Clinical trial results:
A Phase 3, Multicenter, Randomized, Double-Blind, Active-Controlled, 24-Week Study to Evaluate the Efficacy and Safety of Daily Oral TAK-875 50 mg Compared With Sitagliptin 100 mg When Used in Combination With Metformin in Subjects With Type 2 Diabetes

Summary

EudraCT number	2013-000542-19
Trial protocol	HU HR
Global end of trial date	05 March 2014

Results information

Result version number	v1 (current)
This version publication date	04 March 2016
First version publication date	06 August 2015

Trial information

Trial identification

Sponsor protocol code	TAK-875_310

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01834274
WHO universal trial number (UTN)	U1111-1139-0467

Notes:

Sponsors

Sponsor organisation name	Takeda
Sponsor organisation address	One Takeda Parkway, Deerfield, IL, 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	23 October 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 February 2014
Global end of trial reached?	Yes
Global end of trial date	05 March 2014
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of TAK-875 plus metformin compared with sitagliptin plus metformin on glycemic control as measured by change from Baseline in glycosylated hemoglobin (HbA1c) over a 24-week Treatment Period.

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	18 May 2013
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	Canada: 1
Country: Number of subjects enrolled	United States: 95
Worldwide total number of subjects	96
EEA total number of subjects	0

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)	82
From 65 to 84 years	14
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants took part in the study at 25 sites in the United States and 1 site in Canada from 18 May 2013 (first patient to sign informed consent) to 05 March 2014.

Pre-assignment

Screening details:

Participants with a diagnosis of Type 2 Diabetes Mellitis were enrolled equally in 1 of 2 treatment groups, once a day fasiglifam 50 mg or Sitagliptin 100 mg in combination with metformin.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst

Arms

Are arms mutually exclusive?	Yes
Arm title	Fasiglifam 50 mg

Arm description:

TAK-875 50 mg tablets, orally, once daily, sitagliptin placebo-matching tablets, orally, once daily, and metformin stable dose ≥1500 mg (or maximum-tolerated dose), tablets, orally, daily for up to 24 weeks.

Arm type	Experimental
Investigational medicinal product name	Fasiglifam
Investigational medicinal product code	
Other name	TAK-875
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Fasiglifam 50 mg tablets, orally, once daily, Sitagliptin placebo-matching tablets, orally, once daily, and metformin stable dose ≥1500 mg (or maximum-tolerated dose), tablets, orally, daily for up to 24 weeks.

Investigational medicinal product name	Sitagliptin placebo-matching tablets
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Sitagliptin placebo-matching tablets, orally, once daily.

Arm title	Sitagliptin 100 mg

Arm description:

Sitagliptin 100 mg, tablets, once daily, fasiglifam placebo-matching tablets, orally, once daily, and metformin stable dose ≥1500 mg (or maximum tolerated dose), tablets, orally, daily for up to 24 weeks.

Arm type	Active comparator

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

Dosage and administration details:

Sitagliptin 100 mg, tablets, once daily, fasiglifam placebo-matching tablets, orally, once daily, and metformin stable dose ≥1500 mg (or maximum tolerated dose), tablets, orally, daily for up to 24 weeks.

Investigational medicinal product name	Fasiglifam placebo-matching tablets
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.

Number of subjects in period 1	Fasiglifam 50 mg	Sitagliptin 100 mg
Started	50	46
Completed	3	5
Not completed	47	41
Study Termination	41	38
Unknown	2	1
Withdrawal by Subject	1	1
Lost to follow-up	3	1

Baseline characteristics

Reporting groups	
Reporting group title	Fasiglifam 50 mg
Reporting group description:	
TAK-875 50 mg tablets, orally, once daily, sitagliptin placebo-matching tablets, orally, once daily, and metformin stable dose ≥1500 mg (or maximum-tolerated dose), tablets, orally, daily for up to 24 weeks.	
Reporting group title	Sitagliptin 100 mg
Reporting group description:	
Sitagliptin 100 mg, tablets, once daily, fasiglifam placebo-matching tablets, orally, once daily, and metformin stable dose ≥1500 mg (or maximum tolerated dose), tablets, orally, daily for up to 24 weeks.	

Reporting group values	Fasiglifam 50 mg	Sitagliptin 100 mg	Total
Number of subjects	50	46	96
Age categorical Units: Subjects			
< 65 years	41	41	82
≥ 65 years	9	5	14
Age continuous Units: years			
arithmetic mean	57.6	55.1	
standard deviation	± 7.14	± 9.07	-
Gender categorical Units: Subjects			
Female	24	20	44
Male	26	26	52
Race Units: Subjects			
Asian	2	1	3
Black or African American	6	6	12
Native Hawaiian or Other Pacific Islander	0	1	1
White	42	37	79
Multiracial	0	1	1
Ethnicity Units: Subjects			
Hispanic or Latino	34	31	65
Non-Hispanic or Latino	15	15	30
Not Available	1	0	1
Baseline BMI Category Units: Subjects			
< 30 kg/m^2	31	11	42
≥ 30 kg/m^2	19	35	54
Baseline Glycosylated Hemoglobin (HbA)1c Category Units: Subjects			
< 9%	27	28	55
≥ 9 %	23	18	41

Smoking Classification Units: Subjects			
Never smoked	38	29	67
Current smoker	7	9	16
Ex-smoker	5	8	13
Height Units: cm			
arithmetic mean	168.7	169.9	
standard deviation	± 11.45	± 10.79	-
Weight Units: kg			
arithmetic mean	87.5	96.09	
standard deviation	± 18.769	± 19.295	-
Body Mass Index (BMI) Units: kg/m^2			
arithmetic mean	30.77	33.13	
standard deviation	± 6.112	± 4.787	-
Duration of Diabetes Units: years			
arithmetic mean	10.075	8.877	
standard deviation	± 6.53	± 5.942	-

End points

End points reporting groups

Reporting group title	Fasiglifam 50 mg

Reporting group description:

TAK-875 50 mg tablets, orally, once daily, sitagliptin placebo-matching tablets, orally, once daily, and metformin stable dose ≥1500 mg (or maximum-tolerated dose), tablets, orally, daily for up to 24 weeks.

