



Clinical trial results:

An Open-Label, Phase 2a Study to Evaluate the Pharmacodynamics of Different Dosing Regimens of TAK-448, a Kisspeptin Agonist, in Male Overweight/Obese Participants With Hypogonadotropic Hypogonadism Summary

| | |
|--------------------------|------------------|
| EudraCT number | 2014-002155-25 |
| Trial protocol | GB |
| Global end of trial date | 03 November 2015 |

Results information

| | |
|--------------------------------|---|
| Result version number | v3 (current) |
| This version publication date | 01 March 2017 |
| First version publication date | 17 November 2016 |
| Version creation reason | <ul style="list-style-type: none">• Correction of full data set Updates to the Primary endpoint data will be corrected. |

Trial information

Trial identification

| | |
|-----------------------|--------------|
| Sponsor protocol code | TAK-448-2001 |
|-----------------------|--------------|

Additional study identifiers

| | |
|------------------------------------|-----------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02369796 |
| WHO universal trial number (UTN) | U1111-1162-4892 |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Takeda Development Center Americas, Inc. |
| Sponsor organisation address | One Takeda Parkway, Deerfield, United States, IL 60015 |
| Public contact | Medical Director, Clinical Science, Takeda, +1 +18778253327, clinicaltrialregistry@tpna.com |
| Scientific contact | Medical Director, Clinical Science, Takeda, +1 +18778253327, 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 | 03 November 2015 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 08 October 2015 |
| Global end of trial reached? | Yes |
| Global end of trial date | 03 November 2015 |
| Was the trial ended prematurely? | Yes |

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate the effects on serum testosterone (ST) after 4 weeks of subcutaneous (SC) dose administration, with different doses and dosing frequencies of TAK-448 to overweight/obese subjects with hypogonadotropic hypogonadism.

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 | 10 February 2015 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | United Kingdom: 15 |
| Worldwide total number of subjects | 15 |
| EEA total number of subjects | 15 |

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) | 15 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Participants took part in the study at 1 investigative site in the United Kingdom from 10 February 2015 to 3 November 2015.

Pre-assignment

Screening details:

Overweight/obese male participants with a diagnosis of hypogonadotropic hypogonadism were enrolled in 1 of 5 treatment groups: once weekly TAK-448 3 µg, 1 µg or 0.3 µg or twice weekly TAK-448 0.3 µg or 0.1 µg.

Period 1

| | |
|------------------------------|--------------------------------|
| Period 1 title | Overall Study (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|--------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | TAK-448 3 µg once weekly |

Arm description:

TAK-448 3 µg, subcutaneous injection, once weekly on Days 1, 8, 15 and 22.

| | |
|--|--|
| Arm type | Experimental |
| Investigational medicinal product name | TAK-448 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate and solvent for solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

TAK-448 solution for subcutaneous injection

| | |
|------------------|--------------------------|
| Arm title | TAK-448 1 µg once weekly |
|------------------|--------------------------|

Arm description:

TAK-448 1 µg, subcutaneous injection, once weekly on Days 1, 8, 15 and 22.

| | |
|--|--|
| Arm type | Experimental |
| Investigational medicinal product name | TAK-448 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate and solvent for solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

TAK-448 solution for subcutaneous injection.

| | |
|------------------|----------------------------|
| Arm title | TAK-448 0.3 µg once weekly |
|------------------|----------------------------|

Arm description:

TAK-448 0.3 µg, subcutaneous injection, once weekly on Days 1, 8, 15 and 22.

| | |
|--|--|
| Arm type | Experimental |
| Investigational medicinal product name | TAK-448 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate and solvent for solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:
TAK-448 solution for subcutaneous injection.

| | |
|---|--|
| Arm title | TAK-448 0.3 µg twice weekly |
| Arm description: TAK-448 0.3 µg, subcutaneous injection, twice weekly on Days 1, 4, 8, 11, 15, 18, 22, and 25. | |
| Arm type | Experimental |
| Investigational medicinal product name | TAK-448 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate and solvent for solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:
TAK-448 solution for subcutaneous injection.

| | |
|---|--|
| Arm title | TAK-448 0.1 µg twice weekly |
| Arm description: TAK-448 0.1 µg, subcutaneous injection, twice weekly on Days 1, 4, 8, 11, 15, 18, 22, and 25. | |
| Arm type | Experimental |
| Investigational medicinal product name | TAK-448 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate and solvent for solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:
TAK-448 solution for subcutaneous injection.

| Number of subjects in period 1 | TAK-448 3 µg once weekly | TAK-448 1 µg once weekly | TAK-448 0.3 µg once weekly |
|---------------------------------------|--------------------------|--------------------------|----------------------------|
| Started | 3 | 3 | 3 |
| Completed | 3 | 3 | 3 |

| Number of subjects in period 1 | TAK-448 0.3 µg twice weekly | TAK-448 0.1 µg twice weekly |
|---------------------------------------|-----------------------------|-----------------------------|
| Started | 3 | 3 |
| Completed | 3 | 3 |

Baseline characteristics

Reporting groups

| | |
|---|-----------------------------|
| Reporting group title | TAK-448 3 µg once weekly |
| Reporting group description: TAK-448 3 µg, subcutaneous injection, once weekly on Days 1, 8, 15 and 22. | |
| Reporting group title | TAK-448 1 µg once weekly |
| Reporting group description: TAK-448 1 µg, subcutaneous injection, once weekly on Days 1, 8, 15 and 22. | |
| Reporting group title | TAK-448 0.3 µg once weekly |
| Reporting group description: TAK-448 0.3 µg, subcutaneous injection, once weekly on Days 1, 8, 15 and 22. | |
| Reporting group title | TAK-448 0.3 µg twice weekly |
| Reporting group description: TAK-448 0.3 µg, subcutaneous injection, twice weekly on Days 1, 4, 8, 11, 15, 18, 22, and 25. | |
| Reporting group title | TAK-448 0.1 µg twice weekly |
| Reporting group description: TAK-448 0.1 µg, subcutaneous injection, twice weekly on Days 1, 4, 8, 11, 15, 18, 22, and 25. | |

| Reporting group values | TAK-448 3 µg once weekly | TAK-448 1 µg once weekly | TAK-448 0.3 µg once weekly |
|------------------------|--------------------------|--------------------------|----------------------------|
| Number of subjects | 3 | 3 | 3 |
| Age categorical | | | |
| Units: Subjects | | | |
| Adults (18-64 years) | 3 | 3 | 3 |
| Age Continuous | | | |
| Units: years | | | |
| arithmetic mean | 50.7 | 50.7 | 51.7 |
| standard deviation | ± 8.02 | ± 4.62 | ± 3.79 |
| Gender, Male/Female | | | |
| Units: participants | | | |
| Female | 0 | 0 | 0 |
| Male | 3 | 3 | 3 |
| Race | | | |
| Units: Subjects | | | |
| Asian | 2 | 0 | 0 |
| White | 1 | 3 | 3 |
| Smoking Classification | | | |
| Units: Subjects | | | |
| Has never smoked | 3 | 0 | 0 |
| Is current smoker | 0 | 0 | 1 |
| Is an ex-smoker | 0 | 3 | 2 |
| Alcohol Classification | | | |
| Units: Subjects | | | |
| Has never drunk | 0 | 0 | 1 |
| Is current drinker | 3 | 2 | 1 |
| Is an ex-drinker | 0 | 1 | 1 |
| Caffeine Consumption | | | |
| Units: Subjects | | | |

| | | | |
|---|------|------|------|
| Yes | 3 | 3 | 3 |
| No | 0 | 0 | 0 |
| Region of Enrollment: United Kingdom Units: Subjects | | | |
| Subjects | 3 | 3 | 3 |
| Study Specific Characteristic Height Units: cm | | | |
| arithmetic mean | 168 | 174 | 181 |
| standard deviation | ± 7 | ± 6 | ± 18 |
| Study Specific Characteristic Weight Units: kg | | | |
| arithmetic mean | 104 | 113 | 119 |
| standard deviation | ± 30 | ± 10 | ± 26 |
| Study Specific Characteristic Body Mass Index Units: kg/m ² | | | |
| arithmetic mean | 36 | 37 | 36 |
| standard deviation | ± 8 | ± 1 | ± 2 |

| Reporting group values | TAK-448 0.3 µg twice weekly | TAK-448 0.1 µg twice weekly | Total |
|--|--------------------------------|--------------------------------|-------|
| Number of subjects | 3 | 3 | 15 |
| Age categorical Units: Subjects | | | |
| Adults (18-64 years) | 3 | 3 | 15 |
| Age Continuous Units: years | | | |
| arithmetic mean | 56 | 45 | - |
| standard deviation | ± 3.61 | ± 19.16 | |
| Gender, Male/Female Units: participants | | | |
| Female | 0 | 0 | 0 |
| Male | 3 | 3 | 15 |
| Race Units: Subjects | | | |
| Asian | 0 | 0 | 2 |
| White | 3 | 3 | 13 |
| Smoking Classification Units: Subjects | | | |
| Has never smoked | 1 | 1 | 5 |
| Is current smoker | 0 | 0 | 1 |
| Is an ex-smoker | 2 | 2 | 9 |
| Alcohol Classification Units: Subjects | | | |
| Has never drunk | 0 | 0 | 1 |
| Is current drinker | 2 | 2 | 10 |
| Is an ex-drinker | 1 | 1 | 4 |
| Caffeine Consumption Units: Subjects | | | |
| Yes | 2 | 3 | 14 |
| No | 1 | 0 | 1 |
| Region of Enrollment: United Kingdom | | | |

| | | | |
|-----------------|---|---|----|
| Units: Subjects | | | |
| Subjects | 3 | 3 | 15 |

| | | | |
|---|------------|-------------|---|
| Study Specific Characteristic Height Units: cm arithmetic mean standard deviation | 178 ± 6 | 178 ± 12 | - |
| Study Specific Characteristic Weight Units: kg arithmetic mean standard deviation | 115 ± 7 | 110 ± 26 | - |
| Study Specific Characteristic Body Mass Index Units: kg/m ² arithmetic mean standard deviation | 36 ± 2 | 34 ± 4 | - |

End points

End points reporting groups

| | |
|---|-----------------------------|
| Reporting group title | TAK-448 3 µg once weekly |
| Reporting group description: TAK-448 3 µg, subcutaneous injection, once weekly on Days 1, 8, 15 and 22. | |
| Reporting group title | TAK-448 1 µg once weekly |
| Reporting group description: TAK-448 1 µg, subcutaneous injection, once weekly on Days 1, 8, 15 and 22. | |
| Reporting group title | TAK-448 0.3 µg once weekly |
| Reporting group description: TAK-448 0.3 µg, subcutaneous injection, once weekly on Days 1, 8, 15 and 22. | |
| Reporting group title | TAK-448 0.3 µg twice weekly |
| Reporting group description: TAK-448 0.3 µg, subcutaneous injection, twice weekly on Days 1, 4, 8, 11, 15, 18, 22, and 25. | |
| Reporting group title | TAK-448 0.1 µg twice weekly |
| Reporting group description: TAK-448 0.1 µg, subcutaneous injection, twice weekly on Days 1, 4, 8, 11, 15, 18, 22, and 25. | |

Primary: Percent Change from Baseline in Mean Area Under the Effect Curve from Time 0 to 72 hours (AUEC72) of Total Serum Testosterone for Once Weekly Dosing Groups

| | |
|--|---|
| End point title | Percent Change from Baseline in Mean Area Under the Effect Curve from Time 0 to 72 hours (AUEC72) of Total Serum Testosterone for Once Weekly Dosing Groups ^{[1][2]} |
| End point description: Area under the pharmacodynamic (PD) total serum testosterone (ST) concentration-time curve from the time 0 to 72 hours, calculated using the linear trapezoidal rule for baseline profile and those obtained after first and last dose. PD set included all participants who received at least one dose of study drug and had at least 1 valid PD measure. | |
| End point type | Primary |
| End point timeframe: Baseline and Day 22 pre-dose and multiple time points (up to 72 hours) post dose | |

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: This endpoint was planned to be assessed on baseline and Day 22 pre-dose and multiple time points (up to 72 hours) post dose in once weekly arm group.

[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: This endpoint was planned to be assessed on baseline and Day 22 pre-dose and multiple time points (up to 72 hours) post dose in once weekly arm group.

| End point values | TAK-448 3 µg once weekly | TAK-448 1 µg once weekly | TAK-448 0.3 µg once weekly | |
|--------------------------------------|--------------------------|--------------------------|----------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 3 | 3 | 3 | |
| Units: percent change | | | | |
| arithmetic mean (standard deviation) | 1.9 (± 11.3) | 13.5 (± 24.9) | 14.9 (± 16.3) | |

Statistical analyses

No statistical analyses for this end point

Primary: Percent Change from Baseline in Mean Area Under the Effect Curve from Time 0 to 72 hours (AUEC72) of Total Serum Testosterone for Twice Weekly Dosing Groups

| | |
|-----------------|--|
| End point title | Percent Change from Baseline in Mean Area Under the Effect Curve from Time 0 to 72 hours (AUEC72) of Total Serum Testosterone for Twice Weekly Dosing Groups ^{[3][4]} |
|-----------------|--|

End point description:

Area under the PD total ST concentration-time curve from the time 0 to 72 hours, calculated using the linear trapezoidal rule for baseline profile and those obtained after first and last dose. PD set included all participants who received at least one dose of study drug and had at least 1 valid PD measure.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Baseline and Day 25 pre-dose and multiple time points (up to 72 hours) post dose

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: This endpoint was planned to be assessed on baseline and Day 22 pre-dose and multiple time points (up to 72 hours) post dose in once weekly arm group.

[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: This endpoint was planned to be assessed on baseline and Day 25 pre-dose and multiple time points (up to 72 hours) post dose in twice weekly arm group.

| End point values | TAK-448 0.3 µg twice weekly | TAK-448 0.1 µg twice weekly | | |
|--------------------------------------|-----------------------------------|-----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 3 | 3 | | |
| Units: percent change | | | | |
| arithmetic mean (standard deviation) | -2.8 (± 3.7) | 6 (± 12.3) | | |

Statistical analyses

No statistical analyses for this end point

Primary: Percent Change from Baseline in Mean Area Under the Effect Curve from Time 0 to 72 hours (AUEC72) of Free Serum Testosterone for Once Weekly Dosing Groups

| | |
|-----------------|--|
| End point title | Percent Change from Baseline in Mean Area Under the Effect Curve from Time 0 to 72 hours (AUEC72) of Free Serum Testosterone for Once Weekly Dosing Groups ^{[5][6]} |
|-----------------|--|

End point description:

Area under the PD free ST concentration-time curve from the time 0 to 72 hours, calculated using the linear trapezoidal rule for baseline profile and those obtained after first and last dose. PD set included all

participants who received at least one dose of study drug and had at least 1 valid PD measure.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Baseline and Day 22 pre-dose and multiple time points (up to 72 hours) post dose

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: This endpoint was planned to be assessed on baseline and Day 22 pre-dose and multiple time points (up to 72 hours) post dose in once weekly arm group.

[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: This endpoint was planned to be assessed on baseline and Day 22 pre-dose and multiple time points (up to 72 hours) post dose in once weekly arm group.

| End point values | TAK-448 3 µg once weekly | TAK-448 1 µg once weekly | TAK-448 0.3 µg once weekly | |
|--------------------------------------|-----------------------------|-----------------------------|-------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 3 | 3 | 3 | |
| Units: percent change | | | | |
| arithmetic mean (standard deviation) | 3.55 (± 9.08) | 11.1 (± 28) | 7.92 (± 8.88) | |

Statistical analyses

No statistical analyses for this end point

Primary: Percent Change from Baseline in Mean Area Under the Effect Curve from Time 0 to 72 hours (AUEC72) of Free Serum Testosterone for Twice Weekly Dosing Groups

| | |
|-----------------|---|
| End point title | Percent Change from Baseline in Mean Area Under the Effect Curve from Time 0 to 72 hours (AUEC72) of Free Serum Testosterone for Twice Weekly Dosing Groups ^[7] ^[8] |
|-----------------|---|

End point description:

Area under the PD free ST concentration-time curve from the time 0 to 72 hours, calculated using the linear trapezoidal rule for baseline profile and those obtained after first and last dose. PD set included all participants who received at least one dose of study drug and had at least 1 valid PD measure.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Baseline and Day 25 pre-dose and multiple time points (up to 72 hours) post dose

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: This endpoint was planned to be assessed on baseline and Day 25 pre-dose and multiple time points (up to 72 hours) post dose in twice weekly arm group.

[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: This endpoint was planned to be assessed on baseline and Day 25 pre-dose and multiple time points (up to 72 hours) post dose in twice weekly arm group.

| End point values | TAK-448 0.3 µg twice weekly | TAK-448 0.1 µg twice weekly | | |
|--------------------------------------|-----------------------------------|-----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 3 | 3 | | |
| Units: percent change | | | | |
| arithmetic mean (standard deviation) | -9 (± 4.232) | 20.48 (± 5.329) | | |

Statistical analyses

No statistical analyses for this end point

Primary: Trough Serum Concentration (Ctough) of Total Serum Testosterone for Once Weekly Dosing Groups

| | |
|-----------------|--|
| End point title | Trough Serum Concentration (Ctough) of Total Serum Testosterone for Once Weekly Dosing Groups ^{[9][10]} |
|-----------------|--|

End point description:

Trough serum concentration of total ST, defined as lowest baseline concentration compared to pre-dose of the last dose. PD set included all participants who received at least one dose of study drug and had at least 1 valid PD measure.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Day 22 pre-dose

Notes:

[9] - 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 statistics were planned for this endpoint.

[10] - 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: This endpoint was planned to be assessed on baseline and Day 22 pre-dose and multiple time points (up to 72 hours) post dose in once weekly arm group.

| End point values | TAK-448 3 µg once weekly | TAK-448 1 µg once weekly | TAK-448 0.3 µg once weekly | |
|--------------------------------------|-----------------------------|-----------------------------|-------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 3 | 3 | 3 | |
| Units: nmol/L | | | | |
| arithmetic mean (standard deviation) | 5.4 (± 1.3) | 4.4 (± 3.1) | 8.7 (± 1.3) | |

Statistical analyses

No statistical analyses for this end point

Primary: Trough Serum Concentration (Ctough) of Total Serum Testosterone for Twice Weekly Dosing Group

| | |
|-----------------|---|
| End point title | Trough Serum Concentration (Ctough) of Total Serum Testosterone for Twice Weekly Dosing Group ^{[11][12]} |
|-----------------|---|

End point description:

Trough serum concentration of total ST, defined as lowest baseline concentration compared to pre-dose of the last dose. PD set included all participants who received at least one dose of study drug and had at least 1 valid PD measure.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Day 25 pre-dose

Notes:

[11] - 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: This endpoint was planned to be assessed on baseline and Day 25 pre-dose and multiple time points (up to 72 hours) post dose in twice weekly arm group.

[12] - 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: This endpoint was planned to be assessed on baseline and Day 25 pre-dose and multiple time points (up to 72 hours) post dose in twice weekly arm group.

| End point values | TAK-448 0.3 µg twice weekly | TAK-448 0.1 µg twice weekly | | |
|--------------------------------------|-----------------------------------|-----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 3 | 3 | | |
| Units: nmol/L | | | | |
| arithmetic mean (standard deviation) | 4.7 (± 2.8) | 6.9 (± 2.1) | | |

Statistical analyses

No statistical analyses for this end point

Primary: Trough Serum Concentration (Ctrough) of Free Serum Testosterone for Once Weekly Dosing Groups

| | |
|-----------------|---|
| End point title | Trough Serum Concentration (Ctrough) of Free Serum Testosterone for Once Weekly Dosing Groups ^{[13][14]} |
|-----------------|---|

End point description:

Trough serum concentration of free ST, defined as lowest baseline concentration compared to pre-dose of the last dose. PD set included all participants who received at least one dose of study drug and had at least 1 valid PD measure. Number of participants analyzed is number of participants evaluated for this endpoint.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Day 22 pre-dose

Notes:

[13] - 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: This endpoint was planned to be assessed on baseline and Day 22 pre-dose and multiple time points (up to 72 hours) post dose in once weekly arm group.

[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: This endpoint was planned to be assessed on baseline and Day 22 pre-dose and multiple time points (up to 72 hours) post dose in once weekly arm group.

| End point values | TAK-448 3 µg once weekly | TAK-448 1 µg once weekly | TAK-448 0.3 µg once weekly | |
|--------------------------------------|-----------------------------|-----------------------------|-------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 3 | 3 | 2 | |
| Units: nmol/L | | | | |
| arithmetic mean (standard deviation) | 0.16 (± 0.03) | 0.12 (± 0.07) | 0.21 (± 0.004) | |

Statistical analyses

No statistical analyses for this end point

Primary: Trough Serum Concentration (C_{trough}) of Free Serum Testosterone for Twice Weekly Dosing Groups

| | |
|-----------------|---|
| End point title | Trough Serum Concentration (C _{trough}) of Free Serum Testosterone for Twice Weekly Dosing Groups ^{[15][16]} |
|-----------------|---|

End point description:

Trough serum concentration of free ST, defined as lowest baseline concentration compared to pre-dose of the last dose. PD set included all participants who received at least one dose of study drug and had at least 1 valid PD measure.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Day 25 pre-dose

Notes:

[15] - 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 statistics were planned for this endpoint.

[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: This endpoint was planned to be assessed on baseline and Day 25 pre-dose and multiple time points (up to 72 hours) post dose in twice weekly arm group.

| End point values | TAK-448 0.3 µg twice weekly | TAK-448 0.1 µg twice weekly | | |
|--------------------------------------|-----------------------------------|-----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 3 | 3 | | |
| Units: nmol/L | | | | |
| arithmetic mean (standard deviation) | 0.12 (± 0.09) | 0.2 (± 0.06) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: C_{max}: Mean Maximum Observed Plasma Concentration for TAK-448 Free Base Form (TAK-448F)

| | |
|-----------------|---|
| End point title | C _{max} : Mean Maximum Observed Plasma Concentration for TAK-448 Free Base Form (TAK-448F) ^[17] |
|-----------------|---|

End point description:

Maximum observed plasma concentration (C_{max}) is the peak plasma concentration of a drug after

administration, obtained directly from the plasma concentration-time curve. 99999=NA (data was not estimable as plasma concentration was below the lower level of quantification [LLOQ]). Pharmacokinetic (PK) set included all participants who received at least one dose of study drug and had at least 1 measurable concentration of TAK-448F.

| | |
|---|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Day 1 and Day 22 pre-dose and at multiple time points (up to 8 hours) post-dose | |

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: PK endpoints were conducted in PK population (once weekly arm group).

| End point values | TAK-448 3 µg once weekly | TAK-448 1 µg once weekly | TAK-448 0.3 µg once weekly | |
|--------------------------------------|-----------------------------|-----------------------------|-------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 3 | 3 | 1 | |
| Units: pg/mL | | | | |
| arithmetic mean (standard deviation) | | | | |
| Day 1 | 39.5 (± 4.943) | 10.46 (± 1.484) | 99999 (± 99999) | |
| Day 22 | 40.1 (± 6.344) | 12.27 (± 3.618) | 99999 (± 99999) | |

Statistical analyses

No statistical analyses for this end point

Secondary: AUC(0-∞): Mean Area Under the Plasma Concentration-time Curve from Time 0 to Infinity for TAK-448F

| | |
|-----------------|--|
| End point title | AUC(0-∞): Mean Area Under the Plasma Concentration-time Curve from Time 0 to Infinity for TAK-448F ^[18] |
|-----------------|--|

End point description:

AUC(0-∞) is a measure of total plasma exposure to the drug from time zero extrapolated to infinity. 9999 = NA (No participant was analysed at this time point.), 999999 = NA (Only 1 participant was analysed at this time point) and 99999=NA (data was not estimable as plasma concentration was below LLOQ). PK set included all participants who received at least one dose of study drug and had at least 1 measurable concentration of TAK-448F. Here, 'n' is the participants who were analyzed at specific time point.

| | |
|---|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Day 1 and Day 22 pre-dose and at multiple time points (up to 8 hours) post-dose | |

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: PK endpoints were conducted in PK population (once weekly arm group).

| End point values | TAK-448 3 µg once weekly | TAK-448 1 µg once weekly | TAK-448 0.3 µg once weekly | |
|--------------------------------------|-----------------------------|-----------------------------|-------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 3 | 1 | 1 | |
| Units: pg*hr/mL | | | | |
| arithmetic mean (standard deviation) | | | | |
| Day 1 (n=3, 0, 1) | 112 (± 5.686) | 9999 (± 9999) | 99999 (± 99999) | |
| Day 22 (n=3, 1, 1) | 122.33 (± 10.477) | 33.3 (± 999999) | 99999 (± 99999) | |

Statistical analyses

No statistical analyses for this end point

Secondary: AUC(0-tlqc): Mean Area Under the Plasma Concentration-Time Curve From Time 0 to the Time of the Last Quantifiable Concentration for TAK-448F

| | |
|-----------------|--|
| End point title | AUC(0-tlqc): Mean Area Under the Plasma Concentration-Time Curve From Time 0 to the Time of the Last Quantifiable Concentration for TAK-448F ^[19] |
|-----------------|--|

End point description:

AUC(0-tlqc) is a measure of total plasma exposure to the drug from Time 0 to Time of the Last Quantifiable Concentration (AUC[0-tlqc]). 99999 = NA (data was not estimable as plasma concentration was below LLOQ). PK set included all participants who received at least one dose of study drug and had at least 1 measurable concentration of TAK-448F.

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

End point timeframe:

Day 1 and Day 22 pre-dose and at multiple time points (up to 8 hours) post-dose

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: Pharmacokinetic (PK) endpoints were conducted in PK population (once weekly arm group).

| End point values | TAK-448 3 µg once weekly | TAK-448 1 µg once weekly | TAK-448 0.3 µg once weekly | |
|--------------------------------------|-----------------------------|-----------------------------|-------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 3 | 3 | 1 | |
| Units: pg*hr/mL | | | | |
| arithmetic mean (standard deviation) | | | | |
| Day 1 | 92.23 (± 6.732) | 19 (± 3.47) | 99999 (± 99999) | |
| Day 22 | 95.2 (± 11.914) | 18.37 (± 3.069) | 99999 (± 99999) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Terminal Phase Elimination Half-life (T1/2) for TAK-448F

| | |
|-----------------|---|
| End point title | Mean Terminal Phase Elimination Half-life (T1/2) for TAK- |
|-----------------|---|

End point description:

Terminal Phase Elimination Half-life (T1/2) is the time required for half of the drug to be eliminated from the plasma. 9999 = NA (No participant was analysed at this time point.), 999999 = NA (Only 1 participant was analysed at this time point) and 99999=NA (data was not estimable as plasma concentration was below LLOQ). PK set included all participants who received at least one dose of study drug and had at least 1 measurable concentration of TAK-448F. Here, 'n' is the participants who were analyzed at specific time point.

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

End point timeframe:

Day 1 and Day 22 pre-dose and at multiple time points (up to 8 hours) post-dose

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: PK endpoints were conducted in PK population (once weekly arm group).

| End point values | TAK-448 3 µg once weekly | TAK-448 1 µg once weekly | TAK-448 0.3 µg once weekly | |
|--------------------------------------|-----------------------------|-----------------------------|-------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 3 | 1 | 1 | |
| Units: hr | | | | |
| arithmetic mean (standard deviation) | | | | |
| Day 1 (n=3, 0 , 1) | 1.8 (± 0.0751) | 9999 (± 9999) | 99999 (± 99999) | |
| Day 22 (n=3, 1, 1) | 2.073 (± 0.192) | 1.15 (± 999999) | 99999 (± 99999) | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Day 1 up to Day 39

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 | 18.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|--------------------------|
| Reporting group title | TAK-448 3 µg once weekly |
|-----------------------|--------------------------|

Reporting group description:

TAK-448 3 µg, subcutaneous injection, once weekly on Days 1, 8, 15 and 22.

| | |
|-----------------------|--------------------------|
| Reporting group title | TAK-448 1 µg once weekly |
|-----------------------|--------------------------|

Reporting group description:

TAK-448 1 µg, subcutaneous injection, once weekly on Days 1, 8, 15 and 22.

| | |
|-----------------------|----------------------------|
| Reporting group title | TAK-448 0.3 µg once weekly |
|-----------------------|----------------------------|

Reporting group description:

TAK-448 0.3 µg, subcutaneous injection, once weekly on Days 1, 8, 15 and 22.

| | |
|-----------------------|-----------------------------|
| Reporting group title | TAK-448 0.3 µg twice weekly |
|-----------------------|-----------------------------|

Reporting group description:

TAK-448 0.3 µg, subcutaneous injection, twice weekly on Days 1, 4, 8, 11, 15, 18, 22, and 25.

| | |
|-----------------------|-----------------------------|
| Reporting group title | TAK-448 0.1 µg twice weekly |
|-----------------------|-----------------------------|

Reporting group description:

TAK-448 0.1 µg, subcutaneous injection, twice weekly on Days 1, 4, 8, 11, 15, 18, 22, and 25.

| Serious adverse events | TAK-448 3 µg once weekly | TAK-448 1 µg once weekly | TAK-448 0.3 µg once weekly |
|---|--------------------------|--------------------------|----------------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |

| Serious adverse events | TAK-448 0.3 µg twice weekly | TAK-448 0.1 µg twice weekly | |
|---|-----------------------------|-----------------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |

Frequency threshold for reporting non-serious adverse events: 0 %

| Non-serious adverse events | TAK-448 3 µg once weekly | TAK-448 1 µg once weekly | TAK-448 0.3 µg once weekly |
|---|--------------------------|--------------------------|----------------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 1 / 3 (33.33%) | 1 / 3 (33.33%) |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 3 (33.33%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Dizziness | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Hypoaesthesia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Eye disorders | | | |
| Eye haemorrhage | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 0 | 0 | 2 |
| Skin and subcutaneous tissue disorders | | | |
| Acne | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| Non-serious adverse events | TAK-448 0.3 µg twice weekly | TAK-448 0.1 µg twice weekly | |
|---|-----------------------------|-----------------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 3 / 3 (100.00%) | 1 / 3 (33.33%) | |
| Nervous system disorders | | | |

| | | | |
|---|----------------|----------------|--|
| Headache | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 1 / 3 (33.33%) | |
| occurrences (all) | 1 | 1 | |
| Dizziness | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Hypoaesthesia | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 3 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Eye disorders | | | |
| Eye haemorrhage | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 3 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Acne | | | |
| subjects affected / exposed | 2 / 3 (66.67%) | 0 / 3 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 3 (33.33%) | |
| occurrences (all) | 0 | 1 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|--|
| 24 September 2014 | The purpose of this amendment was to update the protocol regarding addition of clinical laboratory testing. |
| 29 September 2014 | The purpose of this amendment was to update the protocol regarding frequency of vital signs, electrocardiograms (ECG), and the addition of a Data Monitoring Committee (DMC). |
| 19 June 2015 | The purpose of this amendment was to allow greater flexibility with dose levels of TAK-448 and the frequency of administration based on available data from dosed subjects, to remove the requirement that subjects should be diagnosed with type 2 diabetes mellitus and to remove the requirement for an Independent Monitoring Committee. |
| 22 October 2015 | The primary purpose of this amendment was to update the details of the new Chief Investigator for the study. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported