Clinical trial results:
A Study to Evaluate the Safety, Tolerability, and Effect of Risperidone Extended-Release Injectable Suspension (TV-46000) for Subcutaneous Use as Maintenance Treatment in Adult and Adolescent Patients with Schizophrenia

Summary

EudraCT number	2019-000063-24
Trial protocol	FR BG
Global end of trial date	02 December 2021

Results information

Result version number	v1 (current)
This version publication date	15 June 2022
First version publication date	15 June 2022

Trial information

Trial identification

Sponsor protocol code	TV46000-CNS-30078

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03893825
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., MedInfo@tevaeu.com
Scientific contact	Director, Clinical Research, Teva Branded Pharmaceutical Products R&D, Inc., 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	20 December 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	02 December 2021
Global end of trial reached?	Yes
Global end of trial date	02 December 2021
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 long-term safety and tolerability of TV-46000 administered in adult and adolescent participants with schizophrenia.

Protection of trial subjects:

This study was conducted in full accordance with the International Conference on 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	17 April 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 300
Country: Number of subjects enrolled	Bulgaria: 36
Worldwide total number of subjects	336
EEA total number of subjects	36

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)	3
Adults (18-64 years)	322
From 65 to 84 years	11
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants who did not experience relapse and completed Study TV46000-CNS-30072 (NCT03503318) (roll-over participants) and new participants entered this study. Open-label oral risperidone (at dose of 2 to 5 milligrams [mg]/day, based on clinical judgment) for 12 weeks was given to stabilize new participants to the treatment before randomization.

Pre-assignment

Screening details:

Participants who were treated with TV-46000 once monthly (q1m) or once every 2 months (q2m) during Study TV46000-CNS-30072, continued their assigned treatment. Participants who were treated with placebo during Study TV46000-CNS-30072 were randomized to receive TV-46000 q1m or q2m SC injections equivalent to oral dose on which they were stabilized.

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
Arm title	TV-46000 q1m

Arm description:

Participants received a subcutaneous (SC) injection of TV-46000 at baseline and every 4 weeks (q4w) thereafter for up to 56 weeks. 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.

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.

Arm title	TV-46000 q2m

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 for up to 56 weeks. 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.

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 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.

Number of subjects in period 1	TV-46000 q1m	TV-46000 q2m
Started	174	162
Received at least 1 dose of study drug	172	162
Completed	135	122
Not completed	39	40
Adverse event, serious fatal	2	1
Consent withdrawn by subject	19	21
Adverse event, non-fatal	-	2
Protocol deviation	1	-
Other than specified	7	6
Lost to follow-up	10	10

Baseline characteristics

Reporting groups	
Reporting group title	TV-46000 q1m
Reporting group description:	
Participants received a subcutaneous (SC) injection of TV-46000 at baseline and every 4 weeks (q4w) thereafter for up to 56 weeks. 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.	
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 for up to 56 weeks. 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.	

Reporting group values	TV-46000 q1m	TV-46000 q2m	Total
Number of subjects	174	162	336
Age categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	51.3	49.8	
standard deviation	± 10.28	± 11.51	-
Sex: Female, Male Units: participants			
Female	61	59	120
Male	113	103	216
Race/Ethnicity, Customized Units: Subjects			
White	80	67	147
Black or African American	91	90	181
Asian	1	2	3
Native Hawaiian or Other Pacific Islander	0	1	1
Not reported	1	1	2
Other	1	1	2
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	56	51	107
Not Hispanic or Latino	118	110	228
Unknown or Not Reported	0	1	1

End points

End points reporting groups

Reporting group title	TV-46000 q1m

Reporting group description:

Participants received a subcutaneous (SC) injection of TV-46000 at baseline and every 4 weeks (q4w) thereafter for up to 56 weeks. 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.

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 for up to 56 weeks. 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.

Primary: Number of Participants With Adverse Events (AEs)

End point title	Number of Participants With Adverse Events (AEs)[1]

End point description:

An AE was defined as any untoward medical occurrence in a participant who received study drug without regard to possibility of causal relationship. 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 Reported AE section. The safety analysis set included all participants who received at least 1 dose of TV46000 in TV-46000-CNS-30072 study or in TV46000-CNS-30078 study.

End point type	Primary

End point timeframe:

Baseline up to Week 64

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The analysis is descriptive in nature.

End point values	TV-46000 q1m	TV-46000 q2m		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	172	162		
Units: participants				
AEs	64	74		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants With Serious Adverse Events

End point title	Number of Participants With Serious Adverse Events[2]

End point description:

An AE was defined as any untoward medical occurrence in a participant who received study drug without regard to possibility of causal relationship. 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 Reported AE section. The safety analysis set included all participants who received at least 1 dose of TV46000 in TV-46000-CNS-30072 study or in TV46000-CNS-30078 study.

End point type	Primary

End point timeframe:

Baseline up to Week 64

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The analysis is descriptive in nature.

End point values	TV-46000 q1m	TV-46000 q2m		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	172	162		
Units: Participants	8	11		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Participants who Were Withdrawn From the Treatment

End point title	Number of Participants who Were Withdrawn From the Treatment

End point description:

The number of participants who were withdrawn from the treatment due to any reason has been reported. The safety analysis set included all participants who received at least 1 dose of TV46000 in TV-46000-CNS-30072 study or in TV46000-CNS-30078 study.

End point type	Other pre-specified

End point timeframe:

Baseline to Week 64

End point values	TV-46000 q1m	TV-46000 q2m		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	172	162		
Units: Participants				
Death	2	1		
Adverse event	2	5		
Withdrawal by participant	21	25		
Non-compliance with study drug	1	0		
Protocol deviation	2	1		
Pregnancy	0	0		
Lost-to-follow up	5	7		
Lack of efficacy	1	0		
Relapse	3	3		

Other	11	11		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to Week 64

Adverse event reporting additional description:

The safety analysis set included all participants who received at least 1 dose of TV46000 in TV-46000-CNS-30072 study or in TV46000-CNS-30078 study. No study drug was administered during the open-label stabilization period. All treatment-emergent adverse events are presented.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	TV-46000 q1m

Reporting group description:

Participants received an SC injection of TV-46000 at baseline and q4w thereafter for up to 56 weeks. 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.

Reporting group title	TV-46000 q2m

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 for up to 56 weeks. 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.

Serious adverse events	TV-46000 q1m	TV-46000 q2m	
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 172 (4.65%)	11 / 162 (6.79%)	
number of deaths (all causes)	2	1	
number of deaths resulting from adverse events			
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 172 (0.58%)	0 / 162 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 172 (0.00%)	1 / 162 (0.62%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Angina pectoris			

subjects affected / exposed	0 / 172 (0.00%)	1 / 162 (0.62%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 172 (0.58%)	0 / 162 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 172 (0.58%)	0 / 162 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 172 (0.58%)	0 / 162 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 172 (0.00%)	1 / 162 (0.62%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 172 (0.00%)	1 / 162 (0.62%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 172 (0.00%)	1 / 162 (0.62%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Major depression			

subjects affected / exposed	1 / 172 (0.58%)	0 / 162 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Panic attack			
subjects affected / exposed	0 / 172 (0.00%)	1 / 162 (0.62%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychotic disorder			
subjects affected / exposed	0 / 172 (0.00%)	1 / 162 (0.62%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Schizophrenia			
subjects affected / exposed	1 / 172 (0.58%)	2 / 162 (1.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Self-injurious ideation			
subjects affected / exposed	0 / 172 (0.00%)	1 / 162 (0.62%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Substance-induced psychotic disorder			
subjects affected / exposed	1 / 172 (0.58%)	0 / 162 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	1 / 172 (0.58%)	1 / 162 (0.62%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	TV-46000 q1m	TV-46000 q2m	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 172 (5.81%)	12 / 162 (7.41%)	
General disorders and administration site conditions			
Injection site nodule			
subjects affected / exposed	3 / 172 (1.74%)	9 / 162 (5.56%)	
occurrences (all)	6	13	
Injection site pain			
subjects affected / exposed	9 / 172 (5.23%)	7 / 162 (4.32%)	
occurrences (all)	24	23	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 June 2020	The following major procedural changes (not all-inclusive) were made to the protocol: - COVID-19 pandemic-related operational updates were added to the study as a new appendix. - To avoid duplication and reduce participant burden, many of the baseline procedures and assessments outlined in this protocol related to the roll-over participants, were performed in the end of treatment visit of study 30072, and the results were transferred to this study's clinical database. - The volume of collected blood samples was corrected accordingly. - The biomarker sample collection became optional. - Gender was removed as a stratification factor for randomization of new participants and roll-over participants previously assigned to placebo. - Various clarifications were made, for example, blinding of personnel to the study treatment assignments in studies TV46000-CNS-30072 and TV46000-CNS-30078 (especially with regard to those also involved in the conduct of study TV46000-CNS-30072). - Since pin-pointing the onset of schizophrenia in adolescents is difficult, the time since the diagnosis of schizophrenia in the inclusion criterion for adolescents (aged 13-17) was reduced to 6 months to better align with the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) criteria, and the requirement for relapse in the last 24 months was removed due to the short time since diagnosis.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported