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	• 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	178	178	
standard deviation	± 6	± 12	-
Study Specific Characteristic | Weight			
Units: kg			
arithmetic mean	115	110	
standard deviation	± 7	± 26	-
Study Specific Characteristic | Body Mass Index			
Units: kg/m^2			
arithmetic mean	36	34	
standard deviation	± 2	± 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 (Ctrough) of Total Serum Testosterone for Once Weekly Dosing Groups

End point title	Trough Serum Concentration (Ctrough) 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 (Ctrough) of Total Serum Testosterone for Twice Weekly Dosing Group

End point title	Trough Serum Concentration (Ctrough) 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 (Ctrough) of Free Serum Testosterone for Twice Weekly Dosing Groups

End point title	Trough Serum Concentration (Ctrough) 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: Cmax: Mean Maximum Observed Plasma Concentration for TAK-448 Free Base Form (TAK-448F)

End point title	Cmax: Mean Maximum Observed Plasma Concentration for TAK-448 Free Base Form (TAK-448F)[17]

End point description:

Maximum observed plasma concentration (Cmax) 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