



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 |
|------------------------------|----|

| | |
|------------------|---------|
| Arm title | 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.

| | |
|------------------|--------------------|
| Arm title | 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.

| | |
|------------------|------------------|
| Arm title | 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.

| | |
|------------------|-----------------------|
| Arm title | 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.

| | |
|------------------|-----------------|
| Arm title | 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.

| Number of subjects in period 1 | 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 | - |

| Number of subjects in period 1 | 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) |

| | | | | |
|-------------------------------------|----------------------|--|--|--|
| End point values | 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

| | |
|---|--------------------------------|
| Statistical analysis title | 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 ^[1] |
| 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.

| | |
|---|---------------------------------|
| Statistical analysis title | 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 ^[2] |
| 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.

| | |
|---|---------------------------------|
| Statistical analysis title | 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 ^[3] |
| 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.

| | |
|---|---------------------------------|
| Statistical analysis title | 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 ^[4] |
| 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 ^[5] |
| 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.

| | |
|---|---|
| Statistical analysis title | 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 ^[6] |
| 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.

| | |
|---|---|
| Statistical analysis title | 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 ^[7] |
| 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.

| | |
|-----------------------------------|---|
| Statistical analysis title | 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 ^[8] |
| 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 = (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)*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

| | |
|---|------------------------------|
| Statistical analysis title | 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 ^[9] |
| 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.

| | |
|---|---------------------------|
| Statistical analysis title | 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 ^[10] |
| 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.

| | |
|-----------------------------------|---------------|
| Statistical analysis title | 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 ^[11] |
| 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.

| | |
|-----------------------------------|---------------|
| Statistical analysis title | 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 ^[12] |
| 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 %

| Non-serious adverse events | 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 |

| | | | |
|---|---------------------|---------------------|--|
| Non-serious adverse events | 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