Clinical trial results:
A Multicenter, Randomized, Double-Blind, Placebo- and Active-Controlled, Phase 3 Study to Evaluate the Efficacy and Safety of TAK-875 25 mg and 50 mg Compared to Placebo and Sitagliptin 100 mg When Used in Combination with Metformin in Subjects with Type 2 Diabetes

Summary

EudraCT number	2011-001752-10
Trial protocol	HU CZ SK BG IT
Global end of trial date	27 March 2014

Results information

Result version number	v1 (current)
This version publication date	04 March 2016
First version publication date	09 July 2015

Trial information

Trial identification

Sponsor protocol code	TAK-875_302

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01549964
WHO universal trial number (UTN)	U1111-1124-2225

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	12 November 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 March 2014
Global end of trial reached?	Yes
Global end of trial date	27 March 2014
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to evaluate the efficacy of 2 doses of TAK-875 (25 mg and 50 mg), once daily (QD), plus metformin compared to placebo plus metformin and sitagliptin plus metformin on lowering blood sugar.

Protection of trial subjects:

All participants were required to read and sign and Informed Consent Form.
Rescue medications were available for participants with hypoglycemia or hyperglycemia.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 April 2012
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: 231
Country: Number of subjects enrolled	Bulgaria: 24
Country: Number of subjects enrolled	Czech Republic: 51
Country: Number of subjects enrolled	Hungary: 206
Country: Number of subjects enrolled	Italy: 9
Country: Number of subjects enrolled	Australia: 18
Country: Number of subjects enrolled	Croatia: 24
Country: Number of subjects enrolled	Korea, Republic of: 12
Country: Number of subjects enrolled	Malaysia: 25
Country: Number of subjects enrolled	Thailand: 48
Country: Number of subjects enrolled	United States: 268
Worldwide total number of subjects	916
EEA total number of subjects	545

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	757
From 65 to 84 years	159
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants took part in the study at 168 investigative sites in Australia, Bulgaria, Croatia, Czech Republic, Hungary, Italy, Korea, Republic, Malaysia, Slovakia, Thailand and the United States from 05 April 2012 to 27 March 2014.

Pre-assignment

Screening details:

Participants with a diagnosis of Type 2 Diabetes Mellitus were randomly enrolled in 1 of 4 treatment groups in a 1:2:2:2 ratio, once a day placebo, 100 mg sitagliptin, 25 mg fasiglifam or 50 mg fasiglifam in combination with metformin.

Period 1

Period 1 title	24-Week Treatment Period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Fasiglifam placebo-matching tablets, orally, once daily for a 24-week Treatment Period followed by an optional 80-week extension period for up to 104 weeks of treatment. Sitagliptin placebo-matching tablets, orally, once daily for a 24-week Treatment Period followed by an optional 80-week extension period for up to 104 weeks of treatment. Metformin ≥1500 mg or Maximum Tolerated Dose (MTD) needs to continue at a stable dose.

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

Dosage and administration details:

Fasiglifam placebo-matching tablets, orally, once daily for a 24-week Treatment Period followed by an optional 80-week extension period for up to 104 weeks of treatment. Sitagliptin placebo-matching tablets, orally, once daily for a 24-week Treatment Period followed by an optional 80-week extension period for up to 104 weeks of treatment. Metformin ≥1500 mg or Maximum Tolerated Dose (MTD) needs to continue at a stable dose.

Arm title	Sitagliptin 100 mg

Arm description:

Sitagliptin 100 mg, tablets, orally, once daily for a 24-week Treatment Period followed by an optional 80-week extension period for up to 104 weeks of treatment. Fasiglifam placebo-matching tablets, orally, once daily for a 24-week Treatment Period followed by an optional 80-week extension period for up to 104 weeks of treatment. Metformin ≥1500 mg or Maximum Tolerated Dose (MTD) needs to continue at a stable dose.

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, orally, once daily for a 24-week Treatment Period followed by an optional 80-week extension period for up to 104 weeks of treatment. Fasiglifam placebo-matching tablets, orally, once daily for a 24-week Treatment Period followed by an optional 80-week extension period for up to 104 weeks of treatment. Metformin ≥1500 mg or Maximum Tolerated Dose (MTD) needs to continue at a stable dose.

Arm title	Fasiglifam 25 mg

Arm description:

Fasiglifam 25 mg, tablets, orally, once daily for a 24-week Treatment Period followed by an optional 80-week extension period for up to 104 weeks of treatment. Sitagliptin placebo-matching tablets, orally, once daily for a 24-week Treatment Period followed by an optional 80-week extension period for up to 104 weeks of treatment. Metformin ≥1500 mg or Maximum Tolerated Dose (MTD) needs to continue at a stable dose.

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 a 24-week Treatment Period followed by an optional 80-week extension period for up to 104 weeks of treatment. Sitagliptin placebo-matching tablets, orally, once daily for a 24-week Treatment Period followed by an optional 80-week extension period for up to 104 weeks of treatment. Metformin ≥1500 mg or Maximum Tolerated Dose (MTD) needs to continue at a stable dose.

Arm title	Fasiglifam 50 mg

Arm description:

Fasiglifam 50 mg, tablets, orally, once daily for a 24-week Treatment Period followed by an optional 80-week extension period for up to 104 weeks of treatment. Sitagliptin placebo-matching tablets, orally, once daily for a 24-week Treatment Period followed by an optional 80-week extension period for up to 104 weeks of treatment. Metformin ≥1500 mg or Maximum Tolerated Dose (MTD) needs to continue at a stable dose.

Arm type	Experimental
Investigational medicinal product name	Fasiglifam 50 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Fasiglifam 50 mg, tablets, orally, once daily for a 24-week Treatment Period followed by an optional 80-week extension period for up to 104 weeks of treatment. Sitagliptin placebo-matching tablets, orally, once daily for a 24-week Treatment Period followed by an optional 80-week extension period for up to 104 weeks of treatment. Metformin ≥1500 mg or Maximum Tolerated Dose (MTD) needs to continue at a stable dose.

Number of subjects in period 1	Placebo	Sitagliptin 100 mg	Fasiglifam 25 mg
Started	132	260	263
Safety Analysis Set=Received Treatment	132	260	263
Completed	71	149	147
Not completed	61	111	116
Pretreatment Event/Adverse Event	1	4	4

Completion Status Unknown	1	-	1
Voluntary Withdrawal	6	3	3
Other	1	-	1
Study Terminated by Sponsor	50	104	104
Metformin/Sitagliptin Contraindication	-	-	1
Lost to follow-up	1	-	1
Randomized but Not Treated	-	-	-
Lack of efficacy	1	-	1

Number of subjects in period 1	Fasiglifam 50 mg
Started	261
Safety Analysis Set=Received Treatment	260
Completed	140
Not completed	121
Pretreatment Event/Adverse Event	4
Completion Status Unknown	-
Voluntary Withdrawal	8
Other	-
Study Terminated by Sponsor	105
Metformin/Sitagliptin Contraindication	-
Lost to follow-up	2
Randomized but Not Treated	1
Lack of efficacy	1

Period 2

Period 2 title	80-Week Extension Period
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Fasiglifam placebo-matching tablets, orally, once daily for a 24-week Treatment Period followed by an optional 80-week extension period for up to 104 weeks of treatment. Sitagliptin placebo-matching tablets, orally, once daily for a 24-week Treatment Period followed by an optional 80-week extension period for up to 104 weeks of treatment. Metformin ≥1500 mg or Maximum Tolerated Dose (MTD) needs to continue at a stable dose.

Arm type	Placebo

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

Dosage and administration details:

Fasiglifam placebo-matching tablets, orally, once daily for a 24-week Treatment Period followed by an optional 80-week extension period for up to 104 weeks of treatment. Sitagliptin placebo-matching tablets, orally, once daily for a 24-week Treatment Period followed by an optional 80-week extension period for up to 104 weeks of treatment. Metformin ≥1500 mg or Maximum Tolerated Dose (MTD) needs to continue at a stable dose.

Arm title	Sitagliptin 100 mg

Arm description:

Sitagliptin 100 mg, tablets, orally, once daily for a 24-week Treatment Period followed by an optional 80-week extension period for up to 104 weeks of treatment. Fasiglifam placebo-matching tablets, orally, once daily for a 24-week Treatment Period followed by an optional 80-week extension period for up to 104 weeks of treatment. Metformin ≥1500 mg or Maximum Tolerated Dose (MTD) needs to continue at a stable dose.

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, orally, once daily for a 24-week Treatment Period followed by an optional 80-week extension period for up to 104 weeks of treatment. Fasiglifam placebo-matching tablets, orally, once daily for a 24-week Treatment Period followed by an optional 80-week extension period for up to 104 weeks of treatment. Metformin ≥1500 mg or Maximum Tolerated Dose (MTD) needs to continue at a stable dose.

Arm title	Fasiglifam 25 mg

Arm description:

Fasiglifam 25 mg, tablets, orally, once daily for a 24-week Treatment Period followed by an optional 80-week extension period for up to 104 weeks of treatment. Sitagliptin placebo-matching tablets, orally, once daily for a 24-week Treatment Period followed by an optional 80-week extension period for up to 104 weeks of treatment. Metformin ≥1500 mg or Maximum Tolerated Dose (MTD) needs to continue at a stable dose.

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 a 24-week Treatment Period followed by an optional 80-week extension period for up to 104 weeks of treatment. Sitagliptin placebo-matching tablets, orally, once daily for a 24-week Treatment Period followed by an optional 80-week extension period for up to 104 weeks of treatment. Metformin ≥1500 mg or Maximum Tolerated Dose (MTD) needs to continue at a stable dose.

Arm title	Fasiglifam 50 mg

Arm description:

Fasiglifam 50 mg, tablets, orally, once daily for a 24-week Treatment Period followed by an optional 80-week extension period for up to 104 weeks of treatment. Sitagliptin placebo-matching tablets, orally, once daily for a 24-week Treatment Period followed by an optional 80-week extension period for up to 104 weeks of treatment. Metformin ≥1500 mg or Maximum Tolerated Dose (MTD) needs to continue at a stable dose.

Arm type	Experimental

Investigational medicinal product name	Fasiglifam 50 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Fasiglifam 50 mg, tablets, orally, once daily for a 24-week Treatment Period followed by an optional 80-week extension period for up to 104 weeks of treatment. Sitagliptin placebo-matching tablets, orally, once daily for a 24-week Treatment Period followed by an optional 80-week extension period for up to 104 weeks of treatment. Metformin ≥1500 mg or Maximum Tolerated Dose (MTD) needs to continue at a stable dose.

Number of subjects in period 2[1]	Placebo	Sitagliptin 100 mg	Fasiglifam 25 mg
Started	66	138	140
Completed	0	0	0
Not completed	66	138	140
Pretreatment Event/Adverse Event	-	-	1
Voluntary Withdrawal	-	1	4
Pregnancy	-	-	1
Study Terminated by Sponsor	65	137	132
Lost to follow-up	1	-	2

Number of subjects in period 2[1]	Fasiglifam 50 mg
Started	137
Completed	0
Not completed	137
Pretreatment Event/Adverse Event	2
Voluntary Withdrawal	2
Pregnancy	-
Study Terminated by Sponsor	132
Lost to follow-up	1

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Of the 507 subjects who completed the 24-week Treatment Period, 481 entered the optional 80-week Extension Period.

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Fasiglifam placebo-matching tablets, orally, once daily for a 24-week Treatment Period followed by an optional 80-week extension period for up to 104 weeks of treatment. Sitagliptin placebo-matching tablets, orally, once daily for a 24-week Treatment Period followed by an optional 80-week extension period for up to 104 weeks of treatment. Metformin ≥1500 mg or Maximum Tolerated Dose (MTD) needs to continue at a stable dose.	
Reporting group title	Sitagliptin 100 mg
Reporting group description:	
Sitagliptin 100 mg, tablets, orally, once daily for a 24-week Treatment Period followed by an optional 80-week extension period for up to 104 weeks of treatment. Fasiglifam placebo-matching tablets, orally, once daily for a 24-week Treatment Period followed by an optional 80-week extension period for up to 104 weeks of treatment. Metformin ≥1500 mg or Maximum Tolerated Dose (MTD) needs to continue at a stable dose.	
Reporting group title	Fasiglifam 25 mg
Reporting group description:	
Fasiglifam 25 mg, tablets, orally, once daily for a 24-week Treatment Period followed by an optional 80-week extension period for up to 104 weeks of treatment. Sitagliptin placebo-matching tablets, orally, once daily for a 24-week Treatment Period followed by an optional 80-week extension period for up to 104 weeks of treatment. Metformin ≥1500 mg or Maximum Tolerated Dose (MTD) needs to continue at a stable dose.	
Reporting group title	Fasiglifam 50 mg
Reporting group description:	
Fasiglifam 50 mg, tablets, orally, once daily for a 24-week Treatment Period followed by an optional 80-week extension period for up to 104 weeks of treatment. Sitagliptin placebo-matching tablets, orally, once daily for a 24-week Treatment Period followed by an optional 80-week extension period for up to 104 weeks of treatment. Metformin ≥1500 mg or Maximum Tolerated Dose (MTD) needs to continue at a stable dose.	

Reporting group values	Placebo	Sitagliptin 100 mg	Fasiglifam 25 mg
Number of subjects	132	260	263
Age categorical Units: Subjects			
< 65 years	107	214	216
≥ 65 years	25	46	47
Age continuous Units: years			
arithmetic mean	55.6	55.8	56.3
standard deviation	± 9.72	± 9.84	± 9.58
Gender categorical Units: Subjects			
Female	66	103	127
Male	66	157	136
Race/Ethnicity, Customized			
[1] Race data is available for 260 participants in the fasiglifam 50 mg treatment arm.			
Units: Subjects			
American Indian or Alaska Native	0	0	2
Asian	12	30	28
Black or African American	8	13	19
Native Hawaiian or Other Pacific Islander	0	0	0

White	112	216	214
Multiracial	0	1	0
Data Not Available	0	0	0
Race/Ethnicity, Customized Units: Subjects			
Hispanic or Latino	13	29	28
Non-Hispanic or Latino	28	59	53
Not Collected	91	172	182
Region of Enrollment Units: Subjects			
Australia	3	5	5
Bulgaria	3	7	7
Croatia	4	6	8
Czech Republic	8	15	14
Hungary	29	56	61
Italy	1	3	3
Korea, Republic of	2	4	4
Malaysia	2	8	7
Slovakia	34	66	65
Thailand	7	14	13
United States	39	76	76
BMI Category			
BMI data is available for 262 and 260 participants in the fasiglifam 25 mg and fasiglifam 50 mg treatment arms, respectively.			
Units: Subjects			
< 30 kg/m^2	53	106	92
≥ 30 kg/m^2	79	154	170
Data Not Available	0	0	1
HbA1c Category			
HbA1c data is available for 260 participants in the fasiglifam 50 mg treatment arm.			
Units: Subjects			
< 8.5%	80	156	154
≥ 8.5%	52	104	109
Data Not Available	0	0	0
Weight			
Weight data is available for 260 participants in the fasiglifam 50 mg treatment arm.			
Units: kg			
arithmetic mean	91.15	91.41	91.44
standard deviation	± 18.988	± 19.664	± 17.859
Height			
Height data is available for 262 and 260 participants in the fasiglifam 25 mg and fasiglifam 50 mg treatment arms, respectively.			
Units: cm			
arithmetic mean	168.2	169.4	168.5
standard deviation	± 10.08	± 10.74	± 10.53
Body Mss Index (BMI)			
BMI data is available for 262 and 260 participants in the fasiglifam 25 mg and fasiglifam 50 mg treatment arms, respectively.			
Units: kg/m^2			
arithmetic mean	32.06	31.68	32.11
standard deviation	± 5.07	± 5.282	± 5.126
Glycosylated Hemoglobin (HbA1c)			

HbA1c data is available for 258 and 260 participants in the sitagliptin 100 mg and fasiglifam 50 mg treatment arms, respectively.			
Units: percent			
arithmetic mean	8.34	8.35	8.41
standard deviation	± 0.739	± 0.694	± 0.712
Duration of Diabetes			
Units: years			
arithmetic mean	6.655	5.94	6.726
standard deviation	± 6.262	± 4.942	± 4.615
Fasting Plasma Glucose			
Data is only available for 258 and 259 participants in the sitagliptin 100 mg and fasiglifam 50 mg treatment arms, respectively.			
Units: ng/dL			
arithmetic mean	178.4	175.6	179
standard deviation	± 36.94	± 37.67	± 33.52

Reporting group values	Fasiglifam 50 mg	Total	
Number of subjects	261	916	
Age categorical			
Units: Subjects			
< 65 years	220	757	
≥ 65 years	41	159	
Age continuous			
Units: years			
arithmetic mean	56		
standard deviation	± 9.37	-	
Gender categorical			
Units: Subjects			
Female	126	422	
Male	135	494	
Race/Ethnicity, Customized			
[1] Race data is available for 260 participants in the fasiglifam 50 mg treatment arm.			
Units: Subjects			
American Indian or Alaska Native	3	5	
Asian	26	96	
Black or African American	12	52	
Native Hawaiian or Other Pacific Islander	2	2	
White	217	759	
Multiracial	0	1	
Data Not Available	1	1	
Race/Ethnicity, Customized			
Units: Subjects			
Hispanic or Latino	28	98	
Non-Hispanic or Latino	55	195	
Not Collected	178	623	
Region of Enrollment			
Units: Subjects			
Australia	5	18	
Bulgaria	7	24	
Croatia	6	24	
Czech Republic	14	51	

Hungary	60	206	
Italy	2	9	
Korea, Republic of	2	12	
Malaysia	8	25	
Slovakia	66	231	
Thailand	14	48	
United States	77	268	
BMI Category			
BMI data is available for 262 and 260 participants in the fasiglifam 25 mg and fasiglifam 50 mg treatment arms, respectively.			
Units: Subjects			
< 30 kg/m^2	101	352	
≥ 30 kg/m^2	159	562	
Data Not Available	1	2	
HbA1c Category			
HbA1c data is available for 260 participants in the fasiglifam 50 mg treatment arm.			
Units: Subjects			
< 8.5%	148	538	
≥ 8.5%	112	377	
Data Not Available	1	1	
Weight			
Weight data is available for 260 participants in the fasiglifam 50 mg treatment arm.			
Units: kg			
arithmetic mean	91.53		
standard deviation	± 18.772	-	
Height			
Height data is available for 262 and 260 participants in the fasiglifam 25 mg and fasiglifam 50 mg treatment arms, respectively.			
Units: cm			
arithmetic mean	168.4		
standard deviation	± 9.85	-	
Body Mss Index (BMI)			
BMI data is available for 262 and 260 participants in the fasiglifam 25 mg and fasiglifam 50 mg treatment arms, respectively.			
Units: kg/m^2			
arithmetic mean	32.16		
standard deviation	± 5.651	-	
Glycosylated Hemoglobin (HbA1c)			
HbA1c data is available for 258 and 260 participants in the sitagliptin 100 mg and fasiglifam 50 mg treatment arms, respectively.			
Units: percent			
arithmetic mean	8.43		
standard deviation	± 0.765	-	
Duration of Diabetes			
Units: years			
arithmetic mean	6.375		
standard deviation	± 5.214	-	
Fasting Plasma Glucose			
Data is only available for 258 and 259 participants in the sitagliptin 100 mg and fasiglifam 50 mg treatment arms, respectively.			
Units: ng/dL			
arithmetic mean	180		
standard deviation	± 37.98	-	

End points

End points reporting groups

Reporting group title	Placebo

Reporting group description:

Fasiglifam placebo-matching tablets, orally, once daily for a 24-week Treatment Period followed by an optional 80-week extension period for up to 104 weeks of treatment. Sitagliptin placebo-matching tablets, orally, once daily for a 24-week Treatment Period followed by an optional 80-week extension period for up to 104 weeks of treatment. Metformin ≥1500 mg or Maximum Tolerated Dose (MTD) needs to continue at a stable dose.

Reporting group title	Sitagliptin 100 mg

Reporting group description:

Sitagliptin 100 mg, tablets, orally, once daily for a 24-week Treatment Period followed by an optional 80-week extension period for up to 104 weeks of treatment. Fasiglifam placebo-matching tablets, orally, once daily for a 24-week Treatment Period followed by an optional 80-week extension period for up to 104 weeks of treatment. Metformin ≥1500 mg or Maximum Tolerated Dose (MTD) needs to continue at a stable dose.

Reporting group title	Fasiglifam 25 mg

Reporting group description:

Fasiglifam 25 mg, tablets, orally, once daily for a 24-week Treatment Period followed by an optional 80-week extension period for up to 104 weeks of treatment. Sitagliptin placebo-matching tablets, orally, once daily for a 24-week Treatment Period followed by an optional 80-week extension period for up to 104 weeks of treatment. Metformin ≥1500 mg or Maximum Tolerated Dose (MTD) needs to continue at a stable dose.

Reporting group title	Fasiglifam 50 mg

Reporting group description:

Fasiglifam 50 mg, tablets, orally, once daily for a 24-week Treatment Period followed by an optional 80-week extension period for up to 104 weeks of treatment. Sitagliptin placebo-matching tablets, orally, once daily for a 24-week Treatment Period followed by an optional 80-week extension period for up to 104 weeks of treatment. Metformin ≥1500 mg or Maximum Tolerated Dose (MTD) needs to continue at a stable dose.

Reporting group title	Placebo

Reporting group description:

Fasiglifam placebo-matching tablets, orally, once daily for a 24-week Treatment Period followed by an optional 80-week extension period for up to 104 weeks of treatment. Sitagliptin placebo-matching tablets, orally, once daily for a 24-week Treatment Period followed by an optional 80-week extension period for up to 104 weeks of treatment. Metformin ≥1500 mg or Maximum Tolerated Dose (MTD) needs to continue at a stable dose.

Reporting group title	Sitagliptin 100 mg

Reporting group description:

Sitagliptin 100 mg, tablets, orally, once daily for a 24-week Treatment Period followed by an optional 80-week extension period for up to 104 weeks of treatment. Fasiglifam placebo-matching tablets, orally, once daily for a 24-week Treatment Period followed by an optional 80-week extension period for up to 104 weeks of treatment. Metformin ≥1500 mg or Maximum Tolerated Dose (MTD) needs to continue at a stable dose.

Reporting group title	Fasiglifam 25 mg

Reporting group description:

Fasiglifam 25 mg, tablets, orally, once daily for a 24-week Treatment Period followed by an optional 80-week extension period for up to 104 weeks of treatment. Sitagliptin placebo-matching tablets, orally, once daily for a 24-week Treatment Period followed by an optional 80-week extension period for up to 104 weeks of treatment. Metformin ≥1500 mg or Maximum Tolerated Dose (MTD) needs to continue at a stable dose.

Reporting group title	Fasiglifam 50 mg

Reporting group description:

Fasiglifam 50 mg, tablets, orally, once daily for a 24-week Treatment Period followed by an optional 80-week extension period for up to 104 weeks of treatment. Sitagliptin placebo-matching tablets, orally, once daily for a 24-week Treatment Period followed by an optional 80-week extension period for up to 104 weeks of treatment. Metformin ≥1500 mg or Maximum Tolerated Dose (MTD) needs to continue at a stable dose.

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 was used for analysis with treatment, country, schedule, 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.

End point type	Primary

End point timeframe:

Baseline and Week 24

End point values	Placebo	Sitagliptin 100 mg	Fasiglifam 25 mg	Fasiglifam 50 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	67	145	144	138
Units: percent				
least squares mean (standard error)	-0.19 (± 0.098)	-1.07 (± 0.074)	-0.75 (± 0.073)	-1.01 (± 0.074)

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Fasiglifam 25 mg
Number of subjects included in analysis	211
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [1]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-0.55
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.77
upper limit	-0.34
Variability estimate	Standard error of the mean
Dispersion value	0.108

Notes:

[1] - MMRM model with treatment, country, schedule, 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	Sitagliptin 100 mg v Fasiglifam 25 mg

Number of subjects included in analysis	289
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [2]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	0.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.15
upper limit	0.49
Variability estimate	Standard error of the mean
Dispersion value	0.087

Notes:

[2] - MMRM model with treatment, country, schedule, 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 3
Comparison groups	Placebo v Fasiglifam 50 mg
Number of subjects included in analysis	205
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [3]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-0.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.03
upper limit	-0.6
Variability estimate	Standard error of the mean
Dispersion value	0.109

Notes:

[3] - MMRM model with treatment, country, schedule, 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 4
Comparison groups	Sitagliptin 100 mg v Fasiglifam 50 mg
Number of subjects included in analysis	283
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.524 [4]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	0.06

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.12
upper limit	0.23
Variability estimate	Standard error of the mean
Dispersion value	0.087

Notes:

[4] - MMRM model with treatment, country, schedule, 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:

Incidence (percentage) of participants with glycosylated hemoglobin (the concentration of glucose bound to hemoglobin as a percent of the absolute maximum that can be bound) less than 7% at Week 24.

End point type	Secondary

End point timeframe:

24 Weeks

End point values	Placebo	Sitagliptin 100 mg	Fasiglifam 25 mg	Fasiglifam 50 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	67	145	144	138
Units: percentage of participants				
number (not applicable)	14.9	42.8	24.3	37

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Fasiglifam 25 mg
Number of subjects included in analysis	211
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.05 [5]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	1
upper limit	5.08

Notes:

[5] - P-Value was obtained from a logistic model with treatment, schedule, baseline HbA1c as explanatory variables.

Statistical analysis title	Statistical Analysis 2
Comparison groups	Sitagliptin 100 mg v Fasiglifam 25 mg
Number of subjects included in analysis	289
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [6]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.23
upper limit	0.67

Notes:

[6] - P-Value was obtained from a logistic model with treatment, schedule, baseline HbA1c as explanatory variables.

Statistical analysis title	Statistical Analysis 3
Comparison groups	Placebo v Fasiglifam 50 mg
Number of subjects included in analysis	205
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [7]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	5.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.24
upper limit	11.42

Notes:

[7] - P-Value was obtained from a logistic model with treatment, schedule, baseline HbA1c as explanatory variables.

Statistical analysis title	Statistical Analysis 4
Comparison groups	Sitagliptin 100 mg v Fasiglifam 50 mg
Number of subjects included in analysis	283
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.493 [8]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5
upper limit	1.39

Notes:

[8] - P-Value was obtained from a logistic model with treatment, schedule, baseline HbA1c as explanatory variables.

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 relative to Baseline. A MMRM model was used for analysis with treatment, country, schedule, 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.

End point type	Secondary

End point timeframe:

Baseline and Week 24

End point values	Placebo	Sitagliptin 100 mg	Fasiglifam 25 mg	Fasiglifam 50 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	67	145	142	135
Units: mg/dL				
least squares mean (standard error)	-1.6 (± 4.07)	-21.7 (± 3.13)	-26.9 (± 3.13)	-32.9 (± 3.18)

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Fasiglifam 25 mg
Number of subjects included in analysis	209
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [9]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-25.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-33.8
upper limit	-16.6
Variability estimate	Standard error of the mean
Dispersion value	4.36

Notes:

[9] - MMRM model with treatment, country, schedule, 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	Sitagliptin 100 mg v Fasiglifam 25 mg

Number of subjects included in analysis	287
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.142 [10]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-5.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12
upper limit	1.7
Variability estimate	Standard error of the mean
Dispersion value	3.49

Notes:

[10] - MMRM model with treatment, country, schedule, 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 3
Comparison groups	Placebo v Fasiglifam 50 mg
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [11]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-31.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-39.9
upper limit	-22.6
Variability estimate	Standard error of the mean
Dispersion value	4.4

Notes:

[11] - MMRM model with treatment, country, schedule, 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 4
Comparison groups	Sitagliptin 100 mg v Fasiglifam 50 mg
Number of subjects included in analysis	280
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002 [12]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-11.2

Confidence interval	
level	95 %
sides	2-sided
lower limit	-18.1
upper limit	-4.2
Variability estimate	Standard error of the mean
Dispersion value	3.53

Notes:

[12] - MMRM model with treatment, country, schedule, 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.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

First dose of study medication to 30 day past last dose of study medication (Up to 637 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	16.1

Reporting groups

Reporting group title	Placebo

Reporting group description:

Fasiglifam placebo-matching tablets, orally, once daily for a 24-week Treatment Period followed by an optional 80-week extension period for up to 104 weeks of treatment. Sitagliptin placebo-matching tablets, orally, once daily for a 24-week Treatment Period followed by an optional 80-week extension period for up to 104 weeks of treatment. Metformin ≥1500 mg or Maximum Tolerated Dose (MTD) needs to continue at a stable dose.

Reporting group title	Sitagliptin 100 mg

Reporting group description:

Sitagliptin 100 mg, tablets, orally, once daily for a 24-week Treatment Period followed by an optional 80-week extension period for up to 104 weeks of treatment. Fasiglifam placebo-matching tablets, orally, once daily for a 24-week Treatment Period followed by an optional 80-week extension period for up to 104 weeks of treatment. Metformin ≥1500 mg or Maximum Tolerated Dose (MTD) needs to continue at a stable dose.

Reporting group title	Fasiglifam 25 mg

Reporting group description:

Fasiglifam 25 mg, tablets, orally, once daily for a 24-week Treatment Period followed by an optional 80-week extension period for up to 104 weeks of treatment. Sitagliptin placebo-matching tablets, orally, once daily for a 24-week Treatment Period followed by an optional 80-week extension period for up to 104 weeks of treatment. Metformin ≥1500 mg or Maximum Tolerated Dose (MTD) needs to continue at a stable dose.

Reporting group title	Fasiglifam 50 mg

Reporting group description:

Fasiglifam 50 mg, tablets, orally, once daily for a 24-week Treatment Period followed by an optional 80-week extension period for up to 104 weeks of treatment. Sitagliptin placebo-matching tablets, orally, once daily for a 24-week Treatment Period followed by an optional 80-week extension period for up to 104 weeks of treatment. Metformin ≥1500 mg or Maximum Tolerated Dose (MTD) needs to continue at a stable dose.

Serious adverse events	Placebo	Sitagliptin 100 mg	Fasiglifam 25 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 132 (1.52%)	10 / 260 (3.85%)	14 / 263 (5.32%)
number of deaths (all causes)	1	1	0
number of deaths resulting from adverse events			0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer female			

subjects affected / exposed	0 / 132 (0.00%)	0 / 260 (0.00%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal carcinoma			
subjects affected / exposed	1 / 132 (0.76%)	0 / 260 (0.00%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Tumour of ampulla of Vater			
subjects affected / exposed	0 / 132 (0.00%)	1 / 260 (0.38%)	0 / 263 (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
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 132 (0.00%)	0 / 260 (0.00%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral artery stenosis			
subjects affected / exposed	0 / 132 (0.00%)	0 / 260 (0.00%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral vascular disorder			
subjects affected / exposed	0 / 132 (0.00%)	1 / 260 (0.38%)	0 / 263 (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
General disorders and administration site conditions			
Non-cardiac chest pain			
subjects affected / exposed	0 / 132 (0.00%)	0 / 260 (0.00%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			

subjects affected / exposed	0 / 132 (0.00%)	0 / 260 (0.00%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 132 (0.00%)	1 / 260 (0.38%)	0 / 263 (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
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 132 (0.00%)	0 / 260 (0.00%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 132 (0.00%)	0 / 260 (0.00%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood bilirubin increased			
subjects affected / exposed	0 / 132 (0.00%)	1 / 260 (0.38%)	0 / 263 (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
Carotid bruit			
subjects affected / exposed	0 / 132 (0.00%)	1 / 260 (0.38%)	0 / 263 (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
Liver function test abnormal			
subjects affected / exposed	0 / 132 (0.00%)	1 / 260 (0.38%)	0 / 263 (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
Injury, poisoning and procedural complications			
Radius fracture			

subjects affected / exposed	0 / 132 (0.00%)	0 / 260 (0.00%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			
Phimosis			
subjects affected / exposed	1 / 132 (0.76%)	0 / 260 (0.00%)	0 / 263 (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
Cardiac disorders			
Angina unstable			
subjects affected / exposed	0 / 132 (0.00%)	0 / 260 (0.00%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block first degree			
subjects affected / exposed	0 / 132 (0.00%)	1 / 260 (0.38%)	0 / 263 (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
Cardiac failure			
subjects affected / exposed	0 / 132 (0.00%)	0 / 260 (0.00%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery disease			
subjects affected / exposed	0 / 132 (0.00%)	0 / 260 (0.00%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 132 (0.00%)	0 / 260 (0.00%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radiculopathy			
subjects affected / exposed	0 / 132 (0.00%)	1 / 260 (0.38%)	0 / 263 (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

Syncope			
subjects affected / exposed	0 / 132 (0.00%)	0 / 260 (0.00%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 132 (0.00%)	0 / 260 (0.00%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Pancreatitis			
subjects affected / exposed	0 / 132 (0.00%)	0 / 260 (0.00%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	0 / 132 (0.00%)	1 / 260 (0.38%)	0 / 263 (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
Cholecystitis			
subjects affected / exposed	0 / 132 (0.00%)	1 / 260 (0.38%)	0 / 263 (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
Cholelithiasis			
subjects affected / exposed	0 / 132 (0.00%)	0 / 260 (0.00%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Liver disorder			
subjects affected / exposed	0 / 132 (0.00%)	1 / 260 (0.38%)	0 / 263 (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
Renal and urinary disorders			
Nephrolithiasis			

subjects affected / exposed	0 / 132 (0.00%)	0 / 260 (0.00%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Intervertebral disc disorder			
subjects affected / exposed	0 / 132 (0.00%)	1 / 260 (0.38%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bronchopneumonia			
subjects affected / exposed	0 / 132 (0.00%)	0 / 260 (0.00%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erysipelas			
subjects affected / exposed	0 / 132 (0.00%)	0 / 260 (0.00%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gangrene			
subjects affected / exposed	0 / 132 (0.00%)	0 / 260 (0.00%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis B			
subjects affected / exposed	0 / 132 (0.00%)	1 / 260 (0.38%)	0 / 263 (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
Pneumonia			
subjects affected / exposed	0 / 132 (0.00%)	0 / 260 (0.00%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 132 (0.00%)	2 / 260 (0.77%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0

Serious adverse events	Fasiglifam 50 mg		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 260 (1.54%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer female			
subjects affected / exposed	0 / 260 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Oesophageal carcinoma			
subjects affected / exposed	0 / 260 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Tumour of ampulla of Vater			
subjects affected / exposed	0 / 260 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 260 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Peripheral artery stenosis			
subjects affected / exposed	1 / 260 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Peripheral vascular disorder			
subjects affected / exposed	0 / 260 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Non-cardiac chest pain			

subjects affected / exposed	0 / 260 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 260 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 260 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 260 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 260 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood bilirubin increased			
subjects affected / exposed	0 / 260 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Carotid bruit			
subjects affected / exposed	0 / 260 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Liver function test abnormal			

subjects affected / exposed	0 / 260 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Radius fracture			
subjects affected / exposed	0 / 260 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Congenital, familial and genetic disorders			
Phimosis			
subjects affected / exposed	0 / 260 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Angina unstable			
subjects affected / exposed	0 / 260 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Atrioventricular block first degree			
subjects affected / exposed	0 / 260 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac failure			
subjects affected / exposed	0 / 260 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Coronary artery disease			
subjects affected / exposed	0 / 260 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Cerebrovascular accident			

subjects affected / exposed	0 / 260 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Radiculopathy			
subjects affected / exposed	0 / 260 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	0 / 260 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 260 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Pancreatitis			
subjects affected / exposed	0 / 260 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	0 / 260 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cholecystitis			
subjects affected / exposed	0 / 260 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cholelithiasis			
subjects affected / exposed	0 / 260 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Liver disorder			
subjects affected / exposed	0 / 260 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	1 / 260 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Intervertebral disc disorder			
subjects affected / exposed	0 / 260 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Bronchopneumonia			
subjects affected / exposed	0 / 260 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Erysipelas			
subjects affected / exposed	0 / 260 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gangrene			
subjects affected / exposed	0 / 260 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatitis B			
subjects affected / exposed	0 / 260 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia			

subjects affected / exposed	1 / 260 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	0 / 260 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Placebo	Sitagliptin 100 mg	Fasiglifam 25 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	17 / 132 (12.88%)	16 / 260 (6.15%)	18 / 263 (6.84%)
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	3 / 132 (2.27%)	8 / 260 (3.08%)	7 / 263 (2.66%)
occurrences (all)	3	11	8
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	14 / 132 (10.61%)	9 / 260 (3.46%)	11 / 263 (4.18%)
occurrences (all)	16	11	11

Non-serious adverse events	Fasiglifam 50 mg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	20 / 260 (7.69%)		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	14 / 260 (5.38%)		
occurrences (all)	15		
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	7 / 260 (2.69%)		
occurrences (all)	7		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 May 2012	• Clarification that 80-week Extension Period was optional • lower limit for BMI changed • exclusion of participants with a history of pancreatitis • telephone follow-up call added for participants who prematurely discontinued • male subjects were not required to use contraception • exclusion of participants with uncontrolled thyroid disease • insulin could be used as rescue medication during the study • hypoglycemic rescue medication complied with local guidelines and clinical practices • clarification of management of hypoglycemic events.
08 April 2013	• Duration of previous stable metformin use that was required before Screening (ie, 8 weeks) • exclusion if laboratory or ECG abnormalities detected at Screening were clinically significant • clarification of the definition of probable symptomatic hypoglycemia • timing of in-clinic study drug administration and provided guidance on missed doses • glimepiride rescue medication dosing recommendations • clearer guidance on the screening and fasting process.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
26 December 2013	Termination of the compound development program by the sponsor.	-

Notes:

Limitations and caveats

None reported