Reporting group title	Sitagliptin 100 mg

Reporting group description:

Sitagliptin 100 mg, tablets, once daily, fasiglifam placebo-matching tablets, orally, once daily, and metformin stable dose ≥1500 mg (or maximum tolerated dose), tablets, orally, daily for up to 24 weeks.

Primary: Change from Baseline in Glycosylated Hemoglobin (HbA1c)

End point title	Change from Baseline in Glycosylated Hemoglobin (HbA1c)[1]

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 or final visit relative to Baseline. A negative change from Baseline indicated improvement.

End point type	Primary

End point timeframe:

Baseline and Week 24

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: Statistics is not reported for this endpoint.

End point values	Fasiglifam 50 mg	Sitagliptin 100 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4[2]	3[3]		
Units: percent				
arithmetic mean (standard deviation)	-0.63 (± 0.34)	-0.43 (± 0.208)		

Notes:

[2] - All randomized participants with data available for analysis.

[3] - All randomized participants with data available for analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with HbA1c <7% at Week 24

End point title	Percentage of Participants with HbA1c <7% at Week 24

End point description:

The percentage of participants with glycosylated hemoglobin less than 9% after 24 weeks of treatment. No summary is provided for the secondary efficacy endpoint incidence of HbA1c <7% at Week 24 due to the limited enrollment and study duration at the time of study termination.

End point type	Secondary

End point timeframe:

Week 24

End point values	Fasiglifam 50 mg	Sitagliptin 100 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[4]	0[5]		
Units: percentage of participants				
number (not applicable)				

Notes:

[4] - Analysis not done.

[5] - Analysis not done.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Fasting Plasma Glucose (FPG)

End point title	Change from Baseline in Fasting Plasma Glucose (FPG)

End point description:

The change between FPG collected at week 24 or final visit relative to baseline. A negative change from Baseline indicated improvement.

End point type	Secondary

End point timeframe:

Baseline and Week 24

End point values	Fasiglifam 50 mg	Sitagliptin 100 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4[6]	3[7]		
Units: mmol/L				
arithmetic mean (standard deviation)	-0.22 (± 1.971)	1.54 (± 5.087)		

Notes:

[6] - All randomized participants with data available for analysis.

[7] - All randomized participants with data available for analysis.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Up to Day 183	
Adverse event reporting additional description:	
Safety population included all randomized participants who received at least one dose of study drug.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups	
Reporting group title	Fasigliflam 50 mg
Reporting group description:	
TAK-875 50 mg tablets, orally, once daily, Sitagliptin placebo-matching tablets, orally, once daily, and metformin stable dose ≥1500 mg (or maximum-tolerated dose), tablets, orally, daily for up to 24 weeks.	
Reporting group title	Sitagliptin 100 mg
Reporting group description:	
Sitagliptin 100 mg, tablets, once daily, TAK-875 placebo-matching tablets, orally, once daily, and metformin stable dose ≥1500 mg (or maximum tolerated dose), tablets, orally, daily for up to 24 weeks.	

Serious adverse events	Fasigliflam 50 mg	Sitagliptin 100 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 50 (2.00%)	0 / 46 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 50 (2.00%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 3 %

Non-serious adverse events	Fasigliflam 50 mg	Sitagliptin 100 mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 50 (8.00%)	5 / 46 (10.87%)	
Nervous system disorders			

Headache			
subjects affected / exposed	2 / 50 (4.00%)	0 / 46 (0.00%)	
occurrences (all)	2	0	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 50 (0.00%)	3 / 46 (6.52%)	
occurrences (all)	0	3	
Diarrhoea			
subjects affected / exposed	1 / 50 (2.00%)	3 / 46 (6.52%)	
occurrences (all)	1	3	
Infections and infestations			
Sinusitis			
subjects affected / exposed	2 / 50 (4.00%)	1 / 46 (2.17%)	
occurrences (all)	2	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 April 2013	Protocol updates for amendment 1: • Number of Sites increased from 95 to 105. • Nonclinical and clinical data in the introduction were updated from the Investgator's brochure. • Study drug would be taken after fasting blood samples were collected. • Added withdrawal criteria applied to adverse events involving liver function results. • Dosing recommendations for the rescue medication glimepiride. • Guidance on missed doses. • Guidance on the screening and fasting process. • Electrocardiograms (ECGs) were to be done before administration of study drug. • Euro Quality of Life5D (EQ-5D) and Diabetes-Management and Impact Questionnaire (D-MIQ) were to be administered before other study procedures, that subjects were required to complete the surveys independently.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
26 December 2013	Termination-due to concerns about potential liver safety.	-

Notes:

Limitations and caveats

None reported