Clinical trial results:
A single-center, randomized, double-blind, placebo-controlled, Phase II study to assess the efficacy of aleglitazar on insulin sensitivity in patients with type 2 diabetes mellitus (T2D) who are inadequately controlled with metformin monotherapy

Summary

EudraCT number	2012-002649-39
Trial protocol	DE
Global end of trial date	03 September 2013

Results information

Result version number	v1 (current)
This version publication date	11 May 2016
First version publication date	12 August 2015

Trial information

Trial identification

Sponsor protocol code	WC28038

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01729403
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124., Basel, Switzerland, CH-4070
Public contact	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com
Scientific contact	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.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	03 September 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 September 2013
Global end of trial reached?	Yes
Global end of trial date	03 September 2013
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To evaluate the effect of aleglitazar on whole body insulin sensitivity compared with placebo after 16 weeks of treatment in patients with type-2 diabetes inadequately controlled with metformin monotherapy, as assessed by hyperinsulinemic-euglycemic clamp. Patients will be randomized to receive either aleglitazar 150 µg or placebo orally daily for 16 weeks, in addition to their existing dose and regimen of metformin.

Protection of trial subjects:

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

Background therapy:

Metformin

Evidence for comparator: -

Actual start date of recruitment	01 December 2012
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	Germany: 57
Worldwide total number of subjects	57
EEA total number of subjects	57

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)	39
From 65 to 84 years	18
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The target population consisted of male and female patients (30-70 years old) with type 2 diabetes inadequately controlled with stable metformin monotherapy for at least 12 weeks prior to screening.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Aleglitazar 150 µg

Arm description:

Participants received aleglitazar 150 µg orally once daily for 16 weeks.

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

Dosage and administration details:

Aleglitazar was supplied in tablets.

Arm title	Placebo

Arm description:

Participants received placebo to aleglitazar orally once daily for 16 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:

Placebo was supplied in tablets.

Number of subjects in period 1	Aleglitazar 150 µg	Placebo
Started	29	28
Completed	16	22
Not completed	13	6
Study terminated by sponsor	12	6

Subject dropped out due to personal reasons	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Aleglitazar 150 µg
Reporting group description:	
Participants received aleglitazar 150 µg orally once daily for 16 weeks.	
Reporting group title	Placebo
Reporting group description:	
Participants received placebo to aleglitazar orally once daily for 16 weeks.	

Reporting group values	Aleglitazar 150 µg	Placebo	Total
Number of subjects	29	28	57
Age categorical			
Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			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)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Units: years			
arithmetic mean	59.4	60.1	
standard deviation	± 8.43	± 7	-
Gender categorical			
Units: Subjects			
Female	6	6	12
Male	23	22	45

End points

End points reporting groups

Reporting group title	Aleglitazar 150 µg
Reporting group description:	
Participants received aleglitazar 150 µg orally once daily for 16 weeks.	
Reporting group title	Placebo
Reporting group description:	
Participants received placebo to aleglitazar orally once daily for 16 weeks.	

Primary: Change from Baseline in unadjusted M-value at Week 16

End point title	Change from Baseline in unadjusted M-value at Week 16
End point description:	
Change from Baseline in whole-body insulin sensitivity was measured using the unadjusted M-value calculated at the end of step 2 of the hyperinsulinemic-euglycemic clamp procedure. During step 1, a primed insulin infusion (20 mU/min/m^2) is used for the assessment of peripheral insulin sensitivity while endogenous glucose production is only partly suppressed. During step 2, the insulin infusion is increased to 80 mU/min/m^2 to assess peripheral insulin sensitivity while endogenous glucose production is entirely suppressed. A higher M value indicates greater whole-body insulin sensitivity. A positive change score indicates an improvement in whole-body insulin sensitivity.	
End point type	Primary
End point timeframe:	
Baseline to Week 16	

End point values	Aleglitazar 150 µg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	24		
Units: mg/min				
arithmetic mean (standard deviation)	668.14 (± 225.96)	739.98 (± 261.92)		

Statistical analyses

Statistical analysis title	Unadjusted M-value
Comparison groups	Aleglitazar 150 µg v Placebo
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0157
Method	ANCOVA
Parameter estimate	Least squares mean difference
Point estimate	118.204

Confidence interval	
level	95 %
sides	2-sided
lower limit	23.61
upper limit	212.8

Primary: Change from Baseline in body-weight corrected M-value at Week 16

End point title	Change from Baseline in body-weight corrected M-value at Week 16

End point description:

Change from Baseline in whole-body insulin sensitivity was measured using the body-weight corrected M-value calculated at the end of step 2 of the hyperinsulinemic-euglycemic clamp procedure. During step 1, a primed insulin infusion (20 mU/min/m^2) is used for the assessment of peripheral insulin sensitivity while endogenous glucose production is only partly suppressed. During step 2, the insulin infusion is increased to 80 mU/min/m^2 to assess peripheral insulin sensitivity while endogenous glucose production is entirely suppressed. A higher M value indicates greater whole-body insulin sensitivity. A positive change score indicates an improvement in whole-body insulin sensitivity.

End point type	Primary

End point timeframe:

Baseline to Week 16

End point values	Aleglitazar 150 µg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	24		
Units: mg/kg/min				
arithmetic mean (standard deviation)	6.892 (± 2.1161)	8.099 (± 3.0354)		

Statistical analyses

Statistical analysis title	Body-weight corrected M-value
Comparison groups	Aleglitazar 150 µg v Placebo
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0468
Method	ANCOVA
Parameter estimate	Least squares mean difference
Point estimate	1.012
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.015
upper limit	2.0082

Secondary: Change from Baseline in glycosylated hemoglobin A1c (HbA1c) at Week 16

End point title	Change from Baseline in glycosylated hemoglobin A1c (HbA1c) at Week 16

End point description:

HbA1C was measured in blood samples at a central laboratory. A higher HbA1c level indicates poorer control of blood glucose levels. A negative change score indicates an improvement in control of blood glucose levels.

End point type	Secondary

End point timeframe:

Baseline to Week 16

End point values	Aleglitazar 150 µg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	24		
Units: Percent				
arithmetic mean (standard deviation)	-0.38 (± 0.468)	-0.08 (± 0.721)		

Statistical analyses

Statistical analysis title	Change from Baseline in HbA1c at Week 16
Comparison groups	Placebo v Aleglitazar 150 µg
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0159
Method	ANCOVA
Parameter estimate	Least squares mean difference
Point estimate	-0.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.855
upper limit	-0.094

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected and reported from the time of randomization until the last study visit of each participant .

Adverse event reporting additional description:

Safety population: All participants who have received at least 1 dose of the study medication (active or placebo).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups

Reporting group title	Aleglitazar 150 µg

Reporting group description:

Participants received aleglitazar 150 µg orally once daily for 16 weeks.

Reporting group title	Placebo

Reporting group description:

Participants received placebo to aleglitazar orally once daily for 16 weeks.

Serious adverse events	Aleglitazar 150 µg	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 29 (3.45%)	2 / 28 (7.14%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Clavicle fracture			
subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	1 / 29 (3.45%)	0 / 28 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Nasopharyngitis			

subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Aleglitazar 150 µg	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 29 (20.69%)	6 / 28 (21.43%)	
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 29 (3.45%)	3 / 28 (10.71%)	
occurrences (all)	1	3	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 29 (0.00%)	2 / 28 (7.14%)	
occurrences (all)	0	2	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	3 / 29 (10.34%)	4 / 28 (14.29%)	
occurrences (all)	3	5	
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	2 / 29 (6.90%)	1 / 28 (3.57%)	
occurrences (all)	2	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 March 2013	The protocol was amended to recommend the systematic and prospective collection of risk factors for gastrointestinal bleeding in each participant's medical history to enable characterization of this potential risk.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
03 September 2013	The study was terminated prematurely following the Sponsor’s decision to discontinue the clinical development program.	-

Notes:

Limitations and caveats

None reported