



## Clinical trial results:

### A Randomized, Double-blind, Placebo-Controlled Study to Evaluate the Efficacy, Safety, and Tolerability of TAK-861 for the Treatment of Narcolepsy With Cataplexy (Narcolepsy Type 1)

#### Summary

EudraCT number	2022-001654-38
Trial protocol	FR NO FI SE NL ES
Global end of trial date	14 December 2023

#### Results information

Result version number	v1 (current)
This version publication date	29 December 2024
First version publication date	29 December 2024

#### Trial information

##### Trial identification

Sponsor protocol code	TAK-861-2001
-----------------------	--------------

##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT05687903
WHO universal trial number (UTN)	U1111-1277-4261
Other trial identifiers	jRCT: jRCT2031220644

Notes:

##### Sponsors

Sponsor organisation name	Takeda Development Center Americas, Inc.
Sponsor organisation address	95 Hayden Avenue, Lexington, Massachusetts, United States, 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	14 December 2023
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	14 December 2023
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

The main objective of this study was to assess the effect of TAK-861 on excessive daytime sleepiness (EDS) as measured by sleep latency from the Maintenance of Wakefulness Test (MWT).

Protection of trial subjects:

All study participants or their guardians were required to read and sign an Informed Consent Form (ICF).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	09 January 2023
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 4
Country: Number of subjects enrolled	Germany: 3
Country: Number of subjects enrolled	France: 17
Country: Number of subjects enrolled	Italy: 22
Country: Number of subjects enrolled	Japan: 5
Country: Number of subjects enrolled	Norway: 2
Country: Number of subjects enrolled	Spain: 23
Country: Number of subjects enrolled	Sweden: 1
Country: Number of subjects enrolled	Netherlands: 4
Country: Number of subjects enrolled	Finland: 1
Country: Number of subjects enrolled	Switzerland: 5
Country: Number of subjects enrolled	United States: 25
Worldwide total number of subjects	112
EEA total number of subjects	73

Notes:

### Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	112
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

Participants took part in the study at 33 investigative sites globally from 09 January 2023 to 14 December 2023.

### Pre-assignment

Screening details:

Participants with a diagnosis of narcolepsy type 1 (NT1) were enrolled in the study to receive either TAK-861 or placebo.

### 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

### Arms

Are arms mutually exclusive?	No
------------------------------	----

<b>Arm title</b>	Placebo
------------------	---------

Arm description:

Participants received placebo tablets matching TAK-861, orally, BID, from Days 1 to 56.

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:

Placebo tablets matching TAK-861, orally, twice daily (BID) from Days 1 to 56.

<b>Arm title</b>	TAK-861 0.5 mg BID
------------------	--------------------

Arm description:

Participants received TAK-861 0.5 mg, orally, BID, from Days 1 to 56.

Arm type	Experimental
Investigational medicinal product name	TAK-861
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

TAK-861 at an oral dose of 0.5 mg, administered BID, from Days 1 to 56.

<b>Arm title</b>	TAK-861 2 mg BID
------------------	------------------

Arm description:

Participants received TAK-861 2 mg, orally, BID, from Days 1 to 56.

Arm type	Experimental
----------	--------------

Investigational medicinal product name	TAK-861
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

TAK-861 at an oral dose of 2 mg, administered BID, from Days 1 to 56.

<b>Arm title</b>	TAK-861 2 mg and 5 mg
------------------	-----------------------

Arm description:

Participants received TAK-861 2 mg followed by the 5 mg dose, orally, from Days 1 to 56.

Arm type	Experimental
Investigational medicinal product name	TAK-861
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

TAK-861 at an oral dose of 2 mg and 5 mg, administered BID, from Days 1 to 56.

<b>Arm title</b>	TAK-861 7 mg QD
------------------	-----------------

Arm description:

Participants received TAK-861 7 mg, orally, QD, from Days 1 to 56. Placebo was given as the second dose.

Arm type	Experimental
Investigational medicinal product name	TAK-861
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

TAK-861 at an oral dose of 7.5 mg, administered once daily (QD), from Days 1 to 56.

<b>Number of subjects in period 1</b>	Placebo	TAK-861 0.5 mg BID	TAK-861 2 mg BID
Started	22	23	21
Completed	21	22	21
Not completed	1	1	0
Protocol deviation	1	1	-

<b>Number of subjects in period 1</b>	TAK-861 2 mg and 5 mg	TAK-861 7 mg QD
Started	23	23
Completed	22	23
Not completed	1	0
Protocol deviation	1	-



## Baseline characteristics

### Reporting groups

Reporting group title	Placebo
Reporting group description:	
Participants received placebo tablets matching TAK-861, orally, BID, from Days 1 to 56.	
Reporting group title	TAK-861 0.5 mg BID
Reporting group description:	
Participants received TAK-861 0.5 mg, orally, BID, from Days 1 to 56.	
Reporting group title	TAK-861 2 mg BID
Reporting group description:	
Participants received TAK-861 2 mg, orally, BID, from Days 1 to 56.	
Reporting group title	TAK-861 2 mg and 5 mg
Reporting group description:	
Participants received TAK-861 2 mg followed by the 5 mg dose, orally, from Days 1 to 56.	
Reporting group title	TAK-861 7 mg QD
Reporting group description:	
Participants received TAK-861 7 mg, orally, QD, from Days 1 to 56. Placebo was given as the second dose.	

Reporting group values	Placebo	TAK-861 0.5 mg BID	TAK-861 2 mg BID
Number of subjects	22	23	21
Age Categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean	37.5	32.7	31.7
standard deviation	± 11.86	± 11.06	± 11.31
Gender categorical			
Units: Subjects			
Female	14	11	9
Male	8	12	12
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	3	2	1
Not Hispanic or Latino	19	21	20
Unknown or Not Reported	0	0	0
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	1	2	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	2	1	2
White	19	19	19
More than one race	0	1	0
Unknown or Not Reported	0	0	0

Average Sleep Latency From the Maintenance of Wakefulness Test (MWT)			
The MWT is a validated, objective measure that evaluates a participant'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	6.1	5.6	3.9
standard deviation	± 8.82	± 7.89	± 5.98

Reporting group values	TAK-861 2 mg and 5 mg	TAK-861 7 mg QD	Total
Number of subjects	23	23	112
Age Categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean	34.7	33.3	
standard deviation	± 11.48	± 11.94	-
Gender categorical			
Units: Subjects			
Female	14	10	58
Male	9	13	54
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	0	2	8
Not Hispanic or Latino	23	20	103
Unknown or Not Reported	0	1	1
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	3	2	8
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	1	6
White	19	20	96
More than one race	1	0	2
Unknown or Not Reported	0	0	0
Average Sleep Latency From the Maintenance of Wakefulness Test (MWT)			
The MWT is a validated, objective measure that evaluates a participant'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	4.2	3.6	
standard deviation	± 3.63	± 4.87	-



## End points

### End points reporting groups

Reporting group title	Placebo
Reporting group description: Participants received placebo tablets matching TAK-861, orally, BID, from Days 1 to 56.	
Reporting group title	TAK-861 0.5 mg BID
Reporting group description: Participants received TAK-861 0.5 mg, orally, BID, from Days 1 to 56.	
Reporting group title	TAK-861 2 mg BID
Reporting group description: Participants received TAK-861 2 mg, orally, BID, from Days 1 to 56.	
Reporting group title	TAK-861 2 mg and 5 mg
Reporting group description: Participants received TAK-861 2 mg followed by the 5 mg dose, orally, from Days 1 to 56.	
Reporting group title	TAK-861 7 mg QD
Reporting group description: Participants received TAK-861 7 mg, orally, QD, from Days 1 to 56. Placebo was given as the second dose.	

### Primary: Change From Baseline in the Average Sleep Latency as Determined From the MWT at Week 8

End point title	Change From Baseline in the Average Sleep Latency as Determined From the MWT at Week 8
End point description: The MWT is a validated, objective measure that evaluates a participant'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 EEG. If no sleep was observed according to these rules, then the latency was defined as 40 minutes. The linear mixed effects model for repeated measures (MMRM) was used for analysis. Full Analysis Set included all participants who were randomized and received at least one dose of study drug and had at least one post-dose efficacy measurement. Subjects analysed is the number of participants with data available for analyses.	
End point type	Primary
End point timeframe: Baseline, Week 8	

End point values	Placebo	TAK-861 0.5 mg BID	TAK-861 2 mg BID	TAK-861 2 mg and 5 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	21	19	21	20
Units: minutes				
least squares mean (standard error)				
Week 8	-1.16 (± 2.061)	12.49 (± 2.128)	23.50 (± 2.042)	25.42 (± 2.071)

<b>End point values</b>	TAK-861 7 mg QD			
Subject group type	Reporting group			
Number of subjects analysed	23			
Units: minutes				
least squares mean (standard error)				
Week 8	14.96 ( $\pm$ 1.953)			

## Statistical analyses

<b>Statistical analysis title</b>	Mean Sleep Latency
Comparison groups	Placebo v TAK-861 0.5 mg BID
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001 <sup>[1]</sup>
Method	MMRM
Parameter estimate	Estimate of LS Mean Difference
Point estimate	13.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	7.74
upper limit	19.57
Variability estimate	Standard error of the mean
Dispersion value	2.983

Notes:

[1] - The analysis used a linear MMRM with fixed effects for Baseline, age, prior use of narcolepsy medications, treatment, visit, and treatment-by-visit interaction as covariates. Reported p-value is adjusted for multiplicity.

<b>Statistical analysis title</b>	Mean Sleep Latency From the MWT
Comparison groups	Placebo v TAK-861 2 mg and 5 mg
Number of subjects included in analysis	41
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 <sup>[2]</sup>
Method	MMRM
Parameter estimate	Estimate of LS Mean Difference
Point estimate	26.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	20.81
upper limit	32.35
Variability estimate	Standard error of the mean
Dispersion value	2.91

Notes:

[2] - The analysis used a linear MMRM with fixed effects for Baseline, age, prior use of narcolepsy medications, treatment, visit, and treatment-by-visit interaction as covariates. Reported p-value is adjusted for multiplicity.

<b>Statistical analysis title</b>	Mean Sleep Latency From the MWT
Comparison groups	Placebo v TAK-861 7 mg QD
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 <sup>[3]</sup>
Method	MMRM
Parameter estimate	Estimate of LS Mean Difference
Point estimate	16.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	10.49
upper limit	21.76
Variability estimate	Standard error of the mean
Dispersion value	2.842

Notes:

[3] - The analysis used a linear MMRM with fixed effects for Baseline, age, prior use of narcolepsy medications, treatment, visit, and treatment-by-visit interaction as covariates. Reported p-value is adjusted for multiplicity.

<b>Statistical analysis title</b>	Mean Sleep Latency From the MWT
Comparison groups	Placebo v TAK-861 2 mg BID
Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 <sup>[4]</sup>
Method	MMRM
Parameter estimate	Estimate of LS Mean Difference
Point estimate	24.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	18.87
upper limit	30.46
Variability estimate	Standard error of the mean
Dispersion value	2.921

Notes:

[4] - The analysis used a linear MMRM with fixed effects for Baseline, age, prior use of narcolepsy medications, treatment, visit, and treatment-by-visit interaction as covariates. Reported p-value is adjusted for multiplicity.

## Secondary: Change From Baseline in Epworth Sleepiness Scale (ESS) Total Score at Week 8

End point title	Change From Baseline in Epworth Sleepiness Scale (ESS) Total
-----------------	--------------------------------------------------------------

## 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. The MMRM was used for analysis. Full Analysis Set included all participants who were randomized and received at least one dose of study drug and had at least one post-dose efficacy measurement. Subjects analysed is the number of participants with data available for analyses.

End point type	Secondary
----------------	-----------

End point timeframe:	
----------------------	--

Baseline, Week 8	
------------------	--

End point values	Placebo	TAK-861 0.5 mg BID	TAK-861 2 mg BID	TAK-861 2 mg and 5 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	21	21	21	22
Units: score on a scale				
least squares mean (standard error)	-2.50 ( $\pm$ 1.109)	-8.92 ( $\pm$ 1.085)	-13.79 ( $\pm$ 1.115)	-12.81 ( $\pm$ 1.073)

End point values	TAK-861 7 mg QD			
Subject group type	Reporting group			
Number of subjects analysed	23			
Units: score on a scale				
least squares mean (standard error)	-11.29 ( $\pm$ 1.064)			

## Statistical analyses

Statistical analysis title	ESS Total Score at Week 8
Comparison groups	Placebo v TAK-861 0.5 mg BID
Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004 <sup>[5]</sup>
Method	MMRM
Parameter estimate	Estimate of LS Mean Difference
Point estimate	-6.42
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.53
upper limit	-3.32
Variability estimate	Standard error of the mean
Dispersion value	1.564

Notes:

[5] - The analysis used a linear MMRM with fixed effects for Baseline, age, prior use of narcolepsy medications, treatment, visit, and treatment-by-visit interaction as covariates. Reported p-value is adjusted for multiplicity.

<b>Statistical analysis title</b>	Change From Baseline in ESS Total Score at Week 8
Comparison groups	Placebo v TAK-861 2 mg BID
Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 <sup>[6]</sup>
Method	MMRM
Parameter estimate	Estimate of LS Mean Difference
Point estimate	-11.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.44
upper limit	-8.16
Variability estimate	Standard error of the mean
Dispersion value	1.581

Notes:

[6] - The analysis used a linear MMRM with fixed effects for Baseline, age, prior use of narcolepsy medications, treatment, visit, and treatment-by-visit interaction as covariates. Reported p-value is adjusted for multiplicity.

<b>Statistical analysis title</b>	Change From Baseline in ESS Total Score at Week 8
Comparison groups	Placebo v TAK-861 2 mg and 5 mg
Number of subjects included in analysis	43
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 <sup>[7]</sup>
Method	MMRM
Parameter estimate	Estimate of LS Mean Difference
Point estimate	-10.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.35
upper limit	-7.27
Variability estimate	Standard error of the mean
Dispersion value	1.53

Notes:

[7] - The analysis used a linear MMRM with fixed effects for Baseline, age, prior use of narcolepsy medications, treatment, visit, and treatment-by-visit interaction as covariates. Reported p-value is adjusted for multiplicity.

<b>Statistical analysis title</b>	Change From Baseline in ESS Total Score at Week 8
Comparison groups	Placebo v TAK-861 7 mg QD

Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 <sup>[8]</sup>
Method	MMRM
Parameter estimate	Estimate of LS Mean Difference
Point estimate	-8.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.84
upper limit	-5.75
Variability estimate	Standard error of the mean
Dispersion value	1.535

Notes:

[8] - The analysis used a linear MMRM with fixed effects for Baseline, age, prior use of narcolepsy medications, treatment, visit, and treatment-by-visit interaction as covariates. Reported p-value is adjusted for multiplicity.

## Secondary: Weekly Cataplexy Rate (WCR) at Week 8

End point title	Weekly Cataplexy Rate (WCR) at Week 8
End point description:	Participants completed a daily patient-reported sleep diary to record self-reported narcolepsy symptoms. Participants recorded episodes of cataplexy attacks in the diary. The total number of events averaged for a week were reported. $WCR = (\text{total number of cataplexy attacks over a number of non-missing diary days for a given duration/number of non-missing diary days in that duration}) \times 7$ . The generalized estimating equations (GEE) model was used for analysis. Full Analysis Set included all participants who were randomized and received at least one dose of study drug and had at least one post-dose efficacy measurement. Subjects analysed is the number of participants with data available for analyses.
End point type	Secondary
End point timeframe:	
Week 8	

End point values	Placebo	TAK-861 0.5 mg BID	TAK-861 2 mg BID	TAK-861 2 mg and 5 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	20	21	21	22
Units: cataplexy attacks per week				
least squares mean (confidence interval 95%)	8.76 (5.68 to 13.51)	4.24 (2.60 to 6.92)	3.14 (1.65 to 5.98)	2.48 (1.30 to 4.73)

End point values	TAK-861 7 mg QD			
Subject group type	Reporting group			
Number of subjects analysed	23			
Units: cataplexy attacks per week				
least squares mean (confidence interval 95%)	5.89 (3.64 to 9.53)			

## Statistical analyses

<b>Statistical analysis title</b>	WCR at Week 8
Statistical analysis description: The GEE model was used for analysis with fixed effects for visit, treatment, treatment-by-visit interaction, Baseline WCR, age, and prior use of narcolepsy medications.	
Comparison groups	Placebo v TAK-861 0.5 mg BID
Number of subjects included in analysis	41
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.25 <sup>[9]</sup>
Method	GEE
Parameter estimate	IRR
Point estimate	0.48
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.25
upper limit	0.93

Notes:

[9] - GEE model featuring negative binomial distribution was used for analysis where incidence rate was exponentiated LS mean & incidence rate ratio (IRR) was the exponentiated LS mean difference from placebo. Reported p-value is adjusted for multiplicity.

<b>Statistical analysis title</b>	WCR at Week 8
Statistical analysis description: The GEE model was used for analysis with fixed effects for visit, treatment, treatment-by-visit interaction, Baseline WCR, age, and prior use of narcolepsy medications.	
Comparison groups	Placebo v TAK-861 7 mg QD
Number of subjects included in analysis	43
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.25 <sup>[10]</sup>
Method	GEE
Parameter estimate	IRR
Point estimate	0.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.35
upper limit	1.29

Notes:

[10] - The GEE model featuring a negative binomial distribution was used for analysis where the incidence rate was the exponentiated LS mean and the IRR was the exponentiated LS mean difference from placebo. Reported p-value is adjusted for multiplicity.

<b>Statistical analysis title</b>	WCR at Week 8
-----------------------------------	---------------

---

**Statistical analysis description:**

The GEE model was used for analysis with fixed effects for visit, treatment, treatment-by-visit interaction, Baseline WCR, age, and prior use of narcolepsy medications.

Comparison groups	Placebo v TAK-861 2 mg and 5 mg
Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.003 <sup>[11]</sup>
Method	GEE
Parameter estimate	IRR
Point estimate	0.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.13
upper limit	0.6

**Notes:**

[11] - The GEE model featuring a negative binomial distribution was used for analysis where the incidence rate was the exponentiated LS mean and the IRR was the exponentiated LS mean difference from placebo. Reported p-value is adjusted for multiplicity.

---

<b>Statistical analysis title</b>	WCR at Week 8
-----------------------------------	---------------

---

**Statistical analysis description:**

The GEE model was used for analysis with fixed effects for visit, treatment, treatment-by-visit interaction, Baseline WCR, age, and prior use of narcolepsy medications.

Comparison groups	Placebo v TAK-861 2 mg BID
Number of subjects included in analysis	41
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.034 <sup>[12]</sup>
Method	GEE
Parameter estimate	IRR
Point estimate	0.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.16
upper limit	0.79

**Notes:**

[12] - The GEE model featuring a negative binomial distribution was used for analysis where the incidence rate was the exponentiated LS mean and the IRR was the exponentiated LS mean difference from placebo. Reported p-value is adjusted for multiplicity.

---

**Secondary: Number of Participants with at Least One Treatment-emergent Adverse Event (TEAE)**

---

End point title	Number of Participants with at Least One Treatment-emergent Adverse Event (TEAE)
-----------------	----------------------------------------------------------------------------------

---

**End point description:**

An adverse event (AE) was defined as any untoward medical occurrence in a clinical study participant, temporally associated with the use of the study intervention, whether or not the occurrence was considered related to the study intervention. 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 was defined as an AE with an onset that occurred after receiving study drug. Safety Analysis Set included all participants who received at least one dose of study drug. Safety Analysis Set included all participants



who received at least one dose of study drug.

End point type	Secondary
End point timeframe:	
From first dose of the study drug up to end of the study (up to 3 months)	

End point values	Placebo	TAK-861 0.5 mg BID	TAK-861 2 mg BID	TAK-861 2 mg and 5 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	22	23	21	23
Units: participants	7	13	15	21

End point values	TAK-861 7 mg QD			
Subject group type	Reporting group			
Number of subjects analysed	23			
Units: participants	21			

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From first dose of the study drug up to end of the study (up to 3 months)

Adverse event reporting additional description:

Safety Analysis Set included all participants who received at least one dose of study drug.

Assessment type	Systematic
-----------------	------------

### Dictionary used

Dictionary name	MedDRA
-----------------	--------

Dictionary version	26.1
--------------------	------

### Reporting groups

Reporting group title	Placebo
-----------------------	---------

Reporting group description:

Participants received placebo tablets matching TAK-861, orally, BID, from Days 1 to 56.

Reporting group title	TAK-861 0.5 mg BID
-----------------------	--------------------

Reporting group description:

Participants received TAK-861 0.5 mg, orally, BID, from Days 1 to 56.

Reporting group title	TAK-861 2 mg BID
-----------------------	------------------

Reporting group description:

Participants received TAK-861 2 mg, orally, BID, from Days 1 to 56.

Reporting group title	TAK-861 2 mg/5 mg
-----------------------	-------------------

Reporting group description:

Participants received TAK-861 2 mg followed by the 5 mg dose, orally, from Days 1 to 56.

Reporting group title	TAK-861 7 mg QD
-----------------------	-----------------

Reporting group description:

Participants received TAK-861 7 mg, orally, QD, from Days 1 to 56. Placebo was given as the second dose.

Serious adverse events	Placebo	TAK-861 0.5 mg BID	TAK-861 2 mg BID
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 22 (0.00%)	0 / 23 (0.00%)	0 / 21 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	0 / 22 (0.00%)	0 / 23 (0.00%)	0 / 21 (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	TAK-861 2 mg/5 mg	TAK-861 7 mg QD	
Total subjects affected by serious adverse events			

subjects affected / exposed	1 / 23 (4.35%)	0 / 23 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	1 / 23 (4.35%)	0 / 23 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

<b>Non-serious adverse events</b>	Placebo	TAK-861 0.5 mg BID	TAK-861 2 mg BID
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 22 (22.73%)	11 / 23 (47.83%)	15 / 21 (71.43%)
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 22 (0.00%)	0 / 23 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Headache			
subjects affected / exposed	1 / 22 (4.55%)	1 / 23 (4.35%)	3 / 21 (14.29%)
occurrences (all)	2	1	4
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 22 (0.00%)	2 / 23 (8.70%)	0 / 21 (0.00%)
occurrences (all)	0	2	0
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 22 (0.00%)	0 / 23 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Salivary hypersecretion			
subjects affected / exposed	1 / 22 (4.55%)	2 / 23 (8.70%)	2 / 21 (9.52%)
occurrences (all)	1	2	2
Nausea			
subjects affected / exposed	0 / 22 (0.00%)	0 / 23 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			

Epistaxis subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	0 / 23 (0.00%) 0	2 / 21 (9.52%) 2
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1	5 / 23 (21.74%) 5	10 / 21 (47.62%) 10
Middle insomnia subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	1 / 23 (4.35%) 1	0 / 21 (0.00%) 0
Renal and urinary disorders Micturition urgency subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1	5 / 23 (21.74%) 5	4 / 21 (19.05%) 5
Pollakiuria subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1	3 / 23 (13.04%) 3	7 / 21 (33.33%) 8
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	0 / 23 (0.00%) 0	2 / 21 (9.52%) 3
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	0 / 23 (0.00%) 0	0 / 21 (0.00%) 0
Increased appetite subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1	0 / 23 (0.00%) 0	2 / 21 (9.52%) 2

<b>Non-serious adverse events</b>	TAK-861 2 mg/5 mg	TAK-861 7 mg QD	
Total subjects affected by non-serious adverse events subjects affected / exposed	20 / 23 (86.96%)	20 / 23 (86.96%)	
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)	0 / 23 (0.00%) 0	2 / 23 (8.70%) 2	
Headache			

subjects affected / exposed occurrences (all)	2 / 23 (8.70%) 2	2 / 23 (8.70%) 2	
General disorders and administration site conditions Pyrexia subjects affected / exposed occurrences (all)	0 / 23 (0.00%) 0	0 / 23 (0.00%) 0	
Gastrointestinal disorders Constipation subjects affected / exposed occurrences (all)  Salivary hypersecretion subjects affected / exposed occurrences (all)  Nausea subjects affected / exposed occurrences (all)	0 / 23 (0.00%) 0  6 / 23 (26.09%) 6  0 / 23 (0.00%) 0	2 / 23 (8.70%) 2  2 / 23 (8.70%) 2  2 / 23 (8.70%) 2	
Respiratory, thoracic and mediastinal disorders Epistaxis subjects affected / exposed occurrences (all)	0 / 23 (0.00%) 0	0 / 23 (0.00%) 0	
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)  Middle insomnia subjects affected / exposed occurrences (all)	13 / 23 (56.52%) 13  3 / 23 (13.04%) 4	15 / 23 (65.22%) 16  0 / 23 (0.00%) 0	
Renal and urinary disorders Micturition urgency subjects affected / exposed occurrences (all)  Pollakiuria subjects affected / exposed occurrences (all)	12 / 23 (52.17%) 14  7 / 23 (30.43%) 7	9 / 23 (39.13%) 10  12 / 23 (52.17%) 14	
Infections and infestations			

Nasopharyngitis subjects affected / exposed occurrences (all)	2 / 23 (8.70%) 2	2 / 23 (8.70%) 2	
Metabolism and nutrition disorders			
Decreased appetite subjects affected / exposed occurrences (all)	1 / 23 (4.35%) 1	2 / 23 (8.70%) 2	
Increased appetite subjects affected / exposed occurrences (all)	1 / 23 (4.35%) 1	1 / 23 (4.35%) 1	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

---

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported