



Clinical trial results:

A Single Center, Double-Blind, Placebo-Controlled, Randomized, Crossover, Phase II Study to Assess the Effect of Alogliptin on Cardiac Energetics and Function in Patients With Uncomplicated Type 2 Diabetes Mellitus (T2D) and no History of Coronary Artery Disease (CAD) who are Drug-Naïve or Treated With Stable Metformin Monotherapy

Summary

| | |
|--------------------------|-------------------|
| EudraCT number | 2012-001639-29 |
| Trial protocol | GB |
| Global end of trial date | 03 September 2013 |

Results information

| | |
|--------------------------------|---------------|
| Result version number | v1 (current) |
| This version publication date | 16 March 2016 |
| First version publication date | 16 March 2016 |

Trial information

Trial identification

| | |
|-----------------------|---------|
| Sponsor protocol code | BC25445 |
|-----------------------|---------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01680978 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | F. Hoffmann-La Roche Ltd |
| 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 | 17 October 2013 |
| Is this the analysis of the primary completion data? | No |
| 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 if aleglitazar improves cardiac energetics, by means of magnetic resonance spectroscopy (MRS), in uncomplicated type 2 diabetes mellitus (T2D) participants with no history of coronary artery disease (CAD), after 6 weeks of treatment

Protection of trial subjects:

The study was conducted in accordance with the principles of the Declaration of Helsinki or with the laws and regulations of the country in which the research was conducted, whichever afforded the greater protection to the individual. Written informed consent was obtained from each participant before they participated in the study.

Background therapy: -

Evidence for comparator: -

| | |
|---|-----------------|
| Actual start date of recruitment | 25 October 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 | United Kingdom: 18 |
| Worldwide total number of subjects | 18 |
| EEA total number of subjects | 18 |

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) | 13 |
| From 65 to 84 years | 5 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

18 participants were recruited from 1 center in UK.

Pre-assignment

Screening details:

A total of 18 participants were enrolled, of which 13 participants (uncomplicated T2DM and no CAD who were drug-naïve or treated with stable metformin monotherapy) were randomized to receive either aloglitazar or placebo and 5 participants were non-diabetic control.

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 |

Blinding implementation details:

Eligible T2D participants were randomized in a 1:1 ratio to the order of receiving 150 µg aloglitazar and matching placebo, in a blinded fashion. No stratification was applied. The Randomization List was not be available at the study center, to the monitors, project statisticians, or to the project team at Roche.

Arms

| | |
|------------------------------|-------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | T2DM Participants |

Arm description:

Eligible T2DM participants were randomized in a 1:1 ratio to one of the two possible sequences: 150 microgram (µg) aloglitazar followed by matching placebo or placebo followed by 150 µg aloglitazar. Each treatment (aloglitazar and placebo) was received for 6 consecutive weeks, in a randomized order, separated by a 6-week treatment-free wash-out period.

| | |
|--|--------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Matching placebo tablets orally once-a-day for 6 weeks.

| | |
|--|-------------------------------|
| Investigational medicinal product name | Aloglitazar |
| Investigational medicinal product code | RO0728804 |
| Other name | dual PPAR alpha/gamma agonist |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Participants received 150 µg aloglitazar once daily for 6 weeks followed by a 6-week washout period.

| | |
|------------------|----------------------|
| Arm title | Non-diabetic Control |
|------------------|----------------------|

Arm description:

Non-diabetic controls (referred to as the calibration group) underwent only the assessments at screening and baseline and did not receive any study drug.

| | |
|---|-----------------|
| Arm type | No intervention |
| No investigational medicinal product assigned in this arm | |

| Number of subjects in period 1 | T2DM Participants | Non-diabetic Control |
|---------------------------------------|-------------------|----------------------|
| Started | 13 | 5 |
| Completed | 8 | 5 |
| Not completed | 5 | 0 |
| Non compliance | 1 | - |
| STUDY TERMINATED BY SPONSOR | 4 | - |

Baseline characteristics

Reporting groups

| | |
|-----------------------|-------------------|
| Reporting group title | T2DM Participants |
|-----------------------|-------------------|

Reporting group description:

Eligible T2DM participants were randomized in a 1:1 ratio to one of the two possible sequences: 150 microgram (µg) aleglitazar followed by matching placebo or placebo followed by 150 µg aleglitazar. Each treatment (aleglitazar and placebo) was received for 6 consecutive weeks, in a randomized order, separated by a 6-week treatment-free wash-out period.

| | |
|-----------------------|----------------------|
| Reporting group title | Non-diabetic Control |
|-----------------------|----------------------|

Reporting group description:

Non-diabetic controls (referred to as the calibration group) underwent only the assessments at screening and baseline and did not receive any study drug.

| Reporting group values | T2DM Participants | Non-diabetic Control | Total |
|------------------------------------|-------------------|----------------------|-------|
| Number of subjects | 13 | 5 | 18 |
| Age categorical Units: Subjects | | | |

| | | | |
|--|------------------|----------------|----|
| Age continuous Units: years arithmetic mean standard deviation | 54.1 ± 9.6 | 54.6 ± 7.8 | - |
| Gender categorical Units: Subjects | | | |
| Female | 6 | 2 | 8 |
| Male | 7 | 3 | 10 |
| Cardiac PCr/ATP ratio | | | |
| Cardiac phosphocreatine/adenosine triphosphate (PCr/ATP) | | | |
| Units: ratio arithmetic mean standard deviation | 1.45 ± 0.35 | 1.89 ± 0.32 | - |
| Cardiac Fat/Water ratio Units: ratio arithmetic mean standard deviation | 1.06 ± 0.62 | 0.47 ± 0.31 | - |
| Hepatic Fat/Water ratio Units: ratio arithmetic mean standard deviation | 14.99 ± 10.77 | 1.6 ± 1.48 | - |

End points

End points reporting groups

| | |
|--|----------------------|
| Reporting group title | T2DM Participants |
| Reporting group description: Eligible T2DM participants were randomized in a 1:1 ratio to one of the two possible sequences: 150 microgram (µg) aleglitazar followed by matching placebo or placebo followed by 150 µg aleglitazar. Each treatment (aleglitazar and placebo) was received for 6 consecutive weeks, in a randomized order, separated by a 6-week treatment-free wash-out period. | |
| Reporting group title | Non-diabetic Control |
| Reporting group description: Non-diabetic controls (referred to as the calibration group) underwent only the assessments at screening and baseline and did not receive any study drug. | |

Primary: Change From Baseline to 6 Weeks After Treatment in Phosphocreatine/Adenosine Triphosphate (PCr/ATP) Ratio

| | |
|---|--|
| End point title | Change From Baseline to 6 Weeks After Treatment in Phosphocreatine/Adenosine Triphosphate (PCr/ATP) Ratio ^[1] |
| End point description: Participants underwent a cardiovascular magnetic resonance (CMR) scan performed on a 3 Tesla magnetic resonance (MR) system to assess cardiac mass, volumes (global function and dilatation), strain and torsion, cardiac and liver lipid content and cardiac energy metabolism. Change from Baseline was calculated as the post-Baseline value minus the Baseline value. Due to the early termination of the study by the sponsor, insufficient data were available to perform all planned analyses. Only available baseline values are reported in the baseline characteristics. | |
| End point type | Primary |
| End point timeframe: Baseline, 6 Weeks after treatment | |
| 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: Due to the early termination of the study by the sponsor, insufficient data were available to perform all planned statistical analyses. | |

| End point values | T2DM Participants | Non-diabetic Control | | |
|--------------------------------------|-------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[2] | 0 ^[3] | | |
| Units: ratio | | | | |
| arithmetic mean (standard deviation) | () | () | | |

Notes:

[2] - Due to early termination of study, insufficient data were available to perform all planned analyses.

[3] - Due to early termination of study, insufficient data were available to perform all planned analyses.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to 6 Weeks in Left Ventricular Diastolic Function

| | |
|---|--|
| End point title | Change From Baseline to 6 Weeks in Left Ventricular Diastolic Function |
| End point description: Transthoracic echocardiography (Phillips iE33) was used to assess diastolic function. For determination | |

of E/A, E deceleration times, and E/E', participants were scanned in a left lateral position with pulse wave velocities obtained at the mitral valve tips and tissue Doppler as an average of the basal septum and lateral walls.

Due to the early termination of the study by the sponsor, insufficient data were available to perform all planned analyses.

| | |
|-----------------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline, 6 Weeks after treatment | |

| End point values | T2DM Participants | Non-diabetic Control | | |
|--------------------------------------|-------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[4] | 0 ^[5] | | |
| Units: ratio | | | | |
| arithmetic mean (standard deviation) | () | () | | |

Notes:

[4] - Due to early termination of study, insufficient data were available to perform all planned analyses.

[5] - Due to early termination of study, insufficient data were available to perform all planned analyses.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to 6 Weeks in Cardiac and Hepatic Triglyceride Content

| | |
|-----------------|---|
| End point title | Change From Baseline to 6 Weeks in Cardiac and Hepatic Triglyceride Content |
|-----------------|---|

End point description:

Measurement of myocardial triglycerides were performed using spin echo imaging for localization of the voxels in the septum followed by 31P and 1H MR to obtain spectra. To obtain hepatic proton MR spectra, a voxel will was positioned in the liver, avoiding gross vascular structures and adipose tissue deposits. Spectra with and without water suppression was obtained to calculate hepatic triglyceride content as a percentage of water.

Due to the early termination of the study by the sponsor, insufficient data were available to perform all planned analyses. Only available baseline values are reported in the baseline characteristics.

| | |
|-----------------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline, 6 Weeks after treatment | |

| End point values | T2DM Participants | Non-diabetic Control | | |
|--------------------------------------|-------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[6] | 0 ^[7] | | |
| Units: ratio | | | | |
| arithmetic mean (standard deviation) | () | () | | |

Notes:

[6] - Due to early termination of study, insufficient data were available to perform all planned analyses.

[7] - Due to early termination of study, insufficient data were available to perform all planned analyses.

Statistical analyses

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to follow-up (6 weeks after the last dose of study medication)

| | |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 16.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|-------------------|
| Reporting group title | T2DM Participants |
|-----------------------|-------------------|

Reporting group description:

Eligible T2DM participants were randomized in a 1:1 ratio to one of two possible sequences: 150 microgram (µg) aleglitazar followed by matching placebo or placebo followed by 150 µg aleglitazar. Each treatment (aleglitazar and placebo) was received for 6 consecutive weeks, in a randomized order, separated by a 6-week treatment-free wash-out period. All adverse events which were observed across both the treatment group (placebo/aleglitazar) and during wash-out/follow-up after treatment completion reported.

| Serious adverse events | T2DM Participants | | |
|---|-------------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | 0 | | |

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

| Non-serious adverse events | T2DM Participants | | |
|---|-------------------|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 5 / 13 (38.46%) | | |
| Injury, poisoning and procedural complications | | | |
| Fall | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| Joint Injury | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| General disorders and administration site conditions | | | |

| | | | |
|--|---------------------|--|--|
| Influenza Like Illness subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 1 | | |
| Skin and subcutaneous tissue disorders Dry Skin subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 1 | | |
| Psoriasis subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 1 | | |
| Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 1 | | |
| Viral Infection subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 1 | | |
| Urinary Tract Infection subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 1 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|--------------|--|
| 05 June 2012 | Modified liver disease characteristic and specified the use of metformin as background therapy. The reasons for participant's discontinuation have been clarified and 2 withdrawal rules were implemented. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

| |
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| Due to the early termination of the study by the sponsor, insufficient data were available to perform all planned analyses. |
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Notes: