Clinical trial results:
A Randomized, Double-Blind, Placebo-Controlled, Multiple Rising Oral Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of TAK-994 in Patients With Narcolepsy With or Without Cataplexy (Narcolepsy Type 1 or Narcolepsy Type 2)

Summary

EudraCT number	2020-000777-24
Trial protocol	HU FR CZ NL FI IT
Global end of trial date	05 November 2021

Results information

Result version number	v3 (current)
This version publication date	20 October 2024
First version publication date	15 December 2022
Version creation reason	• New data added to full data set Full data set
Summary attachment (see zip file)	TAK-994-1501_2020-000777-24_EudraCT PDF_Update Nov 2023 (TAK-994-1501_2020-000777-24_EudraCT PDF_Update Nov 2023.pdf)

Trial information

Trial identification

Sponsor protocol code	TAK-994-1501

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04096560
WHO universal trial number (UTN)	U1111-1240-0346

Notes:

Sponsors

Sponsor organisation name	Takeda
Sponsor organisation address	95 Hayden Avenue, Lexington, United States, MA 02421
Public contact	Study Director, Takeda, TrialDisclosures@takeda.com
Scientific contact	Study Director, Takeda, TrialDisclosures@takeda.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	05 November 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	05 November 2021
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The objective of this study is to assess the safety and tolerability of TAK-994 following multiple oral doses in subjects with narcolepsy with or without cataplexy (NT1 or NT2) and to assess the efficacy of TAK-994 on reducing excessive daytime sleepiness as measured by MWT and ESS.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	27 May 2020
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	Spain: 8
Country: Number of subjects enrolled	France: 7
Country: Number of subjects enrolled	Hungary: 1
Country: Number of subjects enrolled	Italy: 15
Country: Number of subjects enrolled	Canada: 3
Country: Number of subjects enrolled	China: 2
Country: Number of subjects enrolled	Japan: 15
Country: Number of subjects enrolled	Korea, Republic of: 5
Country: Number of subjects enrolled	United States: 41
Worldwide total number of subjects	97
EEA total number of subjects	31

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)	97
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants took part in the study at 35 investigative sites in Canada, China, France, Hungary, Italy, Japan, South Korea, Spain and United States from 27 May 2020 to 05 November 2021. Participants with Narcolepsy Type 1 or Type 2 were planned to be enrolled in study in Parts A, B, C and D to receive TAK-994 or placebo.

Pre-assignment

Screening details:

Due to the early termination of the study, data was not collected for Part C: placebo and was insufficient for Part C: TAK-994 180 mg to allow the pre-planned analyses. Similarly, for Part D, the prespecified sample size at Week 4 was not reached and therefore the pre-planned analyses cannot be adequately interpreted.

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	Part A: Placebo

Arm description:

TAK-994 placebo-matching tablets, orally, twice daily (BID) for 28 days, in participants with NT1.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

TAK-994 placebo-matching tablets, orally, twice daily (BID) for 28 days.

Arm title	Part A: TAK-994 120 mg

Arm description:

TAK-994 120 mg, orally, BID for 28 days, in participants with NT1.

Arm type	Experimental
Investigational medicinal product name	TAK-994
Investigational medicinal product code	
Other name	Firazorexton
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

TAK-994 120 mg, orally, BID for 28 days.

Arm title	Part A: TAK-994 180 mg

Arm description:

TAK-994 180 mg, orally, BID for 28 days, in participants with NT1.

Arm type	Experimental

Investigational medicinal product name	TAK-994
Investigational medicinal product code	
Other name	Firazorexton
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

TAK-994 180 mg, orally, BID for 28 days.

Arm title	Part B: Placebo

Arm description:

TAK-994 placebo-matching tablets, orally, BID for 56 days, in participants with NT1.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

TAK-994 placebo-matching tablets, orally, BID for 56 days.

Arm title	Part B: TAK-994 30 mg

Arm description:

TAK-994 30 mg tablets, orally, BID for 56 days, in participants with NT1.

Arm type	Experimental
Investigational medicinal product name	TAK-994
Investigational medicinal product code	
Other name	Firazorexton
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

TAK-994 30 mg tablets, orally, BID for 56 days.

Arm title	Part B: TAK-994 90 mg

Arm description:

TAK-994 90 mg tablets, orally, BID for 56 days, in participants with NT1.

Arm type	Experimental
Investigational medicinal product name	TAK-994
Investigational medicinal product code	
Other name	Firazorexton
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

TAK-994 90 mg tablets, orally, BID for 56 days.

Arm title	Part B: TAK-994 180 mg

Arm description:

TAK-994 180 mg tablets, orally, BID for 56 days, in participants with NT1.

Arm type	Experimental
Investigational medicinal product name	TAK-994
Investigational medicinal product code	
Other name	Firazorexton
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:
TAK-994 180 mg tablets, orally, BID for 56 days.

Arm title	Part C: TAK-994 180 mg

Arm description:
TAK-994 180 mg tablets, orally, BID for 56 days, in Chinese participants with NT1.

Arm type	Experimental
Investigational medicinal product name	TAK-994
Investigational medicinal product code	
Other name	Firazorexton
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:
TAK-994 180 mg tablets, orally, BID for 56 days.

Number of subjects in period 1	Part A: Placebo	Part A: TAK-994 120 mg	Part A: TAK-994 180 mg
Started	7	7	8
Completed	6	7	8
Not completed	1	0	0
Met the Discontinuation Criteria of the Protocol	-	-	-
Study terminated by sponsor	-	-	-
Pretreatment event (Serious or other adverse event	-	-	-
Reason not specified	1	-	-

Number of subjects in period 1	Part B: Placebo	Part B: TAK-994 30 mg	Part B: TAK-994 90 mg
Started	17	17	20
Completed	12	10	12
Not completed	5	7	8
Met the Discontinuation Criteria of the Protocol	-	-	-
Study terminated by sponsor	5	6	4
Pretreatment event (Serious or other adverse event	-	-	3
Reason not specified	-	1	1

Number of subjects in period 1	Part B: TAK-994 180 mg	Part C: TAK-994 180 mg
Started	19	2
Completed	9	0
Not completed	10	2
Met the Discontinuation Criteria of the Protocol	-	1
Study terminated by sponsor	6	1

Pretreatment event (Serious or other adverse event	3	-
Reason not specified	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Part A: Placebo
Reporting group description:	
TAK-994 placebo-matching tablets, orally, twice daily (BID) for 28 days, in participants with NT1.	
Reporting group title	Part A: TAK-994 120 mg
Reporting group description:	
TAK-994 120 mg, orally, BID for 28 days, in participants with NT1.	
Reporting group title	Part A: TAK-994 180 mg
Reporting group description:	
TAK-994 180 mg, orally, BID for 28 days, in participants with NT1.	
Reporting group title	Part B: Placebo
Reporting group description:	
TAK-994 placebo-matching tablets, orally, BID for 56 days, in participants with NT1.	
Reporting group title	Part B: TAK-994 30 mg
Reporting group description:	
TAK-994 30 mg tablets, orally, BID for 56 days, in participants with NT1.	
Reporting group title	Part B: TAK-994 90 mg
Reporting group description:	
TAK-994 90 mg tablets, orally, BID for 56 days, in participants with NT1.	
Reporting group title	Part B: TAK-994 180 mg
Reporting group description:	
TAK-994 180 mg tablets, orally, BID for 56 days, in participants with NT1.	
Reporting group title	Part C: TAK-994 180 mg
Reporting group description:	
TAK-994 180 mg tablets, orally, BID for 56 days, in Chinese participants with NT1.	

Reporting group values	Part A: Placebo	Part A: TAK-994 120 mg	Part A: TAK-994 180 mg
Number of subjects	7	7	8
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	31.4	38.0	33.4
full range (min-max)	22 to 36	23 to 53	18 to 45
Gender categorical Units: Subjects			
Female	4	2	5
Male	3	5	3
Race Units: Subjects			
Asian	2	0	4
Black or African American	0	3	1
White	5	3	3
More than one race	0	0	0
Unknown or Not Reported	0	1	0

Ethnicity Units: Subjects			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	7	7	8
Unknown or Not Reported	0	0	0
Height Units: centimetres (cm)			
arithmetic mean	168.07	176.61	164.01
full range (min-max)	157.5 to 177.8	162.0 to 187.9	152.8 to 177.8
Weight Units: kilograms (kg)			
arithmetic mean	85.77	80.07	74.33
full range (min-max)	74.2 to 92.7	56.7 to 102.5	60.0 to 91.9
Body Mass Index (BMI)			
BMI= Weight (kg)/[height(m)^2			
Units: kilogram per square metre (kg/m^2)			
arithmetic mean	30.529	25.629	27.575
full range (min-max)	25.3 to 37.4	20.5 to 33.2	23.2 to 33.8
Average Sleep Latency			
The Maintenance of Wakefulness Test (MWT) is a validated, objective measure that evaluates a person's ability to remain awake under soporific conditions for a defined period. During each MWT session (1 session = 40 minutes), participants were instructed to sit quietly and remain awake for as long as possible. Sleep latency in each session was recorded on electroencephalography (EEG). If no sleep was observed according to these rules, then the latency was defined as 40 minutes.			
Units: Minutes			
arithmetic mean	3.30	4.41	2.75
full range (min-max)	1.1 to 8.6	0.3 to 13.4	1.0 to 6.9
Epworth Sleepiness Scale (ESS) Score			
The ESS is a subjective, self-administered, validated scale (scored 0 to 3) to respond to each of the 8 questions of daily life that asks them how likely they are to fall asleep in those situations. The scores are summed to give an overall score of 0 to 24. Higher scores indicate stronger subjective daytime sleepiness, and scores below 10 are considered to be within the normal range.			
Units: score on a scale			
arithmetic mean	18.6	17.4	18.0
full range (min-max)	13 to 21	13 to 24	11 to 23
Weekly Cataplexy Rate (WCR)			
WCR = (Total number of cataplexy over a number of non-missing diary days for a given duration/number of Non-missing diary days in that duration)*7. 999 represents data was not collected as 0 participants were analyzed in part C for endpoint WCR.			
Units: cataplexy attacks per week			
arithmetic mean	19.9	19.1	12.0
full range (min-max)	10 to 49	5 to 41	4 to 28

Reporting group values	Part B: Placebo	Part B: TAK-994 30 mg	Part B: TAK-994 90 mg
Number of subjects	17	17	20
Age categorical Units: Subjects			

Age continuous Units: years			
arithmetic mean	32.6	33.4	28.8
full range (min-max)	18 to 47	18 to 55	18 to 48

Gender categorical Units: Subjects			
Female	8	12	10
Male	9	5	10
Race Units: Subjects			
Asian	1	6	6
Black or African American	3	1	4
White	11	7	8
More than one race	1	1	0
Unknown or Not Reported	1	2	2
Ethnicity Units: Subjects			
Hispanic or Latino	0	2	0
Not Hispanic or Latino	17	14	19
Unknown or Not Reported	0	1	1
Height Units: centimetres (cm)			
arithmetic mean	171.00	164.24	168.38
full range (min-max)	150.4 to 187.0	151.0 to 177.8	151.9 to 182.0
Weight Units: kilograms (kg)			
arithmetic mean	80.75	71.97	77.68
full range (min-max)	46.3 to 126.5	48.0 to 108.0	52.3 to 102.0
Body Mass Index (BMI)			
BMI= Weight (kg)/[height(m)^2			
Units: kilogram per square metre (kg/m^2)			
arithmetic mean	27.48	26.56	27.29
full range (min-max)	20.5 to 38.9	18.2 to 38.3	19.7 to 35.3
Average Sleep Latency			
The Maintenance of Wakefulness Test (MWT) is a validated, objective measure that evaluates a person's ability to remain awake under soporific conditions for a defined period. During each MWT session (1 session = 40 minutes), participants were instructed to sit quietly and remain awake for as long as possible. Sleep latency in each session was recorded on electroencephalography (EEG). If no sleep was observed according to these rules, then the latency was defined as 40 minutes.			
Units: Minutes			
arithmetic mean	6.0	6.1	6.1
full range (min-max)	0 to 31	1 to 21	0 to 19
Epworth Sleepiness Scale (ESS) Score			
The ESS is a subjective, self-administered, validated scale (scored 0 to 3) to respond to each of the 8 questions of daily life that asks them how likely they are to fall asleep in those situations. The scores are summed to give an overall score of 0 to 24. Higher scores indicate stronger subjective daytime sleepiness, and scores below 10 are considered to be within the normal range.			
Units: score on a scale			
arithmetic mean	16.6	18.5	17.5
full range (min-max)	8 to 21	12 to 23	10 to 23
Weekly Cataplexy Rate (WCR)			
WCR = (Total number of cataplexy over a number of non-missing diary days for a given duration/number of Non-missing diary days in that duration)*7. 999 represents data was not collected as 0 participants were analyzed in part C for endpoint WCR.			
Units: cataplexy attacks per week			
arithmetic mean	15.94	14.98	11.68
full range (min-max)	0.0 to 50.0	3.5 to 72.5	4.3 to 36.5

Reporting group values	Part B: TAK-994 180 mg	Part C: TAK-994 180 mg	Total
Number of subjects	19	2	97
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	29.2	38.5	
full range (min-max)	19 to 43	25 to 52	-
Gender categorical Units: Subjects			
Female	12	1	54
Male	7	1	43
Race Units: Subjects			
Asian	3	2	24
Black or African American	0	0	12
White	15	0	52
More than one race	0	0	2
Unknown or Not Reported	1	0	7
Ethnicity Units: Subjects			
Hispanic or Latino	0	0	2
Not Hispanic or Latino	18	2	92
Unknown or Not Reported	1	0	3
Height Units: centimetres (cm)			
arithmetic mean	171.66	169	
full range (min-max)	160.0 to 185.4	163.0 to 175.0	-
Weight Units: kilograms (kg)			
arithmetic mean	80.33	77	
full range (min-max)	56.7 to 102.0	66.0 to 88.0	-
Body Mass Index (BMI)			
BMI= Weight (kg)/[height(m)^2			
Units: kilogram per square metre (kg/m^2)			
arithmetic mean	27.21	26.75	
full range (min-max)	19.2 to 34.0	24.8 to 28.7	-
Average Sleep Latency			
The Maintenance of Wakefulness Test (MWT) is a validated, objective measure that evaluates a person's ability to remain awake under soporific conditions for a defined period. During each MWT session (1 session = 40 minutes), participants were instructed to sit quietly and remain awake for as long as possible. Sleep latency in each session was recorded on electroencephalography (EEG). If no sleep was observed according to these rules, then the latency was defined as 40 minutes.			
Units: Minutes			
arithmetic mean	4.9	17.87	
full range (min-max)	0 to 23	4.5 to 40	-
Epworth Sleepiness Scale (ESS) Score			
The ESS is a subjective, self-administered, validated scale (scored 0 to 3) to respond to each of the 8 questions of daily life that asks them how likely they are to fall asleep in those situations. The scores are summed to give an overall score of 0 to 24. Higher scores indicate stronger subjective daytime sleepiness, and scores below 10 are considered to be within the normal range.			

Units: score on a scale			
arithmetic mean	17.4	20	
full range (min-max)	11 to 23	16 to 24	-
Weekly Cataplexy Rate (WCR)			
WCR = (Total number of cataplexy over a number of non-missing diary days for a given duration/number of Non-missing diary days in that duration)*7. 999 represents data was not collected as 0 participants were analyzed in part C for endpoint WCR.			
Units: cataplexy attacks per week			
arithmetic mean	15.37	999	
full range (min-max)	3.0 to 47.5	999 to 999	-

End points

End points reporting groups

Reporting group title	Part A: Placebo
Reporting group description: TAK-994 placebo-matching tablets, orally, twice daily (BID) for 28 days, in participants with NT1.	
Reporting group title	Part A: TAK-994 120 mg
Reporting group description: TAK-994 120 mg, orally, BID for 28 days, in participants with NT1.	
Reporting group title	Part A: TAK-994 180 mg
Reporting group description: TAK-994 180 mg, orally, BID for 28 days, in participants with NT1.	
Reporting group title	Part B: Placebo
Reporting group description: TAK-994 placebo-matching tablets, orally, BID for 56 days, in participants with NT1.	
Reporting group title	Part B: TAK-994 30 mg
Reporting group description: TAK-994 30 mg tablets, orally, BID for 56 days, in participants with NT1.	
Reporting group title	Part B: TAK-994 90 mg
Reporting group description: TAK-994 90 mg tablets, orally, BID for 56 days, in participants with NT1.	
Reporting group title	Part B: TAK-994 180 mg
Reporting group description: TAK-994 180 mg tablets, orally, BID for 56 days, in participants with NT1.	
Reporting group title	Part C: TAK-994 180 mg
Reporting group description: TAK-994 180 mg tablets, orally, BID for 56 days, in Chinese participants with NT1.	

Primary: Part A: Number of Participants Who Experience at Least One Treatment Emergent Adverse Event (TEAE) During the Study

End point title	Part A: Number of Participants Who Experience at Least One Treatment Emergent Adverse Event (TEAE) During the Study[1][2]

End point description:

An Adverse Event (AE) is defined as any untoward medical occurrence in a clinical investigation participant administered a drug; it does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (example, a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, whether or not it is considered related to the drug. A TEAE is defined as an AE with an onset that occurs after receiving study drug. Safety Analysis Set included all participants who were randomised and received at least 1 dose of study drug.

End point type	Primary

End point timeframe:

First dose of study treatment to end of study follow-up (up to Day 35) in Part A

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: Only descriptive analysis was planned for this endpoint.

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only the drug-treated arms for Part A were to be analysed for this endpoint.

End point values	Part A: Placebo	Part A: TAK-994 120 mg	Part A: TAK-994 180 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	7	7	8	
Units: Participants	2	6	7	

Statistical analyses

No statistical analyses for this end point

Primary: Part A: Number of Participants Who Meet the Markedly Abnormal Value (MAV) Criteria for Safety Laboratory Tests at Least Once Postdose During the Study

End point title	Part A: Number of Participants Who Meet the Markedly Abnormal Value (MAV) Criteria for Safety Laboratory Tests at Least Once Postdose During the Study[3][4]

End point description:

Standard safety laboratory values(hematology,serum chemistry,urinalysis)were collected & compared to pre-specified criteria for MAVs:Erythrocytes(10^12/L:<0.8xlower limit of normal(LLN),>1.2xupper limit of normal(ULN);Hemoglobin grams per litre(g/L):<0.8xLLN, >1.2xULN; Hematocrit voltage/volts(V/V):<0.8xLLN,>1.2xULN;Platelets(10^9/L):<75,>600; Leukocytes(10^9/L):<0.5xLLN,>1.5xULN;Alanine Aminotransferase units/litre(U/L):>3xULN, Aspartate Aminotransferase(U/L):>3xULN;Bilirubin micromoles/litre (umol/L):>1.5xULN; Alkaline Phosphatase(U/L):>3xULN;Gamma Glutamyl Transferase(U/L):>3 x ULN; Albumin(g/L):<25;Protein Total(g/L):<0.8xLLN,>1.2xULN;Glucose millimoles/litre(mmol/L):<2.8, >19.4;Calcium(mmol/L):<1.92, >2.77;Creatinine(umol/L):>1.5xULN;Urea(mmol/L):>10.7; Sodium(mmol/L):<130,>150;Potassium(mmol/L):<3.0,>5.3. Only categories with at least 1 participant with event are reported. Safety Analysis set included all participants who were randomised & received at

End point type	Primary

End point timeframe:

First dose of study treatment to end of study follow-up (up to Day 35) in Part A

Notes:

[3] - 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: Only descriptive analysis was planned for this endpoint.

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only the drug-treated arms for Part A were to be analysed for this endpoint.

End point values	Part A: Placebo	Part A: TAK-994 120 mg	Part A: TAK-994 180 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	7	7	8	
Units: Participants				
Calcium (mmol/L): <1.92	0	1	0	
Sodium (mmol/L): <130	0	1	0	
Potassium (mmol/L): >5.3	1	0	0	

Statistical analyses

No statistical analyses for this end point

Primary: Part A: Number of Participants Who Meet the Markedly Abnormal Value

(MAV) Criteria for Vital Sign Measurements at Least Once Postdose During the Study

End point title	Part A: Number of Participants Who Meet the Markedly Abnormal Value (MAV) Criteria for Vital Sign Measurements at Least Once Postdose During the Study[5][6]

End point description:

Vital signs (body temperature and sitting blood pressure) were collected and compared to pre-specified criteria for MAVs throughout the study. MAV criteria: Heart Rate (beats/min): <40, >115; Systolic Blood Pressure (SBP) millimeters of mercury (mmHg): <90, ≥160, Change from Pre-Dose >20, Change from Pre-Dose >30, Time-matched Change from Baseline (CFB) > 20, Time-matched CFB > 30; Diastolic Blood Pressure (DBP) (mmHg): <50, ≥100, Change from Pre-Dose >20, Change from Pre-Dose >30, Time-matched CFB > 20, Time-matched CFB > 30; Respiratory Rate (breaths/min): >21; Temperature Celsius (C): >38.5. Only categories with at least one participant with event are reported.
Safety Analysis Set included all participants who were randomised and received at least 1 dose of study drug.

End point type	Primary

End point timeframe:

First dose of study treatment to end of study follow-up (up to Day 35) in Part A

Notes:

[5] - 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: Only descriptive analysis was planned for this endpoint.

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only the drug-treated arms for Part A were to be analysed for this endpoint.

End point values	Part A: Placebo	Part A: TAK-994 120 mg	Part A: TAK-994 180 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	7	7	8	
Units: Participants				
SBP (mmHg)<90	2	0	0	
SBP (mmHg): Change From Pre-Dose >20	2	3	2	
SBP (mmHg): Change From Pre-Dose >30	1	1	0	
SBP (mmHg): Time matched CFB>20	4	7	6	
SBP (mmHg): Time matched CFB>30	0	3	0	
DBP (mmHg): Change From Pre-Dose >20	1	3	0	
DBP (mmHg): Time matched CFB>30	1	4	3	
Temperature (C): >38.5	0	1	0	

Statistical analyses

No statistical analyses for this end point

Primary: Part A: Number of Participants Who Meet the Markedly Abnormal Value (MAV) Criteria for Safety Electrocardiogram (ECG) Parameters at Least Once Postdose During the Study

End point title	Part A: Number of Participants Who Meet the Markedly Abnormal Value (MAV) Criteria for Safety Electrocardiogram (ECG) Parameters at Least Once Postdose During the Study[7][8]

End point description:

A 12 lead ECG was performed, the ECG values were compared to pre-specified criteria for MAVs. MAV

criteria: ECG Mean Heart Rate (beats/min): <40, >115; PR Interval milliseconds (msec): ≤80, ≥200; corrected QT interval by Fredericia (QTcF) Interval (msec): ≤300, >500, ≥30 CFB and >450; QRS Duration (msec): ≤80, ≥180. Only categories with at least one participant with event are reported. Safety Analysis Set included all participants who were randomised and received at least 1 dose of study drug.

End point type	Primary

End point timeframe:

First dose of study treatment to end of study follow-up (up to Day 35) in Part A

Notes:

[7] - 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: Only descriptive analysis was planned for this endpoint.

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only the drug-treated arms for Part A were to be analysed for this endpoint.

End point values	Part A: Placebo	Part A: TAK-994 120 mg	Part A: TAK-994 180 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	7	7	8	
Units: participants				
PR Interval (msec): ≥200	0	1	2	
QTcF Interval (msec): ≥30 CFB and >450	1	0	0	
QRS Duration (msec): ≤80	4	0	5	

Statistical analyses

No statistical analyses for this end point

Primary: Parts B and C: Change From Baseline in Average Sleep Latency as Assessed by the Maintenance of Wakefulness Test (MWT)

End point title	Parts B and C: Change From Baseline in Average Sleep Latency as Assessed by the Maintenance of Wakefulness Test (MWT)[9]

End point description:

MWT: validated, objective measure that evaluates person's ability to remain awake under soporific conditions for defined period. During each MWT session (1 session=40 minutes), participants were instructed to sit quietly and remain awake for as long as possible. Sleep latency in each session was recorded on electroencephalography (EEG). If no sleep had been observed according to these rules, then latency= 40 minutes. Mixed-effect model for repeated measures (MMRM) was used for analysis. Due to early termination of the study, no post-baseline efficacy data for this outcome measure was collected and analysed for participants in Part C: TAK-994 180 mg. Full Analysis Set included participants who received at least 1 dose of study drug, had baseline measure and at least 1 evaluable post-dose value. Number of subjects analysed is the number of participants available for analyses.

End point type	Primary

End point timeframe:

Baseline and Week 8 (Day 56) in Parts B and C

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only the drug-treated arms for Parts B and C were to be analysed for this endpoint.

End point values	Part B: Placebo	Part B: TAK-994 30 mg	Part B: TAK-994 90 mg	Part B: TAK-994 180 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	9	11	9
Units: minutes (mins)				
least squares mean (standard error)	-2.5 (± 2.19)	23.9 (± 2.27)	27.4 (± 2.17)	32.6 (± 2.25)

End point values	Part C: TAK-994 180 mg			
Subject group type	Reporting group			
Number of subjects analysed	0[10]			
Units: minutes (mins)				
least squares mean (standard error)	()			

Notes:

[10] - Due to early termination of the study no data was collected and analysed.

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Part B: TAK-994 30 mg v Part B: Placebo
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [11]
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	26.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	20.07
upper limit	32.73
Variability estimate	Standard error of the mean
Dispersion value	3.15

Notes:

[11] - The analysis used a linear MMRM with fixed effects for baseline (Day -1 mean values), treatment, visit, and treatment-by-visit interaction. Visit was repeated factor in the model. The unstructured covariance structure was used for repeated statement.

Statistical analysis title	Statistical Analysis 2
Comparison groups	Part B: Placebo v Part B: TAK-994 90 mg
Number of subjects included in analysis	23
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [12]
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	29.9

Confidence interval	
level	95 %
sides	2-sided
lower limit	23.68
upper limit	36.07
Variability estimate	Standard error of the mean
Dispersion value	3.08

Notes:

[12] - The analysis used a linear MMRM with fixed effects for baseline (Day -1 mean values), treatment, visit, and treatment-by-visit interaction. Visit was repeated factor in the model. The unstructured covariance structure was used for repeated statement.

Statistical analysis title	Statistical Analysis 3
Comparison groups	Part B: Placebo v Part B: TAK-994 180 mg
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [13]
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	35
Confidence interval	
level	95 %
sides	2-sided
lower limit	28.73
upper limit	41.34
Variability estimate	Standard error of the mean
Dispersion value	3.14

Notes:

[13] - The analysis used a linear MMRM with fixed effects for baseline (Day -1 mean values), treatment, visit, and treatment-by-visit interaction. Visit was repeated factor in the model. The unstructured covariance structure was used for repeated statement.

Secondary: Part A: Cmax: Maximum Observed Plasma Concentration After Single Dose of TAK-994 at Day 1

End point title	Part A: Cmax: Maximum Observed Plasma Concentration After Single Dose of TAK-994 at Day 1[14]

End point description:

Pharmacokinetic (PK) Analysis Set included all participants who received at least 1 dose of TAK-994 and had at least 1 measurable plasma concentration. Number of subjects analysed is the number of participants available for analyses.

End point type	Secondary

End point timeframe:

Pre-dose and at multiple time points (up to 14 hours) post-dose at Day 1 in Part A

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only the drug-treated arms for Part A were to be analysed for this endpoint.

End point values	Part A: TAK-994 120 mg	Part A: TAK-994 180 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	8		
Units: nanograms per milliliter (ng/mL)				
geometric mean (geometric coefficient of variation)				
Cmax (ng/mL); Following First (AM) Dose at Day 1	305.5 (± 68.3)	679.1 (± 24.5)		
Cmax (ng/mL); Following Second (PM) Dose at Day 1	437.1 (± 46.9)	1127 (± 26.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Tmax: Time of First Occurrence of Cmax After Single Dose of TAK-994 at Day 1

End point title	Part A: Tmax: Time of First Occurrence of Cmax After Single Dose of TAK-994 at Day 1[15]

End point description:

PK Analysis Set included all participants who received at least 1 dose of TAK-994 and had at least 1 measurable plasma concentration. Number of subjects analysed is the number of participants available for analyses.

End point type	Secondary

End point timeframe:

Pre-dose and at multiple time points (Up to 14 hours) post-dose at Day 1 in Part A

Notes:

[15] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only the drug-treated arms for Part A were to be analysed for this endpoint.

End point values	Part A: TAK-994 120 mg	Part A: TAK-994 180 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	8		
Units: hours (h)				
median (full range (min-max))				
Tmax (h): Following First (AM) Dose at Day 1	1.19 (1.00 to 5.03)	1.00 (1.00 to 5.00)		
Tmax (h): Following Second (PM) Dose at Day 1	2.04 (1.02 to 4.00)	1.75 (1.42 to 2.08)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: AUC(0-last): Area Under the Concentration-time Curve From Time 0 to Time of the Last Quantifiable Concentration After Single Dose of TAK-994

at Day 1

End point title	Part A: AUC(0-last): Area Under the Concentration-time Curve From Time 0 to Time of the Last Quantifiable Concentration After Single Dose of TAK-994 at Day 1[16]

End point description:

PK Analysis Set included all participants who received at least 1 dose of TAK-994 and had at least 1 measurable plasma concentration. Number of subjects analysed is the number of participants available for analyses.

End point type	Secondary

End point timeframe:

Pre-dose and at multiple time points (up to 24 hours) post-dose at Day 1 in Part A

Notes:

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only the drug-treated arms for Part A were to be analysed for this endpoint.

End point values	Part A: TAK-994 120 mg	Part A: TAK-994 180 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	8		
Units: nanograms*hour per milliliter (ng*h/mL)				
geometric mean (geometric coefficient of variation)	3700 (± 63.0)	8559 (± 26.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Cmax: Maximum Observed Plasma Concentration After Multiple Doses of TAK-994 at Day 28

End point title	Part A: Cmax: Maximum Observed Plasma Concentration After Multiple Doses of TAK-994 at Day 28[17]

End point description:

PK Analysis Set included all participants who received at least 1 dose of TAK-994 and had at least 1 measurable plasma concentration.

End point type	Secondary

End point timeframe:

Pre-dose and at multiple time points (up to 14 hours) post-dose at Day 28 in Part A

Notes:

[17] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only the drug-treated arms for Part A were to be analysed for this endpoint.

End point values	Part A: TAK-994 120 mg	Part A: TAK-994 180 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	8		
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
Cmax (ng/mL); Following First (AM) Dose at Day 28	377.5 (± 36.6)	856.9 (± 31.6)		
Cmax (ng/mL); Following Second (PM) Dose at Day 28	416.0 (± 40.9)	829.4 (± 28.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Tmax: Time of First Occurrence of Cmax After Multiple Doses of TAK-994 at Day 28

End point title	Part A: Tmax: Time of First Occurrence of Cmax After Multiple Doses of TAK-994 at Day 28[18]

End point description:

PK analysis set included all participants who received at least 1 dose of TAK-994 and had at least 1 measurable plasma concentration.

End point type	Secondary

End point timeframe:

Pre-dose and at multiple time points (up to 14 hours) post-dose at Day 28 in Part A

Notes:

[18] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only the drug-treated arms for Part A were to be analysed for this endpoint.

End point values	Part A: TAK-994 120 mg	Part A: TAK-994 180 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	8		
Units: hours (h)				
median (full range (min-max))				
Tmax (h): Following First (AM) Dose at Day 28	1.03 (0.93 to 3.10)	1.00 (0.90 to 1.00)		
Tmax (h): Following Second (PM) Dose at Day 28	2.15 (2.00 to 4.05)	3.46 (1.50 to 7.00)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: AUC(0-t): Area Under the Concentration-time Curve From Time 0 to Time Tau Over a Dosing Interval of TAK-994 at Day 28

End point title	Part A: AUC(0-t): Area Under the Concentration-time Curve

	From Time 0 to Time Tau Over a Dosing Interval of TAK-994 at Day 28[19]

End point description:

PK analysis set included all participants who received at least 1 dose of TAK-994 and had at least 1 measurable plasma concentration.

End point type	Secondary

End point timeframe:

Pre-dose and at multiple time points (Up to 12 hours) post-dose at Day 28 in Part A

Notes:

[19] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only the drug-treated arms for Part A were to be analysed for this endpoint.

End point values	Part A: TAK-994 120 mg	Part A: TAK-994 180 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	8		
Units: ng*h/mL				
geometric mean (geometric coefficient of variation)	2968 (± 33.1)	6438 (± 22.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Parts B and C: Change From Baseline in the Epworth Sleepiness Scale (ESS) Total Score to Week 8

End point title	Parts B and C: Change From Baseline in the Epworth Sleepiness Scale (ESS) Total Score to Week 8[20]

End point description:

The ESS is a subjective, self-administered, validated scale (scored 0 to 3) to respond to each of the 8 questions of daily life that asks participants how likely they are to fall asleep in those situations. The scores are summed to give an overall score of 0 to 24. Higher scores indicate stronger subjective daytime sleepiness, and scores below 10 are considered to be within the normal range. MMRM was used for analysis. Due to early termination of the study, no post-baseline efficacy data for this outcome measure was collected and analysed for participants in Part C: TAK-994 180 mg.
Full Analysis Set included participants who received at least 1 dose of study drug, had baseline measure and at least 1 evaluable post-dose value. Number of subjects analysed is the number of participants available for analyses.

End point type	Secondary

End point timeframe:

Baseline and Week 8 (Day 56) in Parts B and C

Notes:

[20] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only the drug-treated arms for Parts B and C were to be analysed for this endpoint.

End point values	Part B: Placebo	Part B: TAK-994 30 mg	Part B: TAK-994 90 mg	Part B: TAK-994 180 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	10	11	9
Units: score on a scale				
least squares mean (standard error)	-2.1 (± 1.35)	-12.2 (± 1.41)	-13.5 (± 1.32)	-15.1 (± 1.41)

End point values	Part C: TAK-994 180 mg			
Subject group type	Reporting group			
Number of subjects analysed	0[21]			
Units: score on a scale				
least squares mean (standard error)	()			

Notes:

[21] - Due to early termination of the study, no data was collected and analyzed.

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Part B: Placebo v Part B: TAK-994 30 mg
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [22]
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	-10.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.07
upper limit	-6.16
Variability estimate	Standard error of the mean
Dispersion value	1.96

Notes:

[22] - The analysis used a linear MMRM with fixed effects for baseline (Day -1 mean values), treatment, visit, and treatment-by-visit interaction. Visit was repeated factor in the model. The unstructured covariance structure was used for repeated statement.

Statistical analysis title	Statistical Analysis 2
Comparison groups	Part B: Placebo v Part B: TAK-994 90 mg
Number of subjects included in analysis	23
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [23]
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	-11.4

Confidence interval	
level	95 %
sides	2-sided
lower limit	-15.2
upper limit	-7.56
Variability estimate	Standard error of the mean
Dispersion value	1.89

Notes:

[23] - The analysis used a linear MMRM with fixed effects for baseline (Day -1 mean values), treatment, visit, and treatment-by-visit interaction. Visit was repeated factor in the model. The unstructured covariance structure was used for repeated statement.

Statistical analysis title	Statistical Analysis 3
Comparison groups	Part B: Placebo v Part B: TAK-994 180 mg
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [24]
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	-13
Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.96
upper limit	-9.09
Variability estimate	Standard error of the mean
Dispersion value	1.95

Notes:

[24] - The analysis used a linear MMRM with fixed effects for baseline (Day -1 mean values), treatment, visit, and treatment-by-visit interaction. Visit was repeated factor in the model. The unstructured covariance structure was used for repeated statement.

Secondary: Parts B and C: Change From Baseline in Weekly Cataplexy Rate (WCR) at Week 8

End point title	Parts B and C: Change From Baseline in Weekly Cataplexy Rate (WCR) at Week 8[25]

End point description:

Participants will complete a daily patient-reported sleep diary to record self-reported narcolepsy symptoms. Participants will record episodes of cataplexy in the diary. The total number of events averaged for a week will be reported. WCR = (Total number of cataplexy over a number of non-missing diary days for a given duration/number of Non-missing diary days in that duration)*7. MMRM was used for the analysis. Due to early termination of the study, no secondary efficacy data was collected and analysed for participants in Part C: TAK-994 180 mg.
Full Analysis Set included participants who received at least 1 dose of study drug, had baseline measure and at least 1 evaluable post-dose value. Number of subjects analysed is the number of participants available for analyses.

End point type	Secondary

End point timeframe:

Baseline and Week 8 (Day 56) in Parts B and C

Notes:

[25] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only the drug-treated arms for Parts B and C were to be analysed for this endpoint.

End point values	Part B: Placebo	Part B: TAK-994 30 mg	Part B: TAK-994 90 mg	Part B: TAK-994 180 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	10	11	8
Units: cataplexy attacks per week				
arithmetic mean (standard deviation)	-6.58 (± 7.433)	-16.17 (± 20.979)	-11.91 (± 10.174)	-15.74 (± 9.978)

End point values	Part C: TAK-994 180 mg			
Subject group type	Reporting group			
Number of subjects analysed	0[26]			
Units: cataplexy attacks per week				
arithmetic mean (standard deviation)	()			

Notes:

[26] - Due to early termination of the study, no data was collected and analysed.

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Part B: Placebo v Part B: TAK-994 30 mg
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002 [27]
Method	MMRM
Parameter estimate	IRR
Point estimate	0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.007
upper limit	0.317

Notes:

[27] - Incidence rate was the exponentiated LS means and the incidence rate ratio (IRR) was exponentiated LS mean differences from generalized estimating equation (GEE) Poisson regression model which with natural log link was on count of cataplexy per week.

Statistical analysis title	Statistical Analysis 2
Comparison groups	Part B: Placebo v Part B: TAK-994 90 mg
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.019 [28]
Method	MMRM
Parameter estimate	IRR
Point estimate	0.2

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.05
upper limit	0.767

Notes:

[28] - The incidence rate was the exponentiated LS means and the IRR was the exponentiated LS mean differences from the GEE Poisson regression model. The Poisson regression with natural log link was on the count of cataplexy per week.

Statistical analysis title	Statistical Analysis 3
Comparison groups	Part B: Placebo v Part B: TAK-994 180 mg
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001 [29]
Method	MMRM
Parameter estimate	IRR
Point estimate	0.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.047
upper limit	0.482

Notes:

[29] - The incidence rate was the exponentiated LS means and the IRR was the exponentiated LS mean differences from the GEE Poisson regression model. The Poisson regression with natural log link was on the count of cataplexy per week.

Secondary: Parts B and C: Number of Participants Who Experience at Least 1 TEAE During the Study

End point title	Parts B and C: Number of Participants Who Experience at Least 1 TEAE During the Study[30]

End point description:

An AE is defined as any untoward medical occurrence in a clinical investigation participant administered a drug; it does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (example, a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, whether or not it is considered related to the drug. A TEAE is defined as an AE with an onset that occurs after receiving study drug.
Safety Analysis Set included all participants who were randomised and received at least 1 dose of the study drug.

End point type	Secondary

End point timeframe:

First dose of study drug to end of study follow-up (up to Day 63) in Parts B and C

Notes:

[30] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only the drug-treated arms for Parts B and C were to be analysed for this endpoint.

End point values	Part B: Placebo	Part B: TAK-994 30 mg	Part B: TAK-994 90 mg	Part B: TAK-994 180 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	17	17	20	19
Units: participants	4	13	17	14

End point values	Part C: TAK-994 180 mg			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: participants	2			

Statistical analyses

No statistical analyses for this end point

Secondary: Parts B and C: Number of Participants Who Met the Markedly Abnormal Value (MAV) Criteria for Safety Laboratory Tests at Least Once Postdose During the Study

End point title	Parts B and C: Number of Participants Who Met the Markedly Abnormal Value (MAV) Criteria for Safety Laboratory Tests at Least Once Postdose During the Study[31]

End point description:

Standard safety laboratory values (serum chemistry, hematology, and urine analysis) were collected and compared to pre-specified criteria for MAV throughout the study. MAV criteria: Alanine Aminotransferase (ALT) [(U/L)]:>3xULN, Aspartate Aminotransferase (AST) [(U/L)]:>3xULN; Bilirubin micromoles/litre (umol/L):>1.5xULN; Calcium(mmol/L):<1.92, >2.77; Potassium(mmol/L):<3.0, >5.3. Only categories with at least one participant with event are reported.
Safety Analysis Set included all participants who were randomised and received at least 1 dose of the study drug.

End point type	Secondary

End point timeframe:

Up to Day 63 in Parts B and C

Notes:

[31] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only the drug-treated arms for Parts B and C were to be analysed for this endpoint.

End point values	Part B: Placebo	Part B: TAK-994 30 mg	Part B: TAK-994 90 mg	Part B: TAK-994 180 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	17	17	20	19
Units: participants				
ALT [U/L)]: >3 × ULN	0	0	3	2
AST (U/L): >3 × ULN	0	0	1	2
Bilirubin (µmol/L): >1.5 × ULN	0	0	0	1
Calcium (mmol/L): <1.92	1	0	0	0
Potassium (mmol/L): <3.0	1	0	0	0
Potassium (mmol/L): >5.3	1	1	0	0

End point values	Part C: TAK-994 180 mg			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: participants				
ALT [U/L)]: >3 × ULN	0			
AST (U/L): >3 × ULN	0			
Bilirubin (µmol/L): >1.5 × ULN	0			
Calcium (mmol/L): <1.92	0			
Potassium (mmol/L): <3.0	0			
Potassium (mmol/L): >5.3	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Parts B and C: Number of Participants Who Met the Markedly Abnormal Value (MAV) Criteria for Vital Sign Measurements at Least Once Postdose During the Study

End point title	Parts B and C: Number of Participants Who Met the Markedly Abnormal Value (MAV) Criteria for Vital Sign Measurements at Least Once Postdose During the Study[32]

End point description:

Vital signs (body temperature and sitting blood pressure) were collected and compared to pre-specified criteria for MAVs throughout the study. MAV criteria: SBP (mmHg): <90, ≥160, Change from Pre-Dose >20, Change from Pre-Dose >30, Time-matched CFB > 20, Time-matched CFB > 30; DBP (mmHg): <50, ≥100, Change from Pre-Dose >20, Change from Pre-Dose >30, Time-matched CFB > 20, Time-matched CFB > 30; Respiratory Rate (breaths/min): >21. Only categories with at least one participant with event are reported.
Safety Analysis Set included all participants who were randomised and received at least 1 dose of the study drug.

End point type	Secondary

End point timeframe:

Up to Day 63 in Parts B and C

Notes:

[32] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only the drug-treated arms for Parts B and C were to be analysed for this endpoint.

End point values	Part B: Placebo	Part B: TAK-994 30 mg	Part B: TAK-994 90 mg	Part B: TAK-994 180 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	17	17	20	19
Units: participants				
SBP (mmHg): <90	2	3	1	1
SBP (mmHg): >= 160	1	0	0	1
SBP (mmHg): Change from Predose > 20	5	7	10	10

SBP (mmHg): Change from Predose >30	2	2	6	5
SBP (mmHg): Time-matched CFB >20	2	11	13	14
SBP (mmHg): Time-matched CFB >30	1	4	3	5
DBP (mmHg): <50	0	1	1	2
DBP (mmHg): >=100	1	1	2	2
DBP (mmHg): Change from Predose >20	0	3	5	9
DBP (mmHg): Change from Predose >30	0	0	1	3
DBP (mmHg): Time-matched CFB >20	2	5	7	7
DBP (mmHg): Time-matched CFB >30	0	0	1	2
Respiratory Rate (breaths/minute): >21	0	2	0	1

End point values	Part C: TAK-994 180 mg			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: participants				
SBP (mmHg): <90	1			
SBP (mmHg): >= 160	0			
SBP (mmHg): Change from Predose > 20	0			
SBP (mmHg): Change from Predose >30	0			
SBP (mmHg): Time-matched CFB >20	1			
SBP (mmHg): Time-matched CFB >30	0			
DBP (mmHg): <50	0			
DBP (mmHg): >=100	1			
DBP (mmHg): Change from Predose >20	0			
DBP (mmHg): Change from Predose >30	0			
DBP (mmHg): Time-matched CFB >20	0			
DBP (mmHg): Time-matched CFB >30	0			
Respiratory Rate (breaths/minute): >21	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Parts B and C: Number of Participants Who Met the Markedly Abnormal Value (MAV) Criteria for ECG Parameters at Least Once Postdose During the Study

End point title	Parts B and C: Number of Participants Who Met the Markedly Abnormal Value (MAV) Criteria for ECG Parameters at Least Once Postdose During the Study[33]

End point description:

A 12 lead ECG was performed, the ECG values were compared to pre-specified criteria for markedly abnormal values. MAV criteria: PR Interval (msec): ≤80, ≥200; QRS Duration (msec): ≤80, ≥180. Only categories with at least one participant with event are reported.
Safety Analysis Set included all participants who were randomised and received at least 1 dose of the

study drug.

End point type	Secondary

End point timeframe:

Up to Day 63 in Parts B and C

Notes:

[33] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only the drug-treated arms for Parts B and C were to be analysed for this endpoint.

End point values	Part B: Placebo	Part B: TAK-994 30 mg	Part B: TAK-994 90 mg	Part B: TAK-994 180 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	17	17	20	19
Units: participants				
PR Interval (msec): >=200	2	2	1	3
QRS Duration (msec):<=80	4	3	7	4

End point values	Part C: TAK-994 180 mg			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: participants				
PR Interval (msec): >=200	0			
QRS Duration (msec):<=80	0			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

First dose of study treatment to end of study follow-up (up to Day 35 in Part A and up to Day 63 in Parts B and C)

Adverse event reporting additional description:

At each visit the investigator had to document any occurrence of adverse events and abnormal laboratory findings. Any event spontaneously reported by the participant or observed by the investigator was recorded, irrespective of the relation to study treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	Part A: Placebo

Reporting group description:

TAK-994 placebo-matching tablets, orally, BID for 28 days, in participants with NT1.

Reporting group title	Part A: TAK-994 120 mg

Reporting group description:

TAK-994 120 mg, orally, BID for 28 days, in participants with NT1.

Reporting group title	Part A: TAK-994 180 mg

Reporting group description:

TAK-994 180 mg, orally, BID for 28 days, in participants with NT1.

Reporting group title	Part B: Placebo

Reporting group description:

TAK-994 placebo-matching tablets, orally, BID for 56 days, in participants with NT1.

Reporting group title	Part B: TAK-994 90 mg

Reporting group description:

TAK-994 90 mg tablets, orally, BID for 56 days, in participants with NT1.

Reporting group title	Part B: TAK-994 30 mg

Reporting group description:

TAK-994 30 mg tablets, orally, BID for 56 days, in participants with NT1.

Reporting group title	Part B: TAK-994 180 mg

Reporting group description:

TAK-994 180 mg tablets, orally, BID for 56 days, in participants with NT1.

Reporting group title	Part C: TAK-994 180 mg

Reporting group description:

TAK-994 180 mg tablets, orally, BID for 56 days, in Chinese participants with NT1.

Serious adverse events	Part A: Placebo	Part A: TAK-994 120 mg	Part A: TAK-994 180 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 8 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Hepatobiliary disorders			
Hepatitis acute			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 8 (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	Part B: Placebo	Part B: TAK-994 90 mg	Part B: TAK-994 30 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	0 / 17 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Hepatobiliary disorders			
Hepatitis acute			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	0 / 17 (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	Part B: TAK-994 180 mg	Part C: TAK-994 180 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 19 (5.26%)	0 / 2 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Hepatobiliary disorders			
Hepatitis acute			
subjects affected / exposed	1 / 19 (5.26%)	0 / 2 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Part A: Placebo	Part A: TAK-994 120 mg	Part A: TAK-994 180 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 7 (28.57%)	6 / 7 (85.71%)	7 / 8 (87.50%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Pleomorphic adenoma			

subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Fatigue			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Feeling jittery			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Injection site pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Puncture site erythema			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Social circumstances			
Ex-tobacco user			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Vulvovaginal inflammation			

subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Sneezing			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	2 / 8 (25.00%)
occurrences (all)	0	1	2
Anxiety			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Agitation			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Hypervigilance			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Initial insomnia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Middle insomnia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Sleep disorder			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Suicidal ideation			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Investigations			
Glutamate dehydrogenase increased			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Alanine aminotransferase increased			

subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Blood pressure increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Blood creatinine increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Blood pressure diastolic increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Blood pressure systolic increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Blood urea increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Hepatic enzyme increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Weight increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Heart rate increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Skin laceration			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Contusion			

subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Vaccination complication			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Tachycardia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Dizziness			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Paraesthesia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Tension headache			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Tremor			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Granulocytopenia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Vision blurred			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Blepharospasm			

subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Salivary hypersecretion			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	3 / 8 (37.50%)
occurrences (all)	0	1	3
Nausea			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Abdominal pain upper			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Constipation			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Faeces discoloured			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Faeces hard			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Diarrhoea			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Abdominal mass			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Dyspepsia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Vomiting			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Hyperhidrosis			

subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Papule			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Rash papular			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Pollakiuria			
subjects affected / exposed	0 / 7 (0.00%)	3 / 7 (42.86%)	5 / 8 (62.50%)
occurrences (all)	0	4	5
Micturition urgency			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	2 / 8 (25.00%)
occurrences (all)	0	1	2
Polyuria			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Dysuria			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Haematuria			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Hypertonic bladder			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Urinary tract pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Urinary incontinence			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			

Rotator cuff syndrome			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Muscle twitching			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Acute sinusitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Bacterial disease carrier			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Gastroenteritis viral			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Giardiasis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Urinary tract infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Decreased appetite			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Increased appetite			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 8 (0.00%)
occurrences (all)	0	1	0

Non-serious adverse events	Part B: Placebo	Part B: TAK-994 90 mg	Part B: TAK-994 30 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 17 (23.53%)	17 / 20 (85.00%)	13 / 17 (76.47%)

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Pleomorphic adenoma			
subjects affected / exposed	0 / 17 (0.00%)	1 / 20 (5.00%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Fatigue			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Feeling jittery			
subjects affected / exposed	1 / 17 (5.88%)	0 / 20 (0.00%)	0 / 17 (0.00%)
occurrences (all)	1	0	0
Injection site pain			
subjects affected / exposed	0 / 17 (0.00%)	1 / 20 (5.00%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
Puncture site erythema			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Social circumstances			
Ex-tobacco user			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	0 / 17 (0.00%)	1 / 20 (5.00%)	0 / 17 (0.00%)
occurrences (all)	0	1	0

Vulvovaginal inflammation			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Sneezing			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 17 (5.88%)	2 / 20 (10.00%)	0 / 17 (0.00%)
occurrences (all)	1	2	0
Anxiety			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Agitation			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Hypervigilance			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Initial insomnia			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Middle insomnia			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Sleep disorder			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Suicidal ideation			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Investigations			
Glutamate dehydrogenase increased			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0

Alanine aminotransferase increased			
subjects affected / exposed	0 / 17 (0.00%)	4 / 20 (20.00%)	0 / 17 (0.00%)
occurrences (all)	0	5	0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 17 (0.00%)	2 / 20 (10.00%)	0 / 17 (0.00%)
occurrences (all)	0	2	0
Blood pressure increased			
subjects affected / exposed	0 / 17 (0.00%)	2 / 20 (10.00%)	0 / 17 (0.00%)
occurrences (all)	0	3	0
Blood creatinine increased			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Blood pressure diastolic increased			
subjects affected / exposed	0 / 17 (0.00%)	1 / 20 (5.00%)	0 / 17 (0.00%)
occurrences (all)	0	2	0
Blood pressure systolic increased			
subjects affected / exposed	0 / 17 (0.00%)	1 / 20 (5.00%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
Blood urea increased			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Hepatic enzyme increased			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Weight increased			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Heart rate increased			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Skin laceration			
subjects affected / exposed	1 / 17 (5.88%)	0 / 20 (0.00%)	1 / 17 (5.88%)
occurrences (all)	1	0	1
Contusion			

subjects affected / exposed	1 / 17 (5.88%)	0 / 20 (0.00%)	0 / 17 (0.00%)
occurrences (all)	1	0	0
Vaccination complication			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Tachycardia			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 17 (0.00%)	1 / 20 (5.00%)	4 / 17 (23.53%)
occurrences (all)	0	1	7
Dizziness			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Paraesthesia			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Tension headache			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Tremor			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Granulocytopenia			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Vision blurred			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Blepharospasm			

subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Salivary hypersecretion			
subjects affected / exposed	0 / 17 (0.00%)	3 / 20 (15.00%)	0 / 17 (0.00%)
occurrences (all)	0	3	0
Nausea			
subjects affected / exposed	0 / 17 (0.00%)	3 / 20 (15.00%)	1 / 17 (5.88%)
occurrences (all)	0	3	1
Abdominal pain upper			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Constipation			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Faeces discoloured			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Faeces hard			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Diarrhoea			
subjects affected / exposed	1 / 17 (5.88%)	0 / 20 (0.00%)	1 / 17 (5.88%)
occurrences (all)	1	0	1
Abdominal mass			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Dyspepsia			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Vomiting			
subjects affected / exposed	0 / 17 (0.00%)	1 / 20 (5.00%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Hyperhidrosis			

subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Papule			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Rash papular			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Pollakiuria			
subjects affected / exposed	1 / 17 (5.88%)	10 / 20 (50.00%)	5 / 17 (29.41%)
occurrences (all)	1	10	5
Micturition urgency			
subjects affected / exposed	1 / 17 (5.88%)	10 / 20 (50.00%)	5 / 17 (29.41%)
occurrences (all)	1	10	5
Polyuria			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Dysuria			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Haematuria			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Hypertonic bladder			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Urinary tract pain			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Urinary incontinence			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			

Rotator cuff syndrome			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Muscle twitching			
subjects affected / exposed	1 / 17 (5.88%)	0 / 20 (0.00%)	0 / 17 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Acute sinusitis			
subjects affected / exposed	1 / 17 (5.88%)	0 / 20 (0.00%)	0 / 17 (0.00%)
occurrences (all)	1	0	0
Bacterial disease carrier			
subjects affected / exposed	0 / 17 (0.00%)	1 / 20 (5.00%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
Gastroenteritis viral			
subjects affected / exposed	0 / 17 (0.00%)	1 / 20 (5.00%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
Giardiasis			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Urinary tract infection			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Decreased appetite			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Increased appetite			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Part B: TAK-994 180 mg	Part C: TAK-994 180 mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 19 (73.68%)	2 / 2 (100.00%)	

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Pleomorphic adenoma			
subjects affected / exposed	0 / 19 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 19 (5.26%)	0 / 2 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 19 (0.00%)	1 / 2 (50.00%)	
occurrences (all)	0	1	
Fatigue			
subjects affected / exposed	1 / 19 (5.26%)	0 / 2 (0.00%)	
occurrences (all)	1	0	
Feeling jittery			
subjects affected / exposed	0 / 19 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Injection site pain			
subjects affected / exposed	0 / 19 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Puncture site erythema			
subjects affected / exposed	1 / 19 (5.26%)	0 / 2 (0.00%)	
occurrences (all)	1	0	
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	0 / 19 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Social circumstances			
Ex-tobacco user			
subjects affected / exposed	1 / 19 (5.26%)	0 / 2 (0.00%)	
occurrences (all)	1	0	
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	0 / 19 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	

Vulvovaginal inflammation			
subjects affected / exposed	0 / 19 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Respiratory, thoracic and mediastinal disorders			
Sneezing			
subjects affected / exposed	0 / 19 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	3 / 19 (15.79%)	2 / 2 (100.00%)	
occurrences (all)	3	4	
Anxiety			
subjects affected / exposed	2 / 19 (10.53%)	0 / 2 (0.00%)	
occurrences (all)	2	0	
Agitation			
subjects affected / exposed	0 / 19 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Hypervigilance			
subjects affected / exposed	0 / 19 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Initial insomnia			
subjects affected / exposed	1 / 19 (5.26%)	0 / 2 (0.00%)	
occurrences (all)	1	0	
Middle insomnia			
subjects affected / exposed	1 / 19 (5.26%)	0 / 2 (0.00%)	
occurrences (all)	1	0	
Sleep disorder			
subjects affected / exposed	1 / 19 (5.26%)	0 / 2 (0.00%)	
occurrences (all)	1	0	
Suicidal ideation			
subjects affected / exposed	1 / 19 (5.26%)	0 / 2 (0.00%)	
occurrences (all)	1	0	
Investigations			
Glutamate dehydrogenase increased			
subjects affected / exposed	0 / 19 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	

Alanine aminotransferase increased			
subjects affected / exposed	1 / 19 (5.26%)	0 / 2 (0.00%)	
occurrences (all)	1	0	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 19 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Blood pressure increased			
subjects affected / exposed	0 / 19 (0.00%)	1 / 2 (50.00%)	
occurrences (all)	0	1	
Blood creatinine increased			
subjects affected / exposed	0 / 19 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Blood pressure diastolic increased			
subjects affected / exposed	0 / 19 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Blood pressure systolic increased			
subjects affected / exposed	0 / 19 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Blood urea increased			
subjects affected / exposed	0 / 19 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Hepatic enzyme increased			
subjects affected / exposed	1 / 19 (5.26%)	0 / 2 (0.00%)	
occurrences (all)	1	0	
Weight increased			
subjects affected / exposed	1 / 19 (5.26%)	0 / 2 (0.00%)	
occurrences (all)	1	0	
Heart rate increased			
subjects affected / exposed	0 / 19 (0.00%)	1 / 2 (50.00%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Skin laceration			
subjects affected / exposed	0 / 19 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Contusion			

subjects affected / exposed	0 / 19 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Vaccination complication			
subjects affected / exposed	1 / 19 (5.26%)	0 / 2 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
Palpitations			
subjects affected / exposed	1 / 19 (5.26%)	0 / 2 (0.00%)	
occurrences (all)	1	0	
Tachycardia			
subjects affected / exposed	1 / 19 (5.26%)	0 / 2 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 19 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Dizziness			
subjects affected / exposed	1 / 19 (5.26%)	1 / 2 (50.00%)	
occurrences (all)	1	2	
Paraesthesia			
subjects affected / exposed	0 / 19 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Tension headache			
subjects affected / exposed	0 / 19 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Tremor			
subjects affected / exposed	0 / 19 (0.00%)	1 / 2 (50.00%)	
occurrences (all)	0	2	
Blood and lymphatic system disorders			
Granulocytopenia			
subjects affected / exposed	1 / 19 (5.26%)	0 / 2 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
Vision blurred			
subjects affected / exposed	1 / 19 (5.26%)	0 / 2 (0.00%)	
occurrences (all)	1	0	
Blepharospasm			

subjects affected / exposed	1 / 19 (5.26%)	0 / 2 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Salivary hypersecretion			
subjects affected / exposed	2 / 19 (10.53%)	1 / 2 (50.00%)	
occurrences (all)	2	1	
Nausea			
subjects affected / exposed	1 / 19 (5.26%)	0 / 2 (0.00%)	
occurrences (all)	1	0	
Abdominal pain upper			
subjects affected / exposed	0 / 19 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Constipation			
subjects affected / exposed	0 / 19 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Faeces discoloured			
subjects affected / exposed	0 / 19 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Faeces hard			
subjects affected / exposed	0 / 19 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Diarrhoea			
subjects affected / exposed	0 / 19 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Abdominal mass			
subjects affected / exposed	0 / 19 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Dyspepsia			
subjects affected / exposed	0 / 19 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Vomiting			
subjects affected / exposed	0 / 19 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Skin and subcutaneous tissue disorders			
Hyperhidrosis			

subjects affected / exposed	2 / 19 (10.53%)	2 / 2 (100.00%)	
occurrences (all)	2	2	
Papule			
subjects affected / exposed	1 / 19 (5.26%)	0 / 2 (0.00%)	
occurrences (all)	1	0	
Rash papular			
subjects affected / exposed	1 / 19 (5.26%)	0 / 2 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Pollakiuria			
subjects affected / exposed	6 / 19 (31.58%)	2 / 2 (100.00%)	
occurrences (all)	7	2	
Micturition urgency			
subjects affected / exposed	8 / 19 (42.11%)	1 / 2 (50.00%)	
occurrences (all)	9	1	
Polyuria			
subjects affected / exposed	0 / 19 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Dysuria			
subjects affected / exposed	1 / 19 (5.26%)	0 / 2 (0.00%)	
occurrences (all)	1	0	
Haematuria			
subjects affected / exposed	1 / 19 (5.26%)	0 / 2 (0.00%)	
occurrences (all)	1	0	
Hypertonic bladder			
subjects affected / exposed	1 / 19 (5.26%)	0 / 2 (0.00%)	
occurrences (all)	2	0	
Urinary tract pain			
subjects affected / exposed	1 / 19 (5.26%)	0 / 2 (0.00%)	
occurrences (all)	1	0	
Urinary incontinence			
subjects affected / exposed	0 / 19 (0.00%)	1 / 2 (50.00%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			

Rotator cuff syndrome			
subjects affected / exposed	0 / 19 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Muscle twitching			
subjects affected / exposed	0 / 19 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Infections and infestations			
Acute sinusitis			
subjects affected / exposed	0 / 19 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Bacterial disease carrier			
subjects affected / exposed	0 / 19 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Gastroenteritis viral			
subjects affected / exposed	0 / 19 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Giardiasis			
subjects affected / exposed	0 / 19 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Urinary tract infection			
subjects affected / exposed	1 / 19 (5.26%)	0 / 2 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	0 / 19 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Decreased appetite			
subjects affected / exposed	2 / 19 (10.53%)	0 / 2 (0.00%)	
occurrences (all)	2	0	
Increased appetite			
subjects affected / exposed	0 / 19 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 March 2020	The updates in Amendment 01 include: • The title of the study was updated to include both participants with narcolepsy type 1 (NT1) and narcolepsy type 2 (NT2). • The EudraCT number and study phase were added to the protocol title page. • The number of participating sites was updated. • The baseline period was added to the study duration overview. • Separate study schematics, outlining key study assessments, were added for Cohorts 4 and Cohorts 5 and 6. • Separate schedules of study procedures, outlining all study assessments, were added for Cohorts 4 and Cohorts 5 and 6. • A collection window of 10 minutes was added for the 5-hour PK sampling/assessments on Days 1, 14, and 28. • The information on disease background was updated. • Data from ongoing Study TAK-994-1001 were updated. • "other exploratory objectives" were removed. • Three additional cohorts were included, 1 consisting of 12 to 18 Chinese subjects with NT1 (Cohort 4) and 2, each consisting of 18 subjects with NT2 (Cohorts 5 and 6). • In inclusion criteria, it was specified that screening labs may be repeated once. • In exclusion criteria, the usual bedtime for subjects was changed from 0100 to no later than 2400 (12:00 AM, midnight). • Instructions related to caffeine use were updated. • BP and heart rate limits leading to discontinuation of subjects were updated. • Procedures around study drug blinding were corrected. • Procedures around randomization code creation and storage were corrected. • A strong recommendation for the same clinician to administer the clinical global impression scales at every visit was added. • Instructions of body position and lighting during the MWT were added. • Analysis methods for Cohorts 1 to 6 were updated. • Description of the planned interim analyses was updated. • Determination of sample size was updated enumerating the range of subjects and randomization ratio (study drug: placebo) in Cohorts 4 (China-specific), 5, and 6.
05 June 2020	The updates in Amendment 02 include: • Overall study description changed due to the study design. • Overall number of participants to be enrolled has increased. • Schematics for different parts of the study have been updated according to the updated design. • BMI criteria was updated to in acknowledgment of the comorbidity of obesity in this subject population. • Study objectives and endpoints have been revised to align with the revised design. • Clinical information has been updated based on emerging data from the study TAK-994-1001, including the blinded safety and preliminary PK data. • Instructions related to excluded medications have been revised to accommodate revised study population. • Text has been revised for criteria for discontinuation or withdrawal of a subject. • Text has been revised for study drug supply, randomization, blinding and storage.

15 January 2021	The updates in Amendment 03 include: • Updated to include recent clinical and nonclinical study data. • Change the study eligibility criteria to better define how the presence of cataplexy is established for participants in Part B and C cohorts. • Revised several protocol sections, including the Schedule of Study Procedures to allow more flexibility for the study participants and the site personnel. • Revise the statistical analysis strategy to reduce the number of times the sponsor unblinded team reviews the data.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
05 November 2021	A safety signal has emerged in Phase 2 studies of TAK-994. As an immediate precautionary measure, Takeda has suspended dosing of participants and has decided to stop Phase 2 studies early.	-

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

A safety signal has emerged in Phase 2 studies of TAK-994. As an immediate precautionary measure, Takeda has suspended dosing of participants and has decided to stop Phase 2 studies early.

Notes: