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

Summary

EudraCT number	2011-001731-24
Trial protocol	LV LT CZ EE BG GB
Global end of trial date	24 April 2014

Results information

Result version number	v1
This version publication date	30 June 2016
First version publication date	31 July 2015

Trial information

Trial identification

Sponsor protocol code	TAK-875_304

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01481116
WHO universal trial number (UTN)	U1111-1124-2296

Notes:

Sponsors

Sponsor organisation name	Takeda
Sponsor organisation address	61 Aldwych, London, United Kingdom, WC2B 4AE
Public contact	Program Manager, Takeda Development Centre Europe Ltd., 004 40203116 8000, clinicaloperations@tgrd.com
Scientific contact	Program Manager, Takeda Development Centre Europe Ltd., 004 40203116 8000, clinicaloperations@tgrd.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	17 December 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	24 April 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 to glimepiride plus metformin on glycemic control as assessed by change from baseline in glycosylated hemoglobin (HbA1c) at Weeks 78 and 104.

Protection of trial subjects:

All study subjects were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 November 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 113
Country: Number of subjects enrolled	Australia: 9
Country: Number of subjects enrolled	Bulgaria: 51
Country: Number of subjects enrolled	Canada: 121
Country: Number of subjects enrolled	Colombia: 3
Country: Number of subjects enrolled	Czech Republic: 93
Country: Number of subjects enrolled	Estonia: 36
Country: Number of subjects enrolled	Hong Kong: 29
Country: Number of subjects enrolled	Israel: 150
Country: Number of subjects enrolled	Latvia: 43
Country: Number of subjects enrolled	Lithuania: 66
Country: Number of subjects enrolled	Malaysia: 50
Country: Number of subjects enrolled	Mexico: 43
Country: Number of subjects enrolled	New Zealand: 44
Country: Number of subjects enrolled	Philippines: 114
Country: Number of subjects enrolled	Poland: 193
Country: Number of subjects enrolled	Romania: 155
Country: Number of subjects enrolled	Russian Federation: 78
Country: Number of subjects enrolled	South Africa: 247
Country: Number of subjects enrolled	Taiwan: 34
Country: Number of subjects enrolled	Ukraine: 239
Country: Number of subjects enrolled	United Kingdom: 51

Country: Number of subjects enrolled	United States: 492
Worldwide total number of subjects	2454
EEA total number of subjects	688

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)	1931
From 65 to 84 years	523
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects took part at 291 sites in Argentina, Australia, Bulgaria, Canada, Colombia, Czech Republic, Estonia, Hong Kong, Israel, Latvia, Lithuania, Malaysia, Mexico, New Zealand, Philippines, Poland, Romania, the Russian Federation, South Africa, Taiwan, Ukraine, the United Kingdom and the United States from 06 November 2011 to 24 April 2014.

Pre-assignment

Screening details:

Subjects with a historical diagnosis of type 2 diabetes mellitus who were inadequately controlled while receiving metformin alone were enrolled in 1 of 3 treatment groups as follows: glimepiride; TAK-875 25 milligram (mg); TAK-875 50 mg.

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, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Glimepiride

Arm description:

TAK-875 placebo-matching tablets, orally, once daily and glimepiride 1 mg, over-encapsulated capsules, orally, once daily for 1 week followed by up-titration in 2 mg increments up to 6 mg, orally, once daily along with metformin greater than or equal to (>=)1500 mg per day or maximum tolerated dose, tablets, orally for up to 104 weeks. Glimepiride dose could be down-titrated from 6 mg in case of recurrent or severe hypoglycemia.

Arm type	Active comparator
Investigational medicinal product name	Glimepiride
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Glimepiride 1 mg, over-encapsulated capsules, orally, once daily for 1 week followed by up-titration in 2 mg increments up to 6 mg, orally, once daily for up to 104 weeks. Glimepiride dose could be down-titrated from 6 mg in case of recurrent or severe hypoglycemia.

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

Dosage and administration details:

TAK-875 placebo-matching tablets, orally, once daily for up to 104 weeks.

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

Dosage and administration details:

Metformin >=1500 mg per day or maximum tolerated dose, tablets, orally for up to 104 weeks

Arm title	TAK-875 25 mg

Arm description:

TAK-875 25 mg, tablets, orally, once daily and glimepiride placebo-matching capsules, orally, once daily along with metformin >=1500 mg per day or maximum tolerated dose, tablets, orally for up to 104 weeks.

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

Dosage and administration details:

TAK-875 25 mg, tablets, orally, once daily for up to 104 weeks.

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

Dosage and administration details:

Glimepiride placebo -matching capsules, orally, once daily for up to 104 weeks.

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

Dosage and administration details:

Metformin >=1500 mg per day or maximum tolerated dose, tablets, orally for up to 104 weeks.

Arm title	TAK-875 50 mg

Arm description:

TAK-875 50 mg, tablets, orally, once daily and glimepiride placebo-matching capsules, orally, once daily along with metformin >=1500 mg per day or maximum tolerated dose, tablets, orally for up to 104 weeks.

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

Dosage and administration details:

TAK-875 50 mg tablets, orally, once daily for up to 104 weeks.

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

Dosage and administration details:

Glimepiride placebo-matching capsules, orally, once daily for up to 104 weeks.

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

Dosage and administration details:
Metformin >=1500 mg per day or maximum tolerated dose, tablets, orally for up to 104 weeks.

Number of subjects in period 1	Glimepiride	TAK-875 25 mg	TAK-875 50 mg
Started	824	817	813
Treated	822	816	813
Completed	0	0	0
Not completed	824	817	813
Consent withdrawn by subject	36	33	37
Study termination	730	729	713
Other	17	6	7
Major protocol deviation	3	7	1
Pregnancy	-	-	1
Adverse event	26	26	42
Contraindications	1	1	-
Lost to follow-up	8	12	11
Lack of efficacy	3	3	1

Baseline characteristics

Reporting groups	
Reporting group title	Glimepiride
Reporting group description:	
TAK-875 placebo-matching tablets, orally, once daily and glimepiride 1 mg, over-encapsulated capsules, orally, once daily for 1 week followed by up-titration in 2 mg increments up to 6 mg, orally, once daily along with metformin greater than or equal to (>=)1500 mg per day or maximum tolerated dose, tablets, orally for up to 104 weeks. Glimepiride dose could be down-titrated from 6 mg in case of recurrent or severe hypoglycemia.	
Reporting group title	TAK-875 25 mg
Reporting group description:	
TAK-875 25 mg, tablets, orally, once daily and glimepiride placebo-matching capsules, orally, once daily along with metformin >=1500 mg per day or maximum tolerated dose, tablets, orally for up to 104 weeks.	
Reporting group title	TAK-875 50 mg
Reporting group description:	
TAK-875 50 mg, tablets, orally, once daily and glimepiride placebo-matching capsules, orally, once daily along with metformin >=1500 mg per day or maximum tolerated dose, tablets, orally for up to 104 weeks.	

Reporting group values	Glimepiride	TAK-875 25 mg	TAK-875 50 mg
Number of subjects	824	817	813
Age categorical Units: Subjects			
Less than (<) 65 years	637	646	648
>=65 years	187	171	165
Age continuous Units: years			
arithmetic mean	57.3	56.8	56.6
standard deviation	± 9.56	± 9.34	± 9.81
Gender categorical Units: Subjects			
Female	428	422	362
Male	396	395	451
Race/Ethnicity, Customized Units: Subjects			
Hispanic or Latino	68	66	70
Non-Hispanic or Latino	105	110	106
Not Available	651	641	637
Race/Ethnicity, Customized Units: Subjects			
American Indian or Alaska Native	8	20	12
Asian	101	99	93
Black or African American	62	70	77
Native Hawaiian or Other Pacific Islander	3	4	7
White	617	598	601
Multiracial	33	26	23
Region of Enrollment Units: Subjects			

Argentina	37	39	37
Australia	4	2	3
Bulgaria	17	18	16
Canada	42	40	39
Colombia	2	0	1
Czech Republic	31	31	31
Estonia	12	12	12
Hong Kong	9	10	10
Israel	50	50	50
Latvia	15	14	14
Lithuania	21	23	22
Malaysia	17	16	17
Mexico	14	14	15
New Zealand	15	14	15
Philippines	39	38	37
Poland	64	66	63
Romania	52	52	51
Russian Federation	26	26	26
South Africa	83	81	83
Taiwan, Province Of China	11	11	12
Ukraine	80	80	79
United Kingdom	18	16	17
United States	165	164	163
Smoking Classification Units: Subjects			
Never smoked	552	533	502
Current smoker	114	143	126
Ex-smoker	158	141	185
Baseline Glycosylated Hemoglobin (HbA1c) Category Units: Subjects			
< 8.5 percent (%)	584	584	592
>=8.5%	238	232	221
Not Available	2	1	0
Height			
For this endpoint, number of subjects evaluable were 823, 817 and 813 for each arm, respectively.			
Units: centimeter			
arithmetic mean	166.2	166.2	167.3
standard deviation	± 10.66	± 10.23	± 10.19
Weight			
For this endpoint, number of subjects evaluable were 822, 816 and 813 for each arm, respectively.			
Units: kilogram (kg)			
arithmetic mean	86.95	87.35	88.37
standard deviation	± 18.415	± 18.283	± 18.796
Body Mass Index (BMI)			
For this endpoint, number of subjects evaluable were 821, 816 and 813 for each arm, respectively.			
Units: kilogram per square meter (kg/m^2)			
arithmetic mean	31.34	31.5	31.43
standard deviation	± 5.334	± 5.253	± 5.403
Duration of Diabetes			
For this endpoint, number of subjects evaluable were 823, 817 and 812 for each arm, respectively.			

Units: years			
arithmetic mean	6.372	6.566	5.995
standard deviation	± 5.293	± 5.132	± 4.711

Reporting group values	Total		
Number of subjects	2454		
Age categorical			
Units: Subjects			
Less than (<) 65 years	1931		
>=65 years	523		
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	1212		
Male	1242		
Race/Ethnicity, Customized			
Units: Subjects			
Hispanic or Latino	204		
Non-Hispanic or Latino	321		
Not Available	1929		
Race/Ethnicity, Customized			
Units: Subjects			
American Indian or Alaska Native	40		
Asian	293		
Black or African American	209		
Native Hawaiian or Other Pacific Islander	14		
White	1816		
Multiracial	82		
Region of Enrollment			
Units: Subjects			
Argentina	113		
Australia	9		
Bulgaria	51		
Canada	121		
Colombia	3		
Czech Republic	93		
Estonia	36		
Hong Kong	29		
Israel	150		
Latvia	43		
Lithuania	66		
Malaysia	50		
Mexico	43		
New Zealand	44		
Philippines	114		
Poland	193		
Romania	155		

Russian Federation	78		
South Africa	247		
Taiwan, Province Of China	34		
Ukraine	239		
United Kingdom	51		
United States	492		
Smoking Classification Units: Subjects			
Never smoked	1587		
Current smoker	383		
Ex-smoker	484		
Baseline Glycosylated Hemoglobin (HbA1c) Category Units: Subjects			
< 8.5 percent (%)	1760		
>=8.5%	691		
Not Available	3		
Height			
For this endpoint, number of subjects evaluable were 823, 817 and 813 for each arm, respectively.			
Units: centimeter arithmetic mean standard deviation	- -		
Weight			
For this endpoint, number of subjects evaluable were 822, 816 and 813 for each arm, respectively.			
Units: kilogram (kg) arithmetic mean standard deviation	- -		
Body Mass Index (BMI)			
For this endpoint, number of subjects evaluable were 821, 816 and 813 for each arm, respectively.			
Units: kilogram per square meter (kg/m^2) arithmetic mean standard deviation	- -		
Duration of Diabetes			
For this endpoint, number of subjects evaluable were 823, 817 and 812 for each arm, respectively.			
Units: years arithmetic mean standard deviation	- -		

End points

End points reporting groups

Reporting group title	Glimepiride
Reporting group description:	
TAK-875 placebo-matching tablets, orally, once daily and glimepiride 1 mg, over-encapsulated capsules, orally, once daily for 1 week followed by up-titration in 2 mg increments up to 6 mg, orally, once daily along with metformin greater than or equal to (>=)1500 mg per day or maximum tolerated dose, tablets, orally for up to 104 weeks. Glimepiride dose could be down-titrated from 6 mg in case of recurrent or severe hypoglycemia.	
Reporting group title	TAK-875 25 mg
Reporting group description:	
TAK-875 25 mg, tablets, orally, once daily and glimepiride placebo-matching capsules, orally, once daily along with metformin >=1500 mg per day or maximum tolerated dose, tablets, orally for up to 104 weeks.	
Reporting group title	TAK-875 50 mg
Reporting group description:	
TAK-875 50 mg, tablets, orally, once daily and glimepiride placebo-matching capsules, orally, once daily along with metformin >=1500 mg per day or maximum tolerated dose, tablets, orally for up to 104 weeks.	

Primary: Change From Baseline in HbA1c at Weeks 78 and 104

End point title	Change From Baseline in HbA1c at Weeks 78 and 104
End point description:	
The change in the value of HbA1c (the concentration of glucose bound to hemoglobin as a percent of the absolute maximum that can be bound) to be collected at Weeks 78 and 104 relative to baseline. Full Analysis Set (FAS) included all randomized subjects who received at least 1 dose of double-blind study medication and who had a baseline and at least 1 post- baseline assessment. Data for Week 104 was not available due to early termination of the study.	
End point type	Primary
End point timeframe:	
Baseline and Weeks 78 and 104	

End point values	Glimepiride	TAK-875 25 mg	TAK-875 50 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	822	816	813	
Units: percentage of glycosylated hemoglobin				
least squares mean (standard error)				
Baseline (n= 813, 805, 800)	7.92 (± 0.045)	7.92 (± 0.046)	7.91 (± 0.046)	
Change at Week 78 (n= 62, 61, 66)	-0.58 (± 0.078)	-0.55 (± 0.078)	-0.83 (± 0.077)	

Statistical analyses

Statistical analysis title	Change at Week 78: Glimepiride vs TAK-875 25 mg

Statistical analysis description:

Assuming a 1.2% standard deviation (SD) for change from Baseline in HbA1c, expected treatment difference between a TAK-875 dose group and glimepiride group of 0.0, and a drop-out rate of 40%, 810 subjects per treatment group would have provided at least 90% power to demonstrate TAK-875 dose group was non-inferior to glimepiride group.Treatment, schedule and visit-by-treatment interaction as fixed factors and with baseline value and baseline value by visit interaction as covariates.

Comparison groups	Glimepiride v TAK-875 25 mg
Number of subjects included in analysis	1638
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
P-value	= 0.738 [2]
Method	Mixed Model Repeated Measures
Parameter estimate	Least Squares Mean Difference
Point estimate	0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.17
upper limit	0.24
Variability estimate	Standard error of the mean
Dispersion value	0.104

Notes:

[1] - Non-inferiority was tested with a margin of 0.3%.

[2] - Stepwise Comparison: 1) TAK-875 50mg versus (vs.) glimepiride non-inferiority (NI) test, 2) TAK-875 25mg vs. glimepiride NI test, 3) TAK-875 50mg vs. glimepiride (0.025 significance level), 4) TAK-875 25mg vs. glimepiride (0.025 significance level).

Statistical analysis title	Change at Week 78: Glimepiride vs TAK-875 50 mg

Statistical analysis description:

Assuming a 1.2% SD for change from Baseline in HbA1c, expected treatment difference between a TAK-875 dose group and glimepiride group of 0.0, and a drop-out rate of 40%, 810 subjects per treatment group would have provided at least 90% power to demonstrate TAK-875 dose group was non-inferior to glimepiride group. Treatment, schedule and visit-by-treatment interaction as fixed factors and with baseline value and baseline value by visit interaction as covariates.

Comparison groups	Glimepiride v TAK-875 50 mg
Number of subjects included in analysis	1635
Analysis specification	Pre-specified
Analysis type	non-inferiority[3]
P-value	= 0.015 [4]
Method	Mixed Model Repeated Measures
Parameter estimate	Least Squares Mean Difference
Point estimate	-0.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.45
upper limit	-0.05
Variability estimate	Standard error of the mean
Dispersion value	0.103

Notes:

[3] - Non-inferiority was tested with a margin of 0.3%.

[4] - Stepwise Comparison: 1) TAK-875 50mg versus (vs.) glimepiride NI test, 2) TAK-875 25mg vs. glimepiride NI test, 3) TAK-875 50mg vs. glimepiride (0.025 significance level), 4) TAK-875 25mg vs.

glimepiride (0.025 significance level).

Secondary: Percentage of Subjects With Hypoglycemia

End point title	Percentage of Subjects With Hypoglycemia

End point description:

Subjects were provided diaries to document any hypoglycemic events that occurred between study visits. Any experience of hypoglycemic signs and symptoms (regardless of the blood glucose value by glucometer) or had a blood glucose value less than or equal to (<=) 70 milligram per deciliter (mg/dL) (3.9 millimole per liter (mmol/L) by glucometer (regardless of symptoms) were to be recorded. Safety analysis set included all subjects who received at least 1 dose of double-blind study medication. Subjects were analyzed according to the study medication they received.

End point type	Secondary

End point timeframe:

Day 1 up to Weeks 78 and 104

End point values	Glimepiride	TAK-875 25 mg	TAK-875 50 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	822	816	813	
Units: percentage of subjects				
number (not applicable)				
Day 1 up to Week 78	30.2	5.4	5.3	
Day 1 up to Week 104	30.2	5.4	5.3	

Statistical analyses

Statistical analysis title	Day 1 up to Week 78: Glimepiride, TAK-875 25 mg

Statistical analysis description:

Odds Ratios, corresponding confidence interval, and p-values were calculated using logistic regression with factors for treatment, country, schedule and baseline HbA1c value.

Comparison groups	Glimepiride v TAK-875 25 mg
Number of subjects included in analysis	1638
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [5]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.09
upper limit	0.18

Notes:

[5] - The testing procedure at 2-sided significance level of 0.025 was as follows: 1) TAK-875 25 mg vs. glimepiride, 2) TAK-875 50 mg vs. glimepiride. If P-value was not greater than 0.025 at Step 1, then Step 2 was carried out.

Statistical analysis title	Day 1 up to Week 78: Glimepiride, TAK-875 50 mg

Statistical analysis description:

Odds Ratios, corresponding confidence interval, and p-values were calculated using logistic regression with factors for treatment, country, schedule and baseline HbA1c value.

Comparison groups	Glimepiride v TAK-875 50 mg
Number of subjects included in analysis	1635
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [6]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.09
upper limit	0.18

Notes:

[6] - The testing procedure at 2-sided significance level of 0.025 was as follows: 1) TAK-875 25 mg vs. glimepiride, 2) TAK-875 50 mg vs. glimepiride. If P-value was not greater than 0.025 at Step 1, then Step 2 was carried out.

Statistical analysis title	Day 1 up to Week 104: Glimepiride, TAK-875 25 mg

Statistical analysis description:

Odds Ratios, corresponding confidence interval, and p-values were calculated using logistic regression with factors for treatment, country, schedule and baseline HbA1c value.

Comparison groups	Glimepiride v TAK-875 25 mg
Number of subjects included in analysis	1638
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [7]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.09
upper limit	0.18

Notes:

[7] - The testing procedure at 2-sided significance level of 0.025 was as follows: 1) TAK-875 25 mg vs. glimepiride, 2) TAK-875 50 mg vs. glimepiride. If P-value was not greater than 0.025 at Step 1, then Step 2 was carried out.

Statistical analysis title	Day 1 up to Week 104: Glimepiride, TAK-875 50 mg

Statistical analysis description:

Odds Ratios, corresponding confidence interval, and p-values were calculated using logistic regression with factors for treatment, country, schedule and baseline HbA1c value.

Comparison groups	Glimepiride v TAK-875 50 mg

Number of subjects included in analysis	1635
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [8]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.09
upper limit	0.18

Notes:

[8] - The testing procedure at 2-sided significance level of 0.025 was as follows: 1) TAK-875 25 mg vs. glimepiride, 2) TAK-875 50 mg vs. glimepiride. If P-value was not greater than 0.025 at Step 1, then Step 2 was carried out.

Secondary: Change From Baseline in Body Weight at Weeks 78 and 104

End point title	Change From Baseline in Body Weight at Weeks 78 and 104

End point description:

The change between the body weight to be collected at Weeks 78 and 104 relative to baseline. FAS included all randomized subjects who received at least 1 dose of double-blind study medication and who had a baseline and at least 1 post- baseline value during the double-blind treatment period. Data for body weight was not available at Week 104 due to early termination of the study.

End point type	Secondary

End point timeframe:

Baseline and Weeks 78 and 104

End point values	Glimepiride	TAK-875 25 mg	TAK-875 50 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	822	816	813	
Units: kilogram				
least squares mean (standard error)				
Baseline (n= 809, 804, 805)	84.32 (± 0.981)	84.55 (± 1.003)	85.67 (± 0.995)	
Change at Week 78 (n= 51, 44, 55)	1.24 (± 0.492)	-0.07 (± 0.524)	-0.21 (± 0.487)	

Statistical analyses

Statistical analysis title	Change at Week 78: Glimepiride vs TAK-875 25 mg

Statistical analysis description:

Treatment, schedule and visit-by-treatment interaction as fixed factors and with baseline value and baseline value by visit interaction as covariates.

Comparison groups	Glimepiride v TAK-875 25 mg

Number of subjects included in analysis	1638
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.065 [9]
Method	Mixed Model Repeated Measures
Parameter estimate	Least Squares Mean Difference
Point estimate	-1.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.7
upper limit	0.08
Variability estimate	Standard error of the mean
Dispersion value	0.707

Notes:

[9] - The testing procedure at 2-sided significance level of 0.025 was as follows: 1) TAK-875 25 mg vs. glimepiride, 2) TAK-875 50 mg vs. glimepiride. If P-value was not greater than 0.025 at Step 1, then Step 2 was carried out.

Statistical analysis title	Change at Week 78: Glimepiride vs TAK-875 50 mg

Statistical analysis description:

Treatment, schedule and visit-by-treatment interaction as fixed factors and with baseline value and baseline value by visit interaction as covariates.

Comparison groups	Glimepiride v TAK-875 50 mg
Number of subjects included in analysis	1635
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.034 [10]
Method	Mixed Model Repeated Measures
Parameter estimate	Least Squares Mean Difference
Point estimate	-1.44
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.78
upper limit	-0.11
Variability estimate	Standard error of the mean
Dispersion value	0.678

Notes:

[10] - The testing procedure at 2-sided significance level of 0.025 was as follows: 1) TAK-875 25 mg vs. glimepiride, 2) TAK-875 50 mg vs. glimepiride. If P-value was not greater than 0.025 at Step 1, then Step 2 was carried out.

Secondary: Change From Baseline in HbA1c at Weeks 26 and 52

End point title	Change From Baseline in HbA1c at Weeks 26 and 52

End point description:

The change in the value of HbA1c collected at Weeks 26 and 52 relative to baseline. FAS included all randomized subjects who received at least 1 dose of double-blind study medication and who had a baseline and at least 1 post- baseline value during the double-blind treatment period.

End point type	Secondary

End point timeframe:

Baseline and Weeks 26 and 52

End point values	Glimepiride	TAK-875 25 mg	TAK-875 50 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	822	816	813	
Units: percentage of glycosylated hemoglobin				
least squares mean (standard error)				
Week 26 (n= 652, 645, 641)	-0.91 (± 0.039)	-0.63 (± 0.039)	-0.81 (± 0.039)	
Week 52 (n= 322, 300, 325)	-0.78 (± 0.043)	-0.65 (± 0.044)	-0.81 (± 0.043)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects With HbA1c <7%

End point title	Percentage of subjects With HbA1c <7%

End point description:

FAS included all randomized subjects who received at least 1 dose of double-blind study medication and who had a baseline and at least 1 post- baseline value during the double-blind treatment period. Here, "99999" for the measure value signifies "Not estimable".

End point type	Secondary

End point timeframe:

Weeks 26, 52, 78 and 104

End point values	Glimepiride	TAK-875 25 mg	TAK-875 50 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	822	816	813	
Units: percentage of subjects				
number (not applicable)				
Week 26 (n= 652, 645, 641)	51.8	38.3	48.7	
Week 52 (n= 322, 300, 325)	47.8	43.3	54.5	
Week 78 (n= 62, 61, 66)	45.2	37.7	54.5	
Week 104 (n= 0, 3, 3)	99999	33.3	33.3	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With HbA1c <7% for Subjects Who Did Not

Report Hypoglycemia

End point title	Percentage of Subjects With HbA1c <7% for Subjects Who Did Not Report Hypoglycemia

End point description:

Data for this endpoint was not analyzed due to change in planned analysis.

End point type	Secondary

End point timeframe:

Weeks 26, 52, 78 and 104

End point values	Glimepiride	TAK-875 25 mg	TAK-875 50 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[11]	0[12]	0[13]	
Units: Percentage of subjects				
number (not applicable)				

Notes:

[11] - Data for this endpoint was not analyzed due to change in planned analysis.

[12] - Data for this endpoint was not analyzed due to change in planned analysis.

[13] - Data for this endpoint was not analyzed due to change in planned analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Fasting Plasma Glucose at Weeks 26, 52, 78 and 104

End point title	Change From Baseline in Fasting Plasma Glucose at Weeks 26, 52, 78 and 104

End point description:

The change between the fasting plasma glucose value to be collected at Weeks 26, 52, 78 and 104 relative to baseline. FAS included all randomized subjects who received at least 1 dose of double-blind study medication and who had a baseline and at least 1 post- baseline value during the double-blind treatment period. Data for FPG was not available at Week 104 due to early termination of the study.

End point type	Secondary

End point timeframe:

Baseline and Weeks 26, 52, 78 and 104

End point values	Glimepiride	TAK-875 25 mg	TAK-875 50 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	822	816	813	
Units: milligram per deciliter (mg/dL)				
least squares mean (standard error)				
Baseline (n= 815, 808, 805)	161.8 (± 2.2)	162.4 (± 2.25)	161.1 (± 2.23)	
Change at Week 26 (n= 635, 629, 626)	-18.8 (± 1.48)	-17.4 (± 1.5)	-23.4 (± 1.5)	
Change at Week 52 (n= 311, 290, 313)	-17.7 (± 1.77)	-18.6 (± 1.83)	-24.6 (± 1.79)	
Change at Week 78 (n= 54, 44, 56)	-6.4 (± 4.32)	-10.8 (± 4.67)	-22.1 (± 4.2)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment-emergent adverse events are adverse events that started after the first dose of double-blind study drug and no more than 30 days for a serious adverse event after the last dose of double-blind study drug.

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 subject 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	Glimepiride

Reporting group description:

TAK-875 placebo-matching tablets, orally, once daily and glimepiride 1 mg, over-encapsulated capsules, orally, once daily for 1 week followed by up-titration in 2 mg increments up to 6 mg, orally, once daily along with metformin >=1500 mg per day or maximum tolerated dose, tablets, orally for up to 104 weeks. Glimepiride dose could be down-titrated from 6 mg in case of recurrent or severe hypoglycemia.

Reporting group title	TAK-875 25 mg

Reporting group description:

TAK-875 25 mg, tablets, orally, once daily and glimepiride placebo-matching capsules, orally, once daily along with metformin >=1500 mg per day or maximum tolerated dose, tablets, orally for up to 104 weeks.

Reporting group title	TAK-875 50 mg

Reporting group description:

TAK-875 50 mg, tablets, orally, once daily and glimepiride placebo-matching capsules, orally, once daily along with metformin >=1500 mg per day or maximum tolerated dose, tablets, orally for up to 104 weeks.

Serious adverse events	Glimepiride	TAK-875 25 mg	TAK-875 50 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	63 / 822 (7.66%)	41 / 816 (5.02%)	58 / 813 (7.13%)
number of deaths (all causes)	5	3	3
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	0 / 822 (0.00%)	1 / 816 (0.12%)	0 / 813 (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
Clear cell renal cell carcinoma			

subjects affected / exposed	0 / 822 (0.00%)	1 / 816 (0.12%)	0 / 813 (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
Colon cancer			
subjects affected / exposed	0 / 822 (0.00%)	1 / 816 (0.12%)	0 / 813 (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
Hepatic cancer metastatic			
subjects affected / exposed	1 / 822 (0.12%)	0 / 816 (0.00%)	0 / 813 (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
Kaposi's sarcoma			
subjects affected / exposed	1 / 822 (0.12%)	0 / 816 (0.00%)	0 / 813 (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
Linitis plastica			
subjects affected / exposed	1 / 822 (0.12%)	0 / 816 (0.00%)	0 / 813 (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
Malignant melanoma			
subjects affected / exposed	2 / 822 (0.24%)	0 / 816 (0.00%)	0 / 813 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neoplasm			
subjects affected / exposed	1 / 822 (0.12%)	0 / 816 (0.00%)	0 / 813 (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
Pancreatic carcinoma			
subjects affected / exposed	0 / 822 (0.00%)	0 / 816 (0.00%)	1 / 813 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Small cell lung cancer			

subjects affected / exposed	0 / 822 (0.00%)	0 / 816 (0.00%)	1 / 813 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thyroid cancer			
subjects affected / exposed	0 / 822 (0.00%)	1 / 816 (0.12%)	0 / 813 (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
Uterine cancer			
subjects affected / exposed	0 / 822 (0.00%)	1 / 816 (0.12%)	0 / 813 (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			
Deep vein thrombosis			
subjects affected / exposed	0 / 822 (0.00%)	1 / 816 (0.12%)	0 / 813 (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
Hypertension			
subjects affected / exposed	1 / 822 (0.12%)	0 / 816 (0.00%)	2 / 813 (0.25%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive crisis			
subjects affected / exposed	0 / 822 (0.00%)	0 / 816 (0.00%)	1 / 813 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intermittent claudication			
subjects affected / exposed	1 / 822 (0.12%)	0 / 816 (0.00%)	0 / 813 (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
Peripheral ischaemia			
subjects affected / exposed	0 / 822 (0.00%)	0 / 816 (0.00%)	1 / 813 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral vascular disorder			

subjects affected / exposed	0 / 822 (0.00%)	1 / 816 (0.12%)	1 / 813 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Coronary artery bypass			
subjects affected / exposed	0 / 822 (0.00%)	0 / 816 (0.00%)	1 / 813 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chest discomfort			
subjects affected / exposed	1 / 822 (0.12%)	0 / 816 (0.00%)	0 / 813 (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
Chest pain			
subjects affected / exposed	3 / 822 (0.36%)	2 / 816 (0.25%)	3 / 813 (0.37%)
occurrences causally related to treatment / all	0 / 3	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed	1 / 822 (0.12%)	0 / 816 (0.00%)	0 / 813 (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
Non-cardiac chest pain			
subjects affected / exposed	1 / 822 (0.12%)	0 / 816 (0.00%)	0 / 813 (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
Sudden death			
subjects affected / exposed	0 / 822 (0.00%)	1 / 816 (0.12%)	0 / 813 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Reproductive system and breast disorders			
Cervical polyp			

subjects affected / exposed	0 / 822 (0.00%)	0 / 816 (0.00%)	1 / 813 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Menorrhagia			
subjects affected / exposed	0 / 822 (0.00%)	0 / 816 (0.00%)	1 / 813 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine polyp			
subjects affected / exposed	1 / 822 (0.12%)	0 / 816 (0.00%)	1 / 813 (0.12%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine prolapse			
subjects affected / exposed	0 / 822 (0.00%)	0 / 816 (0.00%)	1 / 813 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterovaginal prolapse			
subjects affected / exposed	0 / 822 (0.00%)	0 / 816 (0.00%)	1 / 813 (0.12%)
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			
Asthma			
subjects affected / exposed	1 / 822 (0.12%)	0 / 816 (0.00%)	0 / 813 (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
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 822 (0.00%)	1 / 816 (0.12%)	2 / 813 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary hypertension			
subjects affected / exposed	1 / 822 (0.12%)	0 / 816 (0.00%)	0 / 813 (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
Sleep apnoea syndrome			

subjects affected / exposed	0 / 822 (0.00%)	0 / 816 (0.00%)	1 / 813 (0.12%)
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			
Schizophrenia			
subjects affected / exposed	0 / 822 (0.00%)	0 / 816 (0.00%)	1 / 813 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 822 (0.12%)	0 / 816 (0.00%)	0 / 813 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Amylase increased			
subjects affected / exposed	0 / 822 (0.00%)	0 / 816 (0.00%)	1 / 813 (0.12%)
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	1 / 822 (0.12%)	0 / 816 (0.00%)	0 / 813 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood creatinine increased			
subjects affected / exposed	0 / 822 (0.00%)	0 / 816 (0.00%)	1 / 813 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ejection fraction decreased			
subjects affected / exposed	1 / 822 (0.12%)	0 / 816 (0.00%)	0 / 813 (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
Hepatic enzyme increased			
subjects affected / exposed	0 / 822 (0.00%)	0 / 816 (0.00%)	1 / 813 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Lipase increased			
subjects affected / exposed	0 / 822 (0.00%)	0 / 816 (0.00%)	1 / 813 (0.12%)
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 function test abnormal			
subjects affected / exposed	0 / 822 (0.00%)	1 / 816 (0.12%)	0 / 813 (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
Prostatic specific antigen increased			
subjects affected / exposed	1 / 822 (0.12%)	0 / 816 (0.00%)	0 / 813 (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
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 822 (0.00%)	1 / 816 (0.12%)	0 / 813 (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
Fall			
subjects affected / exposed	0 / 822 (0.00%)	0 / 816 (0.00%)	2 / 813 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	0 / 822 (0.00%)	0 / 816 (0.00%)	1 / 813 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	0 / 822 (0.00%)	0 / 816 (0.00%)	1 / 813 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meniscus injury			
subjects affected / exposed	1 / 822 (0.12%)	0 / 816 (0.00%)	0 / 813 (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

Post procedural complication			
subjects affected / exposed	0 / 822 (0.00%)	0 / 816 (0.00%)	1 / 813 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radius fracture			
subjects affected / exposed	0 / 822 (0.00%)	1 / 816 (0.12%)	0 / 813 (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
Subdural haematoma			
subjects affected / exposed	0 / 822 (0.00%)	0 / 816 (0.00%)	1 / 813 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tendon rupture			
subjects affected / exposed	0 / 822 (0.00%)	1 / 816 (0.12%)	0 / 813 (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
Tibia fracture			
subjects affected / exposed	0 / 822 (0.00%)	1 / 816 (0.12%)	0 / 813 (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
Congenital, familial and genetic disorders			
Hypertrophic cardiomyopathy			
subjects affected / exposed	1 / 822 (0.12%)	0 / 816 (0.00%)	0 / 813 (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			
Acute coronary syndrome			
subjects affected / exposed	0 / 822 (0.00%)	0 / 816 (0.00%)	1 / 813 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute myocardial infarction			
subjects affected / exposed	2 / 822 (0.24%)	0 / 816 (0.00%)	1 / 813 (0.12%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Angina unstable			
subjects affected / exposed	1 / 822 (0.12%)	0 / 816 (0.00%)	4 / 813 (0.49%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	5 / 822 (0.61%)	0 / 816 (0.00%)	1 / 813 (0.12%)
occurrences causally related to treatment / all	0 / 5	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial flutter			
subjects affected / exposed	0 / 822 (0.00%)	2 / 816 (0.25%)	0 / 813 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block first degree			
subjects affected / exposed	0 / 822 (0.00%)	1 / 816 (0.12%)	0 / 813 (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
Bundle branch block right			
subjects affected / exposed	1 / 822 (0.12%)	0 / 816 (0.00%)	0 / 813 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	0 / 822 (0.00%)	0 / 816 (0.00%)	1 / 813 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cardiac failure			
subjects affected / exposed	0 / 822 (0.00%)	0 / 816 (0.00%)	1 / 813 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure acute			
subjects affected / exposed	0 / 822 (0.00%)	0 / 816 (0.00%)	1 / 813 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cardiac failure congestive			

subjects affected / exposed	1 / 822 (0.12%)	0 / 816 (0.00%)	1 / 813 (0.12%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiomyopathy			
subjects affected / exposed	1 / 822 (0.12%)	0 / 816 (0.00%)	0 / 813 (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
Coronary artery disease			
subjects affected / exposed	0 / 822 (0.00%)	1 / 816 (0.12%)	2 / 813 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery occlusion			
subjects affected / exposed	1 / 822 (0.12%)	0 / 816 (0.00%)	0 / 813 (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
Ischaemic cardiomyopathy			
subjects affected / exposed	0 / 822 (0.00%)	0 / 816 (0.00%)	1 / 813 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	2 / 822 (0.24%)	0 / 816 (0.00%)	2 / 813 (0.25%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Palpitations			
subjects affected / exposed	1 / 822 (0.12%)	0 / 816 (0.00%)	0 / 813 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Supraventricular tachycardia			
subjects affected / exposed	0 / 822 (0.00%)	1 / 816 (0.12%)	0 / 813 (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
Ventricular extrasystoles			

subjects affected / exposed	0 / 822 (0.00%)	1 / 816 (0.12%)	0 / 813 (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
Nervous system disorders			
Brain stem infarction			
subjects affected / exposed	0 / 822 (0.00%)	1 / 816 (0.12%)	0 / 813 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Carotid artery stenosis			
subjects affected / exposed	0 / 822 (0.00%)	1 / 816 (0.12%)	0 / 813 (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
Cerebral haemorrhage			
subjects affected / exposed	0 / 822 (0.00%)	1 / 816 (0.12%)	0 / 813 (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
Cerebrovascular accident			
subjects affected / exposed	2 / 822 (0.24%)	0 / 816 (0.00%)	1 / 813 (0.12%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Epilepsy			
subjects affected / exposed	1 / 822 (0.12%)	0 / 816 (0.00%)	0 / 813 (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
Ischaemic stroke			
subjects affected / exposed	1 / 822 (0.12%)	0 / 816 (0.00%)	1 / 813 (0.12%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paraesthesia			
subjects affected / exposed	0 / 822 (0.00%)	1 / 816 (0.12%)	0 / 813 (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	1 / 822 (0.12%)	0 / 816 (0.00%)	2 / 813 (0.25%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	1 / 822 (0.12%)	0 / 816 (0.00%)	1 / 813 (0.12%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Meniere's disease			
subjects affected / exposed	0 / 822 (0.00%)	0 / 816 (0.00%)	1 / 813 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vertigo			
subjects affected / exposed	0 / 822 (0.00%)	0 / 816 (0.00%)	1 / 813 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Cataract			
subjects affected / exposed	0 / 822 (0.00%)	0 / 816 (0.00%)	1 / 813 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinal artery thrombosis			
subjects affected / exposed	0 / 822 (0.00%)	0 / 816 (0.00%)	1 / 813 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinal haemorrhage			
subjects affected / exposed	1 / 822 (0.12%)	0 / 816 (0.00%)	0 / 813 (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
Gastrointestinal disorders			
Abdominal hernia obstructive			
subjects affected / exposed	1 / 822 (0.12%)	0 / 816 (0.00%)	0 / 813 (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

Abdominal pain			
subjects affected / exposed	0 / 822 (0.00%)	1 / 816 (0.12%)	0 / 813 (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
Gastritis			
subjects affected / exposed	1 / 822 (0.12%)	0 / 816 (0.00%)	0 / 813 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 822 (0.00%)	0 / 816 (0.00%)	1 / 813 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 822 (0.12%)	1 / 816 (0.12%)	0 / 813 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhoids			
subjects affected / exposed	0 / 822 (0.00%)	1 / 816 (0.12%)	0 / 813 (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
Intestinal polyp haemorrhage			
subjects affected / exposed	1 / 822 (0.12%)	0 / 816 (0.00%)	0 / 813 (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
Lumbar hernia			
subjects affected / exposed	0 / 822 (0.00%)	1 / 816 (0.12%)	0 / 813 (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
Megacolon			
subjects affected / exposed	0 / 822 (0.00%)	1 / 816 (0.12%)	0 / 813 (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
Oesophagitis			

subjects affected / exposed	1 / 822 (0.12%)	0 / 816 (0.00%)	0 / 813 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis acute			
subjects affected / exposed	0 / 822 (0.00%)	1 / 816 (0.12%)	0 / 813 (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
Umbilical hernia, obstructive			
subjects affected / exposed	0 / 822 (0.00%)	0 / 816 (0.00%)	1 / 813 (0.12%)
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			
Cholecystitis acute			
subjects affected / exposed	1 / 822 (0.12%)	0 / 816 (0.00%)	0 / 813 (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 chronic			
subjects affected / exposed	1 / 822 (0.12%)	0 / 816 (0.00%)	0 / 813 (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
Cholelithiasis			
subjects affected / exposed	2 / 822 (0.24%)	0 / 816 (0.00%)	1 / 813 (0.12%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic failure			
subjects affected / exposed	1 / 822 (0.12%)	0 / 816 (0.00%)	0 / 813 (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
Hepatitis			
subjects affected / exposed	1 / 822 (0.12%)	0 / 816 (0.00%)	0 / 813 (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
Hepatitis toxic			

subjects affected / exposed	0 / 822 (0.00%)	0 / 816 (0.00%)	1 / 813 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jaundice			
subjects affected / exposed	0 / 822 (0.00%)	0 / 816 (0.00%)	1 / 813 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Calculus ureteric			
subjects affected / exposed	1 / 822 (0.12%)	0 / 816 (0.00%)	0 / 813 (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
Haematuria			
subjects affected / exposed	0 / 822 (0.00%)	0 / 816 (0.00%)	1 / 813 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrolithiasis			
subjects affected / exposed	0 / 822 (0.00%)	1 / 816 (0.12%)	0 / 813 (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 colic			
subjects affected / exposed	0 / 822 (0.00%)	1 / 816 (0.12%)	0 / 813 (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 failure			
subjects affected / exposed	1 / 822 (0.12%)	1 / 816 (0.12%)	1 / 813 (0.12%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Renal failure acute			
subjects affected / exposed	1 / 822 (0.12%)	0 / 816 (0.00%)	0 / 813 (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
Urethral stenosis			

subjects affected / exposed	1 / 822 (0.12%)	0 / 816 (0.00%)	0 / 813 (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
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 822 (0.00%)	1 / 816 (0.12%)	0 / 813 (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
Intervertebral disc degeneration			
subjects affected / exposed	0 / 822 (0.00%)	0 / 816 (0.00%)	1 / 813 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc protrusion			
subjects affected / exposed	1 / 822 (0.12%)	0 / 816 (0.00%)	0 / 813 (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
Joint swelling			
subjects affected / exposed	1 / 822 (0.12%)	0 / 816 (0.00%)	0 / 813 (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
Musculoskeletal chest pain			
subjects affected / exposed	0 / 822 (0.00%)	0 / 816 (0.00%)	1 / 813 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal pain			
subjects affected / exposed	0 / 822 (0.00%)	1 / 816 (0.12%)	0 / 813 (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
Myopathy			
subjects affected / exposed	0 / 822 (0.00%)	0 / 816 (0.00%)	1 / 813 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neck pain			

subjects affected / exposed	1 / 822 (0.12%)	0 / 816 (0.00%)	0 / 813 (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
Osteochondrosis			
subjects affected / exposed	0 / 822 (0.00%)	0 / 816 (0.00%)	1 / 813 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal osteoarthritis			
subjects affected / exposed	1 / 822 (0.12%)	0 / 816 (0.00%)	0 / 813 (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
Infections and infestations			
Abscess oral			
subjects affected / exposed	0 / 822 (0.00%)	1 / 816 (0.12%)	0 / 813 (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
Appendicitis			
subjects affected / exposed	0 / 822 (0.00%)	0 / 816 (0.00%)	2 / 813 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	0 / 822 (0.00%)	1 / 816 (0.12%)	0 / 813 (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
Cellulitis			
subjects affected / exposed	2 / 822 (0.24%)	0 / 816 (0.00%)	0 / 813 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dengue fever			
subjects affected / exposed	1 / 822 (0.12%)	0 / 816 (0.00%)	0 / 813 (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
Gastroenteritis			

subjects affected / exposed	0 / 822 (0.00%)	0 / 816 (0.00%)	4 / 813 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Groin abscess			
subjects affected / exposed	1 / 822 (0.12%)	0 / 816 (0.00%)	0 / 813 (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
Keratitis fungal			
subjects affected / exposed	1 / 822 (0.12%)	0 / 816 (0.00%)	0 / 813 (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
Liver abscess			
subjects affected / exposed	0 / 822 (0.00%)	0 / 816 (0.00%)	1 / 813 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Otitis media chronic			
subjects affected / exposed	1 / 822 (0.12%)	0 / 816 (0.00%)	0 / 813 (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
Peritonitis			
subjects affected / exposed	0 / 822 (0.00%)	0 / 816 (0.00%)	1 / 813 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	3 / 822 (0.36%)	3 / 816 (0.37%)	0 / 813 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis acute			
subjects affected / exposed	1 / 822 (0.12%)	1 / 816 (0.12%)	0 / 813 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			

subjects affected / exposed	1 / 822 (0.12%)	0 / 816 (0.00%)	0 / 813 (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
Tonsillitis			
subjects affected / exposed	0 / 822 (0.00%)	1 / 816 (0.12%)	0 / 813 (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
Urinary tract infection			
subjects affected / exposed	0 / 822 (0.00%)	0 / 816 (0.00%)	2 / 813 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	0 / 822 (0.00%)	0 / 816 (0.00%)	1 / 813 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			
subjects affected / exposed	1 / 822 (0.12%)	0 / 816 (0.00%)	0 / 813 (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
Hypokalaemia			
subjects affected / exposed	0 / 822 (0.00%)	1 / 816 (0.12%)	0 / 813 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Obesity			
subjects affected / exposed	1 / 822 (0.12%)	0 / 816 (0.00%)	0 / 813 (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

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Glimepiride	TAK-875 25 mg	TAK-875 50 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	334 / 822 (40.63%)	337 / 816 (41.30%)	323 / 813 (39.73%)
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	17 / 822 (2.07%)	22 / 816 (2.70%)	24 / 813 (2.95%)
occurrences (all)	21	24	25
Blood creatine phosphokinase increased			
subjects affected / exposed	26 / 822 (3.16%)	15 / 816 (1.84%)	17 / 813 (2.09%)
occurrences (all)	30	17	19
Vascular disorders			
Hypertension			
subjects affected / exposed	47 / 822 (5.72%)	28 / 816 (3.43%)	26 / 813 (3.20%)
occurrences (all)	54	31	30
Nervous system disorders			
Dizziness			
subjects affected / exposed	20 / 822 (2.43%)	16 / 816 (1.96%)	9 / 813 (1.11%)
occurrences (all)	24	19	9
Headache			
subjects affected / exposed	47 / 822 (5.72%)	42 / 816 (5.15%)	34 / 813 (4.18%)
occurrences (all)	52	54	43
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	10 / 822 (1.22%)	6 / 816 (0.74%)	17 / 813 (2.09%)
occurrences (all)	11	6	19
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	28 / 822 (3.41%)	35 / 816 (4.29%)	36 / 813 (4.43%)
occurrences (all)	35	44	41
Nausea			
subjects affected / exposed	18 / 822 (2.19%)	18 / 816 (2.21%)	16 / 813 (1.97%)
occurrences (all)	18	21	19
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	24 / 822 (2.92%)	26 / 816 (3.19%)	16 / 813 (1.97%)
occurrences (all)	25	30	17
Musculoskeletal and connective tissue			

disorders			
Arthralgia			
subjects affected / exposed	29 / 822 (3.53%)	28 / 816 (3.43%)	22 / 813 (2.71%)
occurrences (all)	30	32	25
Back pain			
subjects affected / exposed	31 / 822 (3.77%)	33 / 816 (4.04%)	29 / 813 (3.57%)
occurrences (all)	31	40	29
Pain in extremity			
subjects affected / exposed	20 / 822 (2.43%)	13 / 816 (1.59%)	14 / 813 (1.72%)
occurrences (all)	22	15	16
Infections and infestations			
Bronchitis			
subjects affected / exposed	25 / 822 (3.04%)	22 / 816 (2.70%)	25 / 813 (3.08%)
occurrences (all)	27	22	28
Gastroenteritis			
subjects affected / exposed	11 / 822 (1.34%)	12 / 816 (1.47%)	17 / 813 (2.09%)
occurrences (all)	11	14	20
Influenza			
subjects affected / exposed	38 / 822 (4.62%)	31 / 816 (3.80%)	31 / 813 (3.81%)
occurrences (all)	47	38	37
Nasopharyngitis			
subjects affected / exposed	44 / 822 (5.35%)	38 / 816 (4.66%)	45 / 813 (5.54%)
occurrences (all)	48	46	54
Pharyngitis			
subjects affected / exposed	16 / 822 (1.95%)	10 / 816 (1.23%)	17 / 813 (2.09%)
occurrences (all)	18	13	28
Upper respiratory tract infection			
subjects affected / exposed	55 / 822 (6.69%)	73 / 816 (8.95%)	59 / 813 (7.26%)
occurrences (all)	69	87	74
Urinary tract infection			
subjects affected / exposed	28 / 822 (3.41%)	22 / 816 (2.70%)	29 / 813 (3.57%)
occurrences (all)	35	31	42
Metabolism and nutrition disorders			
Dyslipidaemia			
subjects affected / exposed	15 / 822 (1.82%)	10 / 816 (1.23%)	17 / 813 (2.09%)
occurrences (all)	15	10	19
Hyperuricaemia			

subjects affected / exposed occurrences (all)	19 / 822 (2.31%) 23	12 / 816 (1.47%) 15	15 / 813 (1.85%) 19

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
31 May 2012	1- Secondary objective was modified by adding measures including incidence of hypoglycemic events, change from baseline in body weight and change from baseline in HbA1c at specific time points. 2- Period of evaluation was changed from 118 weeks to 118-122 weeks in schedule B subjects (on a lower metformin daily dose (<1500 mg) with no documentation of MTD. 3- Provided additional guidance for investigators to be actively engaged in identifying and reporting subjects with potential cardiovascular (CV) events for the study and to clarify reporting procedures for non-serious CV events.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
26 December 2013	Due to specific liver- related safety signals that emerged in the phase 3 program, Takeda concluded that based on all available information, the benefits of treating subjects with fasiglifam do not outweigh the potential risks, thus Takeda decided voluntarily to terminate all development activities for fasiglifam based on liver safety concerns.	-

Notes:

Limitations and caveats

None reported