 dose of study drug	179	183	180
Completed	142	144	140
Not completed	39	39	40
Adverse event, serious fatal	1	-	4
Consent withdrawn by subject	12	17	16
Adverse event, non-fatal	3	4	2
Other than specified	1	3	3
Lost to follow-up	17	15	12
Protocol deviation	5	-	3

## Baseline characteristics

### Reporting groups

Reporting group title	Placebo
Reporting group description:	
Participants received an SC injection of placebo matched to TV-46000 at baseline and every 4 weeks (q4w) thereafter. Participants continued treatment until they experienced a relapse event; met 1 or more of the study discontinuation or withdrawal criteria; or remained relapse-free during the double-blind phase until the study was terminated.	
Reporting group title	TV-46000 q1m
Reporting group description:	
Participants received an SC injection of TV-46000 at baseline and q4w thereafter. The maximal dose administered to adult participants was comparable to an oral risperidone dose of 5 mg/day, and the maximal dose administered to adolescents was comparable to 4 mg/day. Participants continued treatment until they experienced a relapse event; met 1 or more of the study discontinuation or withdrawal criteria; or remained relapse-free during the double-blind phase until the study was terminated.	
Reporting group title	TV-46000 q2m
Reporting group description:	
Participants received an SC injection of TV-46000 at baseline and every 8 weeks (q8w) thereafter, and a placebo SC injection 4 weeks after baseline and q8w thereafter. The maximal dose administered to adult participants was comparable to an oral risperidone dose of 5 mg/day, and the maximal dose administered to adolescents was comparable to 4 mg/day. Participants continued treatment until they experienced a relapse event; met 1 or more of the study discontinuation or withdrawal criteria; or remained relapse-free during the double-blind phase until the study was terminated.	

Reporting group values	Placebo	TV-46000 q1m	TV-46000 q2m
Number of subjects	181	183	180
Age categorical			
Units: Subjects			

Age Continuous			
Units: years			
arithmetic mean	49.2	50.6	48.1
standard deviation	± 11.43	± 10.30	± 11.09
Sex: Female, Male			
Units: participants			
Female	71	71	70
Male	110	112	110
Race/Ethnicity, Customized			
Units: Subjects			
White	68	72	66
Black or African American	104	108	110
Asian	4	1	2
Native Hawaiian or Other Pacific Islander	1	1	0
Not Reported	2	1	0
Other	2	0	2
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	42	39	36
Not Hispanic or Latino	139	144	144
Unknown or Not Reported	0	0	0

<b>Reporting group values</b>	Total		
Number of subjects	544		
Age categorical Units: Subjects			
Age Continuous Units: years arithmetic mean standard deviation	-		
Sex: Female, Male Units: participants			
Female	212		
Male	332		
Race/Ethnicity, Customized Units: Subjects			
White	206		
Black or African American	322		
Asian	7		
Native Hawaiian or Other Pacific Islander	2		
Not Reported	3		
Other	4		
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	117		
Not Hispanic or Latino	427		
Unknown or Not Reported	0		

## End points

### End points reporting groups

Reporting group title	Placebo
Reporting group description: Participants received an SC injection of placebo matched to TV-46000 at baseline and every 4 weeks (q4w) thereafter. Participants continued treatment until they experienced a relapse event; met 1 or more of the study discontinuation or withdrawal criteria; or remained relapse-free during the double-blind phase until the study was terminated.	
Reporting group title	TV-46000 q1m
Reporting group description: Participants received an SC injection of TV-46000 at baseline and q4w thereafter. The maximal dose administered to adult participants was comparable to an oral risperidone dose of 5 mg/day, and the maximal dose administered to adolescents was comparable to 4 mg/day. Participants continued treatment until they experienced a relapse event; met 1 or more of the study discontinuation or withdrawal criteria; or remained relapse-free during the double-blind phase until the study was terminated.	
Reporting group title	TV-46000 q2m
Reporting group description: Participants received an SC injection of TV-46000 at baseline and every 8 weeks (q8w) thereafter, and a placebo SC injection 4 weeks after baseline and q8w thereafter. The maximal dose administered to adult participants was comparable to an oral risperidone dose of 5 mg/day, and the maximal dose administered to adolescents was comparable to 4 mg/day. Participants continued treatment until they experienced a relapse event; met 1 or more of the study discontinuation or withdrawal criteria; or remained relapse-free during the double-blind phase until the study was terminated.	

### Primary: Number of Participants With Impending Relapse (Intent-to-treat [ITT] Analysis Set)

End point title	Number of Participants With Impending Relapse (Intent-to-treat [ITT] Analysis Set)
End point description: Relapse was defined as 1 or more of following items: • Clinical Global Impression–Improvement (CGI-I) of $\geq 5$ , and - an increase of any of 4 Positive and Negative Syndrome Scale (PANSS) items: conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content, to a score $>4$ with an absolute increase of $\geq 2$ on specific item or $\geq 4$ on combined score of 4 items since randomization; • hospitalization due to worsening of psychotic symptoms; • Clinical Global Impression–Severity of Suicidality (CGI-SS) of 4 (severely suicidal) or 5 (attempted suicide) on Part 1 and/or 6 (much worse) or 7 (very much worse) on Part 2; • violent behavior resulting in clinically significant self-injury, injury to another person, or property damage. Data is presented as distribution of relapsing participants (number of participants with impending relapse). ITT analysis set: adult participants randomized to double-blind maintenance treatment, regardless if they received treatment or not.	
End point type	Primary
End point timeframe: From randomization up to 108 weeks	

End point values	Placebo	TV-46000 q1m	TV-46000 q2m	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	181	183	179	
Units: participants	53	13	23	

## Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Analysis was performed using the stratified Cox proportional hazard model, with treatment (placebo, TV-46000 q1m and TV-46000 q2m or placebo and TV-46000 overall [including q1m and q2m]) as explanatory variable and sex-dose as a stratification factor, and the stratified log rank test p-value (sex-dose as a stratification factor) referred to (TV-46000/placebo) comparison.	
Comparison groups	Placebo v TV-46000 q1m
Number of subjects included in analysis	364
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001 <sup>[1]</sup>
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.109
upper limit	0.367

Notes:

[1] - Threshold for significance at 0.05 level.

Statistical analysis title	Statistical Analysis 2
Statistical analysis description:	
Analysis was performed using the stratified Cox proportional hazard model, with treatment (placebo, TV-46000 q1m and TV-46000 q2m or placebo and TV-46000 overall [including q1m and q2m]) as explanatory variable and sex-dose as a stratification factor, and the stratified log rank test p-value (sex-dose as a stratification factor) referred to (TV-46000/placebo) comparison.	
Comparison groups	Placebo v TV-46000 q2m
Number of subjects included in analysis	360
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001 <sup>[2]</sup>
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.375
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.227
upper limit	0.618

Notes:

[2] - Threshold for significance at 0.05 level.



## Secondary: Number of Participants With Impending Relapse (Extended ITT [eITT] Analysis Set)

End point title	Number of Participants With Impending Relapse (Extended ITT [eITT] Analysis Set)
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End point description:

Relapse was defined as 1 or more of the following items: • CGI-I of  $\geq 5$ , and - an increase of any of the 4 PANSS items: conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content, to a score  $>4$  with an absolute increase of  $\geq 2$  on specific item or  $\geq 4$  on combined score of 4 items since randomization; • hospitalization due to worsening of psychotic symptoms; • CGI-SS of 4 (severely suicidal) or 5 (attempted suicide) on Part 1 and/or 6 (much worse) or 7 (very much worse) on Part 2; • violent behavior resulting in clinically significant self-injury, injury to another person, or property damage. Data is presented as distribution of relapsing participants (adults and adolescents) (number of participants with impending relapse). eITT analysis set included all participants (adults and adolescents) randomized to the double-blind maintenance stage treatment, regardless if they had received treatment or not.

End point type	Secondary
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End point timeframe:

From randomization up to 108 weeks

End point values	Placebo	TV-46000 q1m	TV-46000 q2m	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	181	183	180	
Units: participants	53	13	24	

## Statistical analyses

No statistical analyses for this end point

## Secondary: Proportion of Participants With Impending Relapse

End point title	Proportion of Participants With Impending Relapse
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End point description:

Relapse was defined as 1 or more of the following items: • CGI-I of  $\geq 5$ , and - an increase of any of the 4 PANSS items: conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content, to a score  $>4$  with an absolute increase of  $\geq 2$  on specific item or  $\geq 4$  on combined score of 4 items since randomization; • hospitalization due to worsening of psychotic symptoms; • CGI-SS of 4 (severely suicidal) or 5 (attempted suicide) on Part 1 and/or 6 (much worse) or 7 (very much worse) on Part 2; • violent behavior resulting in clinically significant self-injury, injury to another person, or property damage. Impending relapse rate at Week 24 was estimated using the Kaplan-Meier product estimate. ITT analysis set included adult participants randomized to the double-blind maintenance treatment, regardless if they had received treatment or not.

End point type	Secondary
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End point timeframe:

Week 24

End point values	Placebo	TV-46000 q1m	TV-46000 q2m	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	181	183	179	
Units: proportion of participants				
number (confidence interval 95%)	0.28 (0.205 to 0.347)	0.07 (0.03 to 0.109)	0.11 (0.065 to 0.165)	

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Participants Who Maintain Stability at the Endpoint

End point title	Number of Participants Who Maintain Stability at the Endpoint
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End point description:

Stability is defined as meeting all of the following criteria for at least 4 consecutive weeks: outpatient status; PANSS total score  $\leq 80$ ; minimal presence of specific psychotic symptoms on the PANSS, as measured by a score of  $\leq 4$  on each of the following items: conceptual disorganization, suspiciousness, hallucinatory behavior, and unusual thought content; Clinical Global Impression of Severity (CGI-S) score  $\leq 4$  (moderately ill); and CGI-SS score  $\leq 2$  (mildly suicidal) on Part 1 and  $\leq 5$  (minimally worsened) on Part 2. The last valid participant assessment was used as the endpoint. ITT analysis set included adult participants randomized to the double-blind maintenance treatment, regardless if they had received treatment or not.

End point type	Secondary
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End point timeframe:

At the endpoint (up to 108 weeks)

End point values	Placebo	TV-46000 q1m	TV-46000 q2m	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	181	183	179	
Units: Participants	110	159	143	

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Participants Achieving Remission at the Endpoint

End point title	Number of Participants Achieving Remission at the Endpoint
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End point description:

The remission was achieved for participants that did not relapse during the study and in addition, over a period of at least 6 months preceding the endpoint, maintained scores of  $\leq 3$  on each of the 8 specific PANSS items: P1 (delusions), G9 (unusual thought content), P3 (hallucinatory behavior), P2 (conceptual disorganization), G5 (mannerisms/posturing), N1 (blunted affect), N4 (social withdrawal), and N6 (lack of spontaneity). The last valid participant assessment was used as the endpoint. The participant population was limited to treated by the study drug for at least 6 months. ITT analysis set included adult participants randomized to the double-blind maintenance treatment, regardless if they had received treatment or not.

End point type	Secondary
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End point timeframe:  
At Endpoint (up to 108 weeks)

End point values	Placebo	TV-46000 q1m	TV-46000 q2m	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	181	183	179	
Units: Participants	30	39	42	

### Statistical analyses

No statistical analyses for this end point

### Secondary: Observed Rate of Impending Relapse (Number of Participants With Impending Relapse) at the Endpoint

End point title	Observed Rate of Impending Relapse (Number of Participants With Impending Relapse) at the Endpoint
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End point description:

Relapse was defined as 1 or more of the following items: • CGI-I of  $\geq 5$ , and - an increase of any of the 4 PANSS items: conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content, to a score  $>4$  with an absolute increase of  $\geq 2$  on specific item or  $\geq 4$  on combined score of 4 items since randomization; • hospitalization due to worsening of psychotic symptoms; • CGI-SS of 4 (severely suicidal) or 5 (attempted suicide) on Part 1 and/or 6 (much worse) or 7 (very much worse) on Part 2; • violent behavior resulting in clinically significant self-injury, injury to another person, or property damage. Observed rate of impending relapse was calculated as the number of participants who relapsed by endpoint divided by the number of participants in each treatment group, using the last valid participant assessment as the endpoint. ITT analysis set: adult participants randomized to double-blind maintenance treatment, regardless if they received treatment or not.

End point type	Secondary
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End point timeframe:

At the Endpoint (up to 108 weeks)

End point values	Placebo	TV-46000 q1m	TV-46000 q2m	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	181	183	179	
Units: Participants	53	13	23	

### Statistical analyses

No statistical analyses for this end point

### Secondary: Time to Impending Relapse (Number of Participants With Impending Relapse) in the Adolescent Participants

End point title	Time to Impending Relapse (Number of Participants With Impending Relapse) in the Adolescent Participants
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**End point description:**

Relapse was defined as 1 or more of the following items: • CGI-I of  $\geq 5$ , and - an increase of any of the 4 PANSS items: conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content, to a score  $>4$  with an absolute increase of  $\geq 2$  on specific item or  $\geq 4$  on combined score of 4 items since randomization; • hospitalization due to worsening of psychotic symptoms; • CGI-SS of 4 (severely suicidal) or 5 (attempted suicide) on Part 1 and/or 6 (much worse) or 7 (very much worse) on Part 2; • violent behavior resulting in clinically significant self-injury, injury to another person, or property damage. Data is presented as distribution of relapsing participants (adolescents) (number of participants with impending relapse). eITT analysis set: all participants (adults and adolescents) randomized to the double-blind maintenance stage treatment, regardless if they received treatment or not. Here, 'Overall number of participants analysed' = adolescent participants.

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End point type	Secondary
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**End point timeframe:**

From randomization up to 108 weeks

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End point values	Placebo	TV-46000 q1m	TV-46000 q2m	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0 <sup>[3]</sup>	0 <sup>[4]</sup>	1	
Units: participants			1	

Notes:

[3] - There were no adolescent participants in this arm.

[4] - There were no adolescent participants in this arm.

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**Statistical analyses**

No statistical analyses for this end point

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**Secondary: Change From Baseline in Drug Attitudes Inventory 10-item Version (DAI-10) Total Score at the Endpoint and End of Treatment**

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End point title	Change From Baseline in Drug Attitudes Inventory 10-item Version (DAI-10) Total Score at the Endpoint and End of Treatment
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**End point description:**

DAI-10 contains 6 items (1, 3, 4, 7, 9, and 10) that a participant who was fully adherent to the prescribed medication answered as "True" and 4 items (2, 5, 6, and 8) that a participant who was fully adherent to the prescribed medication answered as "False." A correct answer was scored +1 and an incorrect answer was scored -1. The total score was the sum of pluses and minuses, which ranged from -10 to 10 in increments of 2. A positive total score indicated a positive subjective response (compliant) and a negative total score indicated a negative subjective response (non-compliance). Higher scores denoted better compliance. The last valid participant assessment was used as the endpoint. ITT analysis set included adult participants randomized to the double-blind maintenance treatment, regardless if they received treatment or not. Here, 'Overall number of participants analysed' = participants evaluable for this endpoint, 'n' = participants evaluable at specified timepoint.

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End point type	Secondary
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**End point timeframe:**

Baseline, endpoint and end of treatment (up to Week 108)

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End point values	Placebo	TV-46000 q1m	TV-46000 q2m	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	178	182	179	
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n=178,182,179)	6.1 (± 3.23)	5.8 (± 3.63)	5.7 (± 3.13)	
Change at the Endpoint (n=125,139,137)	-0.8 (± 3.88)	0.1 (± 3.34)	-0.3 (± 3.65)	
Change at the End of Treatment (n=55,84,79)	-0.9 (± 3.42)	0.3 (± 2.84)	0.3 (± 3.51)	

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in Schizophrenia Quality of Life Scale (SQLS) Total Score at the Endpoint and End of Treatment

End point title	Change From Baseline in Schizophrenia Quality of Life Scale (SQLS) Total Score at the Endpoint and End of Treatment
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End point description:

The SQLS comprises 33 items categorized in 2 domains: psychosocial feelings (20 items) and cognition and vitality (13 items). The items were 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 to a 0 (best health status) to 100 (worst health status) scale, with higher scores indicating comparatively lower quality of life. The last valid participant assessment was used as the endpoint. ITT analysis set included adult participants randomized to the double-blind maintenance treatment, regardless if they had received treatment or not. Here, 'Overall number of participants analysed' signifies participants evaluable for this endpoint, 'n' signifies participants evaluable at specified timepoint.

End point type	Secondary
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End point timeframe:

Baseline, endpoint and end of treatment (up to Week 108)

End point values	Placebo	TV-46000 q1m	TV-46000 q2m	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	178	182	179	
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n=178,182,179)	34.0 (± 16.06)	33.1 (± 16.79)	34.2 (± 15.70)	
Change at the Endpoint (n=158,172,163)	0.9 (± 14.24)	-4.5 (± 14.31)	-4.1 (± 15.23)	
Change at the End of Treatment (n=55,85,79)	-2.3 (± 13.26)	-7.2 (± 13.79)	-7.3 (± 12.30)	

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Participants With Treatment-Emergent Adverse Events (TEAEs)

End point title	Number of Participants With Treatment-Emergent Adverse Events (TEAEs)
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End point description:

An adverse event (AE) was defined as any untoward medical occurrence in a participant who received study drug without regard to possibility of causal relationship. TEAEs were defined as AEs occurring after the first dose of the study drug until 120 days after the last dose of study drug. Serious AEs 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 Reported AE section. Safety analysis set included all randomized participants who received  $\geq 1$  dose of study treatment or placebo.

End point type	Secondary
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End point timeframe:

From randomization up to 120 days after last dose of study drug (up to Week 125)

End point values	Placebo	TV-46000 q1m	TV-46000 q2m	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	179	183	180	
Units: participants	92	111	121	

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in Total Abnormal Involuntary Movement Scale (AIMS) Score at the End of Treatment

End point title	Change From Baseline in Total Abnormal Involuntary Movement Scale (AIMS) Score at the End of Treatment
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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. Total AIMS score is a sum of item 1 through 7. Items 1 through 7 include facial and oral movements (Items 1-4), extremity movements (Items 5-6), and trunk movements (Item 7). Each item was rated on a 0 (no dyskinesia) to 4 (severe dyskinesia) scale. Total AIMS score for Items 1-7 ranged from 0 to 28; with higher scores indicating greater severity of the condition. Safety analysis set included all randomized participants who received  $\geq 1$  dose of study treatment or placebo. Here, n' signifies participants evaluable at specified timepoint.

End point type	Secondary
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End point timeframe:

Baseline, end of treatment (up to 108 weeks)

End point values	Placebo	TV-46000 q1m	TV-46000 q2m	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	179	183	180	
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n=179,183,180)	0.4 (± 1.30)	0.5 (± 1.83)	0.2 (± 0.79)	
Change at the End of Treatment (n=55,93,81)	0.0 (± 1.10)	0.1 (± 0.62)	0.1 (± 1.00)	

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in Simpson-Angus Scale (SAS) Mean Score at the End of Treatment

End point title	Change From Baseline in Simpson-Angus Scale (SAS) Mean Score at the End of Treatment
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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 [None/Normal] to 4 [Extreme/Severe]). The mean score was calculated by adding the individual item scores and dividing by 10. The total mean score ranged from 0-40, with a higher score indicating greater severity of symptoms. Safety analysis set included all randomized participants who received ≥1 dose of study treatment or placebo. Here, 'n' signifies participants evaluable at specified timepoint.

End point type	Secondary
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End point timeframe:

Baseline, end of treatment (up to 108 weeks)

End point values	Placebo	TV-46000 q1m	TV-46000 q2m	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	179	183	180	
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n=179,183,180)	0.07 (± 0.137)	0.09 (± 0.195)	0.06 (± 0.134)	
Change at the End of Treatment (n=55,93,81)	0.04 (± 0.134)	0.02 (± 0.211)	0.00 (± 0.102)	

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in Total Barnes Akathisia Rating Scale (BARS) Score at the End of Treatment

End point title	Change From Baseline in Total Barnes Akathisia Rating Scale (BARS) Score at the End of Treatment
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End point description:

The BARS is an instrument that assesses the severity of drug-induced akathisia. The BARS includes 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/no distress) to 3 (constant restlessness/severe distress). Total score was the sum of scores of each item and ranged from 0-9, with higher scores indicating greater severity of akathisia. Safety analysis set included all randomized participants who received  $\geq 1$  dose of study treatment or placebo. Here, 'n' signifies participants evaluable at specified timepoint.

End point type	Secondary
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End point timeframe:

Baseline, end of treatment (up to 108 weeks)

End point values	Placebo	TV-46000 q1m	TV-46000 q2m	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	179	183	180	
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n=179,183,180)	0.2 ( $\pm$ 0.63)	0.1 ( $\pm$ 0.39)	0.2 ( $\pm$ 0.57)	
Change at the End of Treatment (n=55,93,81)	-0.1 ( $\pm$ 0.56)	0.0 ( $\pm$ 0.51)	-0.1 ( $\pm$ 0.56)	

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Participants Reporting Suicidal Behavior and Suicidal Ideation Using Columbia-Suicide Severity Rating Scale (C-SSRS) at Baseline and Post-Baseline

End point title	Number of Participants Reporting Suicidal Behavior and Suicidal Ideation Using Columbia-Suicide Severity Rating Scale (C-SSRS) at Baseline and Post-Baseline
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End point description:

The C-SSRS is a semi-structured interview that captures the occurrence, severity, and frequency of suicide-related thoughts and behaviors. 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, and 4 different categories of active suicidal ideation. Safety analysis set included all randomized participants who received  $\geq 1$  dose of study treatment or placebo.

End point type	Secondary
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End point timeframe:

Baseline, post-baseline (up to 108 weeks)



End point values	Placebo	TV-46000 q1m	TV-46000 q2m	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	179	183	180	
Units: participants				
Baseline: Suicidal behavior	0	0	3	
Baseline: Suicidal ideation	6	5	7	
Post-baseline: Suicidal behavior	3	1	1	
Post-baseline: Suicidal ideation	12	7	12	

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in Calgary Depression Scale for Schizophrenia (CDSS) Score at the End of Treatment

End point title	Change From Baseline in Calgary Depression Scale for Schizophrenia (CDSS) Score at the End of Treatment
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End point description:

The CDSS is specifically designed to assess the level of depression separate from the positive, negative, and EPS in schizophrenia. This clinician-administered instrument consists of 9 items, each rated on a 4-point scale from 0 (absent) to 3 (severe) that were added together to form the total CDSS depression score of the participant. The total score ranged from 0-27, with higher scores indicating greater severity of the condition. Safety analysis set included all randomized participants who received  $\geq 1$  dose of study treatment or placebo. Here, 'n' signifies participants evaluable at specified timepoint.

End point type	Secondary
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End point timeframe:

Baseline, end of treatment (up to 108 weeks)

End point values	Placebo	TV-46000 q1m	TV-46000 q2m	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	179	183	180	
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n=179,183,180)	1.6 ( $\pm$ 2.14)	1.3 ( $\pm$ 1.92)	1.5 ( $\pm$ 1.93)	
Change at the End of Treatment (n=55,93,81)	-0.4 ( $\pm$ 2.72)	-0.3 ( $\pm$ 1.39)	-0.8 ( $\pm$ 2.24)	

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in Clinical Global Impression-Severity of Suicidality (CGI-SS) Score at the End of Treatment

End point title	Change From Baseline in Clinical Global Impression-Severity of Suicidality (CGI-SS) Score at the End of Treatment
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**End point description:**

The CGI-SS scale provides an overall clinician-rated assessment of the risk of suicidality. The CGI-SS consists of a 5-point scale in Part 1 (the most severe level of suicidality experience) ranging from 1 (not at all suicidal) to 5 (attempted suicide) and a 7-point scale in Part 2 (change in participant suicidality) ranging from 1 (very much improved) to 7 (very much worse). Safety analysis set included all randomized participants who received  $\geq 1$  dose of study treatment or placebo. Here, 'Overall number of participants analysed' signifies participants evaluable for this endpoint, 'n' signifies participants evaluable at specified timepoint.

End point type	Secondary
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**End point timeframe:**

Baseline, end of treatment (up to 108 weeks)

End point values	Placebo	TV-46000 q1m	TV-46000 q2m	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	179	183	179	
Units: units on a scale				
arithmetic mean (standard deviation)				
Part 1 at Baseline (n=179,183,179)	1.0 ( $\pm$ 0.00)	1.0 ( $\pm$ 0.00)	1.0 ( $\pm$ 0.00)	
Part 2 at the End of Treatment (n=55,93,81)	4.0 ( $\pm$ 0.00)	4.0 ( $\pm$ 0.00)	4.0 ( $\pm$ 0.00)	

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Plasma Concentration of Risperidone, 9-OH-risperidone, and Total Active Moiety (Sum of Risperidone and 9-OH-risperidone)**

End point title	Plasma Concentration of Risperidone, 9-OH-risperidone, and Total Active Moiety (Sum of Risperidone and 9-OH-risperidone)
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**End point description:**

Pharmacokinetics (PK) analysis set included all randomized participants who received  $\geq 1$  dose of study treatment or placebo and who also had  $\geq 1$  plasma concentration measured. Here, 'Number analysed' signifies participants evaluable for specified categories.

End point type	Secondary
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**End point timeframe:**

1 hour prior to dosing at Baseline (Day 1) and at the end of treatment (EOT) visit (up to 108 weeks)

End point values	Placebo	TV-46000 q1m	TV-46000 q2m	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	178	178	177	
Units: ng/mL				
arithmetic mean (full range (min-max))				
Risperidone at Baseline (n=178,178,177)	4.694 (0.050 to 58.376)	6.452 (0.050 to 97.935)	5.364 (0.05 to 125.524)	
Risperidone at EOT (n=52,87,79)	1.323 (0.050 to 47.683)	13.215 (0.050 to 136.184)	8.838 (0.05 to 75.95)	

9-OH-Risperidone at Baseline (n=178,178,177)	14.965 (0.150 to 84.471)	18.473 (0.15 to 105.26)	15.187 (0.15 to 107.316)	
9-OH-Risperidone at EOT (n=52,87,79)	2.982 (0.150 to 40.730)	26.202 (0.15 to 101.354)	17.778 (0.15 to 88.333)	
Total Active Moiety at Baseline (n=178,178,177)	19.060 (0.050 to 95.595)	24.200 (0.050 to 134.202)	19.945 (0.05 to 172.763)	
Total Active Moiety at EOT (n=52,87,79)	4.078 (0.050 to 62.621)	38.429 (0.050 to 159.498)	25.947 (0.05 to 135.823)	

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From randomization up to 120 days after last dose of study drug (up to Week 125)

Adverse event reporting additional description:

Safety analysis set included all randomized participants who received  $\geq 1$  dose of study treatment or placebo.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	23.0
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### Reporting groups

Reporting group title	Placebo
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Reporting group description:

Participants received an SC injection of placebo matched to TV-46000 at baseline and q4w thereafter. Participants continued treatment until they experienced a relapse event; met 1 or more of the study discontinuation or withdrawal criteria; or remained relapse-free during the double-blind phase until the study was terminated.

Reporting group title	TV-46000 q2m
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Reporting group description:

Participants received an SC injection of TV-46000 at baseline and q8w thereafter, and a placebo SC injection 4 weeks after baseline and q8w thereafter. The maximal dose administered to adult participants was comparable to an oral risperidone dose of 5 mg/day, and the maximal dose administered to adolescents was comparable to 4 mg/day. Participants continued treatment until they experienced a relapse event; met 1 or more of the study discontinuation or withdrawal criteria; or remained relapse-free during the double-blind phase until the study was terminated.

Reporting group title	TV-46000 q1m
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Reporting group description:

Participants received an SC injection of TV-46000 at baseline and q4w thereafter. The maximal dose administered to adult participants was comparable to an oral risperidone dose of 5 mg/day, and the maximal dose administered to adolescents was comparable to 4 mg/day. Participants continued treatment until they experienced a relapse event; met 1 or more of the study discontinuation or withdrawal criteria; or remained relapse-free during the double-blind phase until the study was terminated.

Serious adverse events	Placebo	TV-46000 q2m	TV-46000 q1m
Total subjects affected by serious adverse events			
subjects affected / exposed	14 / 179 (7.82%)	10 / 180 (5.56%)	8 / 183 (4.37%)
number of deaths (all causes)	1	4	0
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	0 / 179 (0.00%)	1 / 180 (0.56%)	0 / 183 (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
Respiratory tract procedural			

complication			
subjects affected / exposed	0 / 179 (0.00%)	1 / 180 (0.56%)	0 / 183 (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
Toxicity to various agents			
subjects affected / exposed	0 / 179 (0.00%)	1 / 180 (0.56%)	0 / 183 (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			
Myocardial infarction			
subjects affected / exposed	1 / 179 (0.56%)	0 / 180 (0.00%)	0 / 183 (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
Nervous system disorders			
Encephalopathy			
subjects affected / exposed	0 / 179 (0.00%)	1 / 180 (0.56%)	0 / 183 (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
Syncope			
subjects affected / exposed	1 / 179 (0.56%)	0 / 180 (0.00%)	0 / 183 (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			
Intestinal perforation			
subjects affected / exposed	0 / 179 (0.00%)	0 / 180 (0.00%)	1 / 183 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis acute			
subjects affected / exposed	1 / 179 (0.56%)	0 / 180 (0.00%)	0 / 183 (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
Hepatobiliary disorders			
Cholelithiasis			

subjects affected / exposed	1 / 179 (0.56%)	0 / 180 (0.00%)	0 / 183 (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
<b>Respiratory, thoracic and mediastinal disorders</b>			
Acute respiratory failure			
subjects affected / exposed	0 / 179 (0.00%)	1 / 180 (0.56%)	0 / 183 (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
Pneumonia aspiration			
subjects affected / exposed	0 / 179 (0.00%)	0 / 180 (0.00%)	1 / 183 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 179 (0.00%)	0 / 180 (0.00%)	1 / 183 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 179 (0.00%)	1 / 180 (0.56%)	0 / 183 (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
<b>Psychiatric disorders</b>			
Acute psychosis			
subjects affected / exposed	1 / 179 (0.56%)	0 / 180 (0.00%)	0 / 183 (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
Mental status changes			
subjects affected / exposed	0 / 179 (0.00%)	0 / 180 (0.00%)	1 / 183 (0.55%)
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	2 / 179 (1.12%)	1 / 180 (0.56%)	0 / 183 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Psychotic symptom			
subjects affected / exposed	2 / 179 (1.12%)	0 / 180 (0.00%)	0 / 183 (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
Schizophrenia			
subjects affected / exposed	4 / 179 (2.23%)	2 / 180 (1.11%)	0 / 183 (0.00%)
occurrences causally related to treatment / all	1 / 5	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicidal ideation			
subjects affected / exposed	1 / 179 (0.56%)	0 / 180 (0.00%)	2 / 183 (1.09%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Spinal pain			
subjects affected / exposed	0 / 179 (0.00%)	1 / 180 (0.56%)	0 / 183 (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
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 179 (0.00%)	1 / 180 (0.56%)	0 / 183 (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
COVID-19			
subjects affected / exposed	0 / 179 (0.00%)	0 / 180 (0.00%)	1 / 183 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteomyelitis			
subjects affected / exposed	0 / 179 (0.00%)	1 / 180 (0.56%)	0 / 183 (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
Pelvic abscess			
subjects affected / exposed <sup>[1]</sup>	0 / 71 (0.00%)	0 / 70 (0.00%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pneumonia			
subjects affected / exposed	1 / 179 (0.56%)	0 / 180 (0.00%)	0 / 183 (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
Sepsis			
subjects affected / exposed	0 / 179 (0.00%)	1 / 180 (0.56%)	0 / 183 (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
Upper respiratory tract infection			
subjects affected / exposed	0 / 179 (0.00%)	0 / 180 (0.00%)	1 / 183 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 179 (0.00%)	0 / 180 (0.00%)	1 / 183 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: This is a gender-specific AE that affects only female participants

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

<b>Non-serious adverse events</b>	Placebo	TV-46000 q2m	TV-46000 q1m
Total subjects affected by non-serious adverse events			
subjects affected / exposed	35 / 179 (19.55%)	48 / 180 (26.67%)	49 / 183 (26.78%)
Investigations			
Weight increased			
subjects affected / exposed	6 / 179 (3.35%)	13 / 180 (7.22%)	10 / 183 (5.46%)
occurrences (all)	6	14	10
Nervous system disorders			
Headache			
subjects affected / exposed	10 / 179 (5.59%)	11 / 180 (6.11%)	9 / 183 (4.92%)
occurrences (all)	11	11	10
General disorders and administration site conditions			
Injection site nodule			



subjects affected / exposed occurrences (all)	6 / 179 (3.35%) 20	13 / 180 (7.22%) 23	12 / 183 (6.56%) 29
Injection site pain subjects affected / exposed occurrences (all)	11 / 179 (6.15%) 37	12 / 180 (6.67%) 14	9 / 183 (4.92%) 13
Injection site pruritus subjects affected / exposed occurrences (all)	4 / 179 (2.23%) 5	7 / 180 (3.89%) 10	10 / 183 (5.46%) 17
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	10 / 179 (5.59%) 11	5 / 180 (2.78%) 6	12 / 183 (6.56%) 13

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 December 2018	<p>The following major procedural changes (not all-inclusive) were made to the protocol:</p> <ul style="list-style-type: none"><li>• various revisions due to the introduced possibility of enrolling adolescent participants (including eligibility criteria, maximum dose to be administered, up to 3 additional PK samples to be collected from adolescents)</li><li>• urine pregnancy test was added to the baseline visit clarification which scales were only performed in adult participants</li><li>• definition of study completers added</li><li>• clarification that collection of the unscheduled PK samples is only relevant for Stage 2</li><li>• clarification regarding blinding per updated sponsor template to enhance participant safety and ensure that the participant's needs are first addressed</li><li>• correction of blood volumes per updated laboratory manual</li><li>• clarification regarding a positive urine drug screen result due to the high prevalence of recreational and medical use of various substances in this participant population.</li></ul>
16 October 2019	<p>The following major procedural changes (not all-inclusive) were made to the protocol:</p> <ul style="list-style-type: none"><li>• in addition to the originally planned, single interim analysis that was to be conducted when 125 relapse events were observed, an earlier interim analysis (when 90 relapse events were reached) was introduced</li><li>• prolongation of study duration (although in case of a successful interim analysis, the study would be terminated earlier)</li><li>• change of inclusion criterion to omit the body mass index (BMI) percentile limitation</li><li>• updates to the planned number of enrolled participants per updated projections</li><li>• clarification of procedures to be performed during unscheduled visits</li><li>• updates to vendor information and personnel details following changes of responsibilities</li><li>• clarification regarding highly effective birth control methods (that is, only highly effective birth control methods should have been used in this study).</li></ul>
19 April 2020	<p>The following major procedural changes (not all-inclusive) were made to the protocol:</p> <ul style="list-style-type: none"><li>• changes to various sections due to the planned earlier final analysis</li><li>• change of responsibilities in the sponsor's medical expert</li><li>• blood volumes updated to reflect longer treatment duration in Stage 2 of the study</li><li>• COVID-19 pandemic-related operational updates and contingency measures were added to the study as a new appendix.</li></ul>

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported