



## Clinical trial results:

### **A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled, 24-Week Study to Evaluate the Efficacy and Safety of Daily Oral TAK-875 50mg Compared With Placebo as an Add-On to Glimepiride in Subjects With Type 2 Diabetes**

#### **Summary**

EudraCT number	2013-000007-17
Trial protocol	SK HU BG PL
Global end of trial date	11 February 2014

#### **Results information**

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

#### **Trial information**

##### **Trial identification**

Sponsor protocol code	TAK-875_309
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##### **Additional study identifiers**

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01829477
WHO universal trial number (UTN)	U1111-1138-8680

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., 0044 0203116 8000, clinicaloperations@tgrd.com
Scientific contact	Program Manager, Takeda Development Centre Europe Ltd., 0044 0203116 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	08 September 2014
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	11 February 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 compared to placebo on glycemic control as assessed by glycosylated hemoglobin (HbA1c) change from baseline over a 24-week treatment period when used as an add-on to glimepiride in addition to diet and exercise.

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	19 April 2013
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	Slovakia: 11
Country: Number of subjects enrolled	Bulgaria: 3
Country: Number of subjects enrolled	Hungary: 1
Country: Number of subjects enrolled	United States: 17
Country: Number of subjects enrolled	Canada: 1
Worldwide total number of subjects	33
EEA total number of subjects	15

Notes:

### Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	22

From 65 to 84 years	11
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

Subjects took part in the study at 18 investigative sites in the United States, Slovakia, Bulgaria, Hungary, and Canada from 19 April 2013 to 11 February 2014.

### Pre-assignment

Screening details:

Subjects with a historical diagnosis of type 2 diabetes mellitus (T2DM), inadequately controlled when treated with only diet, exercise and a sulfonylurea for at least 12 weeks prior to screening, were enrolled in 1 of 2 treatment groups: placebo; fasiglifam 50 milligram (mg).

### Period 1

Period 1 title	Overall Trial (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
<b>Arm title</b>	Placebo

Arm description:

Fasiglifam placebo-matching tablet, orally, once daily and glimepiride 6 mg (or maximum tolerated dose), tablet, orally, once daily for up to 24 weeks.

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 tablet, orally, once daily for up to 24 weeks.

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

Dosage and administration details:

Glimepiride 6 mg (or maximum tolerated dose), tablet, orally, once daily for up to 24 weeks.

<b>Arm title</b>	Fasiglifam 50 mg
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Arm description:

Fasiglifam 50 mg, tablet, orally, once daily and glimepiride 6 mg (or maximum tolerated dose), tablet, orally, once daily for up to 24 weeks.

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

Dosage and administration details:

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

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

Dosage and administration details:

Glimepiride 6 mg (or maximum tolerated dose), tablet, orally, once daily for up to 24 weeks.

<b>Number of subjects in period 1</b>	Placebo	Fasiglifam 50 mg
Started	17	16
Completed	1	1
Not completed	16	15
Consent withdrawn by subject	1	-
'Study Terminated by Sponsor '	15	15

## Baseline characteristics

### Reporting groups

Reporting group title	Placebo
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Reporting group description:

Fasiglifam placebo-matching tablet, orally, once daily and glimepiride 6 mg (or maximum tolerated dose), tablet, orally, once daily for up to 24 weeks.

Reporting group title	Fasiglifam 50 mg
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Reporting group description:

Fasiglifam 50 mg, tablet, orally, once daily and glimepiride 6 mg (or maximum tolerated dose), tablet, orally, once daily for up to 24 weeks.

Reporting group values	Placebo	Fasiglifam 50 mg	Total
Number of subjects	17	16	33
Age categorical			
Units: Subjects			
18-64 years	10	12	22
65-84 years	7	4	11
Age continuous			
Units: years			
arithmetic mean	59.8	58.5	
standard deviation	± 11.82	± 9.7	-
Gender categorical			
Units: Subjects			
Female	7	6	13
Male	10	10	20
Race/Ethnicity, Customized			
Units: Subjects			
Black or African American	3	1	4
White	14	15	29
Race/Ethnicity, Customized			
Units: Subjects			
Hispanic or Latino	6	5	11
Not Hispanic or Latino	5	2	7
Not Applicable	6	9	15
Baseline Glycosylated Hemoglobin (HbA1c) Category			
Units: Subjects			
Less Than (<) 8.5 Percent (%)	10	11	21
Greater Than or Equal to (>=) 8.5%	7	5	12

## End points

### End points reporting groups

Reporting group title	Placebo
Reporting group description: Fasiglifam placebo-matching tablet, orally, once daily and glimepiride 6 mg (or maximum tolerated dose), tablet, orally, once daily for up to 24 weeks.	
Reporting group title	Fasiglifam 50 mg
Reporting group description: Fasiglifam 50 mg, tablet, orally, once daily and glimepiride 6 mg (or maximum tolerated dose), tablet, orally, once daily for up to 24 weeks.	

### Primary: Change From Baseline in Glycosylated Hemoglobin (HbA1c) at Week 24

End point title	Change From Baseline in Glycosylated Hemoglobin (HbA1c) at Week 24 <sup>[1]</sup>
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. In accordance with the Statistical Analysis Plan (SAP), due to the limited enrollment at the time of study termination, the summaries and statistical analyses of primary and secondary efficacy parameters originally intended and described in the protocol were not produced.	
End point type	Primary
End point timeframe: Baseline and Week 24	

#### Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: In accordance with the SAP, due to the limited enrollment at the time of study termination, the summaries and statistical analyses of primary and secondary efficacy parameters originally intended and described in the protocol were not produced.

End point values	Placebo	Fasiglifam 50 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 <sup>[2]</sup>	0 <sup>[3]</sup>		
Units: percentage of glycosylated hemoglobin				
least squares mean (standard error)	()	()		

#### Notes:

[2] - Limited enrollment at the time of study termination.

[3] - Limited enrollment at the time of study termination.

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Subjects With HbA1c <7 % at Week 24

End point title	Percentage of Subjects With HbA1c <7 % at Week 24
End point description: In accordance with the SAP, due to the limited enrollment at the time of study termination, the summaries and statistical analyses of primary and secondary efficacy parameters originally intended and described in the protocol were not produced.	
End point type	Secondary

End point timeframe:

Week 24

<b>End point values</b>	Placebo	Fasiglifam 50 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 <sup>[4]</sup>	0 <sup>[5]</sup>		
Units: percentage of subjects				
number (not applicable)				

Notes:

[4] - Limited enrollment at the time of study termination.

[5] - Limited enrollment at the time of study termination.

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in Fasting Plasma Glucose (FPG) at Week 24

End point title	Change From Baseline in Fasting Plasma Glucose (FPG) at Week 24
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End point description:

The change between the fasting plasma glucose value collected at week 24 or final visit relative to baseline. In accordance with the SAP, due to the limited enrollment at the time of study termination, the summaries and statistical analyses of primary and secondary efficacy parameters originally intended and described in the protocol were not produced.

End point type	Secondary
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End point timeframe:

Baseline and Week 24

<b>End point values</b>	Placebo	Fasiglifam 50 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 <sup>[6]</sup>	0 <sup>[7]</sup>		
Units: millimole per liter (mmol/L)				
least squares mean (standard error)	( )	( )		

Notes:

[6] - Limited enrollment at the time of study termination.

[7] - Limited enrollment at the time of study termination.

### 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 after the last dose of double-blinded 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 participant or observed by the investigator was recorded, irrespective of the relation to study treatment.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	16.1
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### Reporting groups

Reporting group title	Placebo
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Reporting group description:

Fasiglifam placebo-matching tablet, orally, once daily and glimepiride 6 mg (or maximum tolerated dose), tablet, orally, once daily for up to 24 weeks.

Reporting group title	Fasiglifam 50 mg
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Reporting group description:

Fasiglifam 50 mg, orally, once daily and glimepiride 6 mg (or maximum tolerated dose), tablet, orally, once daily for up to 24 weeks.

<b>Serious adverse events</b>	Placebo	Fasiglifam 50 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 17 (0.00%)	0 / 16 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

<b>Non-serious adverse events</b>	Placebo	Fasiglifam 50 mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 17 (29.41%)	3 / 16 (18.75%)	
Investigations			
Electrocardiogram (ECG) abnormal subjects affected / exposed	0 / 17 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Cardiac disorders			

Myocardial ischemia subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	1 / 16 (6.25%) 1	
Nervous system disorders Hypoaesthesia subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1	1 / 16 (6.25%) 1	
Eye disorders Episcleritis subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1	0 / 16 (0.00%) 0	
Gastrointestinal disorders Constipation subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1	0 / 16 (0.00%) 0	
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	1 / 16 (6.25%) 1	
Nasal congestion subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	1 / 16 (6.25%) 1	
Nasal polyps subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	1 / 16 (6.25%) 1	
Rhinitis allergic subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1	0 / 16 (0.00%) 0	
Musculoskeletal and connective tissue disorders Rotator cuff syndrome subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	1 / 16 (6.25%) 1	
Infections and infestations Gastroenteritis subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1	0 / 16 (0.00%) 0	
Nasopharyngitis			

subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	1 / 16 (6.25%) 1	
Sinusitis subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1	0 / 16 (0.00%) 0	
Metabolism and nutrition disorders Hyperuricemia subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1	0 / 16 (0.00%) 0	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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### 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