EU Clinical Trials Register

Clinical trial results:
A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study to Evaluate the Efficacy and Safety of Daily Oral TAK-875 25 mg and 50 mg Compared with Placebo in Subjects with Type 2 Diabetes

Summary

EudraCT number	2011-002741-35
Trial protocol	SK HU BG
Global end of trial date	30 July 2013

Results information

Result version number	v1 (current)
This version publication date	04 March 2016
First version publication date	08 July 2015

Trial information

Trial identification

Sponsor protocol code	TAK-875_301

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01456195
WHO universal trial number (UTN)	U1111-1124-2154

Notes:

Sponsors

Sponsor organisation name	Takeda
Sponsor organisation address	One Takeda Parkway, Deerfield, United States, 60015
Public contact	Medical Director, Clinical Science, Takeda , +1 877-825-3327, trialdisclosures@takeda.com
Scientific contact	Medical Director, Clinical Science, Takeda , +1 877-825-3327, 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	25 March 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 June 2013
Global end of trial reached?	Yes
Global end of trial date	30 July 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to determine the efficacy and safety of TAK-875 (fasiglifam), once daily (QD), in participants with type 2 diabetes mellitus (T2DM).

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	02 November 2011
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	Slovakia: 72
Country: Number of subjects enrolled	Bulgaria: 24
Country: Number of subjects enrolled	Hungary: 23
Country: Number of subjects enrolled	Argentina: 30
Country: Number of subjects enrolled	Guatemala: 42
Country: Number of subjects enrolled	Mexico: 18
Country: Number of subjects enrolled	Ukraine: 28
Country: Number of subjects enrolled	United States: 184
Worldwide total number of subjects	421
EEA total number of subjects	119

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)	352
From 65 to 84 years	69
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants took part in the study at 109 investigative sites in United States, Bulgaria, Argentina, Ukraine, Guatemala, Slovakia, Mexico and Hungary from 02 November 2011 to 30 July 2013.

Pre-assignment

Screening details:

Participants with a diagnosis of Type 2 Diabetes Mellitis were enrolled equally in 1 of 3 treatment groups, once a day placebo, 25 mg fasiglifam or 50 mg fasiglifam.

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	Investigator, Monitor, Data analyst, Carer, Subject, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Fasiglifam placebo-matching tablets, orally, once daily for up to 24 weeks.

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

Dosage and administration details:

Fasiglifam placebo-matching tablets, orally, once daily for up to 24 weeks.

Arm title	Fasiglifam 25 mg

Arm description:

Fasiglifam 25 mg, tablets, orally, once daily for up to 24 weeks.

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

Dosage and administration details:

Fasiglifam 25 mg, tablets, orally, once daily for up to 24 weeks.

Arm title	Fasiglifam 50 mg

Arm description:

Fasiglifam 50 mg, tablets, orally, once daily for up to 24 weeks.

Arm type	Experimental

Investigational medicinal product name	Fasiglifam
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Fasiglifam 25 or 50 mg, tablets, orally, once daily for up to 24 weeks.

Number of subjects in period 1	Placebo	Fasiglifam 25 mg	Fasiglifam 50 mg
Started	143	137	141
Completed	131	127	125
Not completed	12	10	16
Pretreatment Event/Adverse Event	1	4	-
Voluntary Withdrawal	5	3	8
Other Reasons	3	-	-
Other	-	1	4
Lost to follow-up	3	1	4
Lack of efficacy	-	1	-

Baseline characteristics

Reporting groups

Reporting group title	Placebo
Reporting group description:	
Fasiglifam placebo-matching tablets, orally, once daily for up to 24 weeks.	
Reporting group title	Fasiglifam 25 mg
Reporting group description:	
Fasiglifam 25 mg, tablets, orally, once daily for up to 24 weeks.	
Reporting group title	Fasiglifam 50 mg
Reporting group description:	
Fasiglifam 50 mg, tablets, orally, once daily for up to 24 weeks.	

Reporting group values	Placebo	Fasiglifam 25 mg	Fasiglifam 50 mg
Number of subjects	143	137	141
Age categorical			
Units: Subjects			
< 65 years	124	114	114
≥ 65 years	19	23	27
Age continuous			
Units: years			
arithmetic mean	53.1	53.2	54.2
standard deviation	± 10.61	± 11.31	± 10.57
Gender categorical			
Units: Subjects			
Female	68	65	73
Male	75	72	68
Race/Ethnicity			
Units: Subjects			
Hispanic or Latino	22	25	22
Non-Hispanic or Latino	39	36	41
Not Applicable	82	76	78
Race/Ethnicity			
Units: Subjects			
American Indian or Alaska Native	19	15	16
Asian	5	4	0
Black or African American	8	6	12
White	110	112	113
Multiracial	1	0	0
Region of Enrollment			
Units: Subjects			
Argentina	10	10	10
Bulgaria	8	7	9
Guatemala	15	14	13
Hungary	8	7	8
Mexico	6	5	7
Slovakia	24	24	24
Ukraine	11	9	8
United States	61	61	62

Baseline BMI Group Units: Subjects			
< 30 kg/m^2	54	49	56
≥ 30 kg/m^2	89	88	85
Baseline HbA1c Category Units: Subjects			
< 8.5%	102	91	102
≥ 8.5 %	41	46	39
Smoking Classification Units: Subjects			
Never smoked	99	98	97
Current smoker	21	17	23
Ex-smoker	23	22	21
Height Units: cm			
arithmetic mean	166.3	165.3	166.7
standard deviation	± 10.63	± 11.17	± 11.11
Weight Units: kg			
arithmetic mean	89.66	89.24	89.43
standard deviation	± 18.858	± 18.541	± 18.706
Body Mass Index (BMI) Units: kg/m^2			
arithmetic mean	32.33	32.5	32.05
standard deviation	± 5.714	± 5.256	± 5.369
Duration of Diabetes Units: years			
arithmetic mean	3.048	3.29	3.7
standard deviation	± 3.164	± 3.447	± 4.56

Reporting group values	Total		
Number of subjects	421		
Age categorical Units: Subjects			
< 65 years	352		
≥ 65 years	69		
Age continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical Units: Subjects			
Female	206		
Male	215		
Race/Ethnicity Units: Subjects			
Hispanic or Latino	69		
Non-Hispanic or Latino	116		
Not Applicable	236		
Race/Ethnicity Units: Subjects			

American Indian or Alaska Native	50		
Asian	9		
Black or African American	26		
White	335		
Multiracial	1		
Region of Enrollment Units: Subjects			
Argentina	30		
Bulgaria	24		
Guatemala	42		
Hungary	23		
Mexico	18		
Slovakia	72		
Ukraine	28		
United States	184		
Baseline BMI Group Units: Subjects			
< 30 kg/m^2	159		
≥ 30 kg/m^2	262		
Baseline HbA1c Category Units: Subjects			
< 8.5%	295		
≥ 8.5 %	126		
Smoking Classification Units: Subjects			
Never smoked	294		
Current smoker	61		
Ex-smoker	66		
Height Units: cm			
arithmetic mean			
standard deviation	-		
Weight Units: kg			
arithmetic mean			
standard deviation	-		
Body Mass Index (BMI) Units: kg/m^2			
arithmetic mean			
standard deviation	-		
Duration of Diabetes Units: years			
arithmetic mean			
standard deviation	-		

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Fasiglifam placebo-matching tablets, orally, once daily for up to 24 weeks.	
Reporting group title	Fasiglifam 25 mg
Reporting group description:	
Fasiglifam 25 mg, tablets, orally, once daily for up to 24 weeks.	
Reporting group title	Fasiglifam 50 mg
Reporting group description:	
Fasiglifam 50 mg, tablets, orally, once daily for up to 24 weeks.	

Primary: Change From Baseline in Glycosylated Hemoglobin (HbA1c)

End point title	Change From Baseline in Glycosylated Hemoglobin (HbA1c)
End point description:	
The change in the value of glycosylated hemoglobin (the concentration of glucose bound to hemoglobin as a percent of the absolute maximum that can be bound) collected at Week 24 relative to Baseline. A mixed model repeated measures (MMRM) model with treatment, country, visit and visit by treatment interaction as fixed factors and with Baseline value and Baseline value by visit interaction as covariates with an unstructured covariance structure was used for analysis.	
End point type	Primary
End point timeframe:	
Baseline and Week 24	

End point values	Placebo	Fasiglifam 25 mg	Fasiglifam 50 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	101	119	116	
Units: percent				
least squares mean (standard error)	-0.17 (± 0.09)	-0.65 (± 0.087)	-0.93 (± 0.087)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Fasiglifam 25 mg
Number of subjects included in analysis	220
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [1]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-0.48

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.72
upper limit	-0.24
Variability estimate	Standard error of the mean
Dispersion value	0.122

Notes:

[1] - MMRM model with treatment, country, visit and visit by treatment interaction as fixed factors and with baseline value and baseline value by visit interaction as covariates with an unstructured covariance structure.

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v Fasiglifam 50 mg
Number of subjects included in analysis	217
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [2]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-0.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	-0.52
Variability estimate	Standard error of the mean
Dispersion value	0.122

Notes:

[2] - MMRM model with treatment, country, visit and visit by treatment interaction as fixed factors and with baseline value and baseline value by visit interaction as covariates with an unstructured covariance structure.

Secondary: Incidence of HbA1c <7%

End point title	Incidence of HbA1c <7%

End point description:

The incidence (percentage of participants with) HbA1c (the concentration of glucose bound to hemoglobin as a percent of the absolute maximum that can be bound) of less than seven percent for target glycemic control at Week 24.

End point type	Secondary

End point timeframe:

Week 24

End point values	Placebo	Fasiglifam 25 mg	Fasiglifam 50 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	137	136	139	
Units: percentage of participants				
number (not applicable)	24.1	36	50.4	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Fasiglifam 25 mg
Number of subjects included in analysis	273
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.01 [3]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.2
upper limit	3.79

Notes:

[3] - P-Value used a logistic model with treatment, country and baseline HbA1c as explanatory variables.

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v Fasiglifam 50 mg
Number of subjects included in analysis	276
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [4]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	4.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.48
upper limit	7.82

Notes:

[4] - P-Value used a logistic model with treatment, country and baseline HbA1c as explanatory variables.

Secondary: Change From Baseline in Fasting Plasma Glucose

End point title	Change From Baseline in Fasting Plasma Glucose

End point description:

The change between the fasting plasma glucose value collected at Week 24 relative to Baseline measured in milligrams per deciliter (mg/dL). A MMRM model with treatment, country, visit and visit by treatment interaction as fixed factors and with Baseline value and Baseline value by visit interaction as covariates with an unstructured covariance structure was used for analysis.

End point type	Secondary

End point timeframe:

Baseline and Week 24

End point values	Placebo	Fasiglifam 25 mg	Fasiglifam 50 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	101	116	116	
Units: mg/dL				
least squares mean (standard error)	1.4 (± 3.45)	-12.3 (± 3.29)	-20.9 (± 3.26)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Fasiglifam 25 mg
Number of subjects included in analysis	217
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.003 [5]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-13.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-22.7
upper limit	-4.6
Variability estimate	Standard error of the mean
Dispersion value	4.59

Notes:

[5] - Mixed Model Repeated Measures (MMRM) model with treatment, country, visit and visit by treatment interaction as fixed factors and with baseline value and baseline value by visit interaction as covariates with an unstructured covariance structure.

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v Fasiglifam 50 mg
Number of subjects included in analysis	217
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [6]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-22.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-31.4
upper limit	-13.2

Variability estimate	Standard error of the mean
Dispersion value	4.6

Notes:

[6] - MMRM model with treatment, country, visit and visit by treatment interaction as fixed factors and with baseline value and baseline value by visit interaction as covariates with an unstructured covariance structure.

Secondary: Change From Baseline in 2-hour Postprandial Glucose (PPG) Following a Meal Tolerance Test (MTT)

End point title	Change From Baseline in 2-hour Postprandial Glucose (PPG) Following a Meal Tolerance Test (MTT)

End point description:

The change between the value of glucose after a meal, measured by the meal tolerance test collected at Week 24 relative to Baseline. Meal tolerance test measures blood glucose through blood samples drawn before a meal and 2 hours after the start of the meal measured in millimoles per liter (mmol/L). An Analysis of Covariance (ANCOVA) model with treatment and country as fixed factors and Baseline value as covariate was used for analysis.

End point type	Secondary

End point timeframe:

Baseline and Week 24

End point values	Placebo	Fasiglifam 25 mg	Fasiglifam 50 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	18	20	18	
Units: mmol/L				
least squares mean (standard error)	-0.6 (± 12.47)	-29.4 (± 11.82)	-30.6 (± 12.5)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Fasiglifam 25 mg
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1 [7]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-28.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-63.2
upper limit	5.7
Variability estimate	Standard error of the mean
Dispersion value	17.17

Notes:

[7] - ANCOVA model with treatment and country as fixed factors and baseline value as covariate.

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v Fasiglifam 50 mg
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.096 [8]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-30
Confidence interval	
level	95 %
sides	2-sided
lower limit	-65.5
upper limit	5.5
Variability estimate	Standard error of the mean
Dispersion value	17.7

Notes:

[8] - ANCOVA model with treatment and country as fixed factors and baseline value as covariate.

Adverse events

Adverse events information

Timeframe for reporting adverse events:	
Randomization to 30 days past last dose (up to 219 days)	
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	16.0

Reporting groups

Reporting group title	Placebo
Reporting group description:	
Fasiglifam placebo-matching tablets, orally, once daily for up to 24 weeks.	
Reporting group title	Fasiglifam 25 mg
Reporting group description:	
Fasiglifam 25 mg, tablets, orally, once daily for up to 24 weeks.	
Reporting group title	Fasiglifam 50 mg
Reporting group description:	
Fasiglifam 50 mg, tablets, orally, once daily for up to 24 weeks.	

Serious adverse events	Placebo	Fasiglifam 25 mg	Fasiglifam 50 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 143 (2.10%)	3 / 137 (2.19%)	3 / 141 (2.13%)
number of deaths (all causes)	0	0	1
number of deaths resulting from adverse events			
Cardiac disorders			
Cardio-respiratory arrest			
subjects affected / exposed	0 / 143 (0.00%)	0 / 137 (0.00%)	1 / 141 (0.71%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Gastrointestinal disorders			
Abdominal hernia			
subjects affected / exposed	0 / 143 (0.00%)	1 / 137 (0.73%)	0 / 141 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal fistula			

subjects affected / exposed	0 / 143 (0.00%)	0 / 137 (0.00%)	1 / 141 (0.71%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematochezia			
subjects affected / exposed	0 / 143 (0.00%)	1 / 137 (0.73%)	0 / 141 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 143 (0.70%)	0 / 137 (0.00%)	0 / 141 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis acute			
subjects affected / exposed	0 / 143 (0.00%)	0 / 137 (0.00%)	1 / 141 (0.71%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	1 / 143 (0.70%)	0 / 137 (0.00%)	0 / 141 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	1 / 143 (0.70%)	0 / 137 (0.00%)	1 / 141 (0.71%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 143 (0.00%)	1 / 137 (0.73%)	0 / 141 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Placebo	Fasiglifam 25 mg	Fasiglifam 50 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 143 (6.29%)	6 / 137 (4.38%)	7 / 141 (4.96%)
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	9 / 143 (6.29%)	6 / 137 (4.38%)	7 / 141 (4.96%)
occurrences (all)	10	6	8

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 September 2011	Amendment 1: 13 Sept 2011: -Meal Tolerance Test (MTT) was optional for participants. - The blood volume for the MTT and the total blood volume for the study were updated. - Text was added to indicate that abnormal LFT results would be recorded on the LFT increases page of the eCRF.. - The exclusion period for investigational medications other than antidiabetic medications was changed.
08 May 2012	Amendment 2: 08 May 2012: The primary purpose amendment 2 was to update inclusion and exclusion criteria, excluded medications, statistical analysis section, and safety information including contraceptive language, removal of partner pregnancy, and special interest adverse events.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported