Clinical trial results:
Effect of Saxagliptin in Addition to Dapagliflozin and Metformin on Insulin Resistance, Islet Cell Dysfunction, and Metabolic Control in Subjects with Type 2 Diabetes Mellitus on Previous Metformin Treatment

Summary

EudraCT number	2014-003788-39
Trial protocol	DE
Global end of trial date	15 August 2016

Results information

Result version number	v1 (current)
This version publication date	26 May 2022
First version publication date	26 May 2022

Trial information

Trial identification

Sponsor protocol code	ESR-14-10231

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02304081
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Profil Mainz GmbH & Co KG
Sponsor organisation address	Rheinstr. 4c, Mainz, Germany, 55116
Public contact	Prof. Dr. Thomas Forst, Profil Mainz GmbH & Co KG, thomas.forst@profil.com
Scientific contact	Prof. Dr. Thomas Forst, Profil Mainz GmbH & Co KG, thomas.forst@profil.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	30 December 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 August 2016
Global end of trial reached?	Yes
Global end of trial date	15 August 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate alpha- and beta-cell function during combination treatment with dapagliflozin plus saxagliptin compared to dapagliflozin alone in subjects with T2DM on stable metformin background therapy

Protection of trial subjects:

Both drugs have been approved for single and combination treatment in the population defined by the eligibility criteria of this trial. Therefore, no specific risks are expected.
Trial-related risks are mainly associated with venous blood sampling and insertion of intravenous catheters for the clamp experiment. Blood sampling and the insertion of intravenous catheters will be performed with all caution by trained investigators or study nurses.

Background therapy:

Stable metformin background therapy

Evidence for comparator: -

Actual start date of recruitment	27 January 2015
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: 25
Worldwide total number of subjects	25
EEA total number of subjects	25

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)	12
From 65 to 84 years	13

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment from the own database; advertisement on homepage

Pre-assignment

Screening details:

1. Subjects with Diabetes mellitus type 2
2. HbA1c 7.0%–9.9%, both inclusive
3. Treatment with metformin for at least six months (daily dose 1500 – 3000 mg)
4. Age 30–75 years, both inclusive
5. BMI 25–35 kg/m^2, both inclusive

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Dapagliflozin/Saxagliptin arm

Arm description:

Saxagliptin as add on to Dapagliflozin

Arm type	Experimental
Investigational medicinal product name	Dapagliflozin (Forxiga)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

10 mg per day for up to 34 days

Investigational medicinal product name	Saxagliptin (Onglyza)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

5 mg per day for up to 34 days

Arm title	Dapagliflozin/Placebo arm

Arm description:

Dapagliflozin + Placebo to compare to Dapagliflozin/Saxagliptin treatment

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

Dosage and administration details:

Placebo to match Saxagliptin; administration for up to 34 days

Investigational medicinal product name	Dapagliflozin (Forxiga)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

10 mg per day for up to 34 days

Number of subjects in period 1	Dapagliflozin/Saxagliptin arm	Dapagliflozin/Placebo arm
Started	12	13
Completed	12	12
Not completed	0	1
Physician decision	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Dapagliflozin/Saxagliptin arm
Reporting group description:	
Saxagliptin as add on to Dapagliflozin	
Reporting group title	Dapagliflozin/Placebo arm
Reporting group description:	
Dapagliflozin + Placebo to compare to Dapagliflozin/Saxagliptin treatment	

Reporting group values	Dapagliflozin/Saxagliptin arm	Dapagliflozin/Placebo arm	Total
Number of subjects	12	13	25
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	5	7	12
From 65-84 years	7	6	13
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	63.5	63.2	
standard deviation	± 8.45	± 5.96	-
Gender categorical			
Units: Subjects			
Female	0	6	6
Male	12	7	19
Weight			
Units: kg			
arithmetic mean	91.29	87.78	
standard deviation	± 9.882	± 10.124	-
Height			
Units: meter			
arithmetic mean	1.750	1.707	
standard deviation	± 0.0374	± 0.0824	-
BMI			
Units: kg/m²			
arithmetic mean	29.78	30.12	
standard deviation	± 2.915	± 2.895	-
Waist Circumference			
Units: cm			
arithmetic mean	106.0	105.7	
standard deviation	± 10.90	± 6.26	-

Hip Circumference Units: cm arithmetic mean standard deviation	 100.8 ± 5.87	 105.2 ± 7.78	 -
HbA1c Units: percent arithmetic mean standard deviation	 8.03 ± 0.610	 8.03 ± 0.711	 -
Diabetes Duration Units: years arithmetic mean standard deviation	 10.6 ± 5.20	 7.1 ± 3.80	 -

End points

End points reporting groups	
Reporting group title	Dapagliflozin/Saxagliptin arm
Reporting group description: Saxagliptin as add on to Dapagliflozin	
Reporting group title	Dapagliflozin/Placebo arm
Reporting group description: Dapagliflozin + Placebo to compare to Dapagliflozin/Saxagliptin treatment	

Primary: Glucagon / insulin ratio	
End point title	Glucagon / insulin ratio
End point description: Glucagon / insulin ratio during hyperglycaemic clamp phase	
End point type	Primary
End point timeframe: during hyperglycaemic clamp phase	

End point values	Dapagliflozin/Saxagliptin arm	Dapagliflozin/Placebo arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	12		
Units: pmol/mU				
arithmetic mean (standard deviation)	-0.38 (± 0.412)	-0.05 (± 0.373)		

Statistical analyses

Statistical analysis title	Primary Endpoint
Comparison groups	Dapagliflozin/Saxagliptin arm v Dapagliflozin/Placebo arm
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0404
Method	ANCOVA
Parameter estimate	Mean difference (final values)

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Overall trial	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.0
Reporting groups	
Reporting group title	Overall trial

Reporting group description: -

Serious adverse events	Overall trial		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 25 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Overall trial		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 25 (44.00%)		
Injury, poisoning and procedural complications			
Catheter site haematoma			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Periorbital haematoma			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Cardiac disorders			
Palpitations			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Nervous system disorders			

Headache subjects affected / exposed occurrences (all) Intercostal neuralgia subjects affected / exposed occurrences (all)	 3 / 25 (12.00%) 3 1 / 25 (4.00%) 1		
Immune system disorders Seasonal allergy subjects affected / exposed occurrences (all)	 1 / 25 (4.00%) 1		
Eye disorders Eye swelling subjects affected / exposed occurrences (all)	 1 / 25 (4.00%) 1		
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) Epigastric discomfort subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	 2 / 25 (8.00%) 2 1 / 25 (4.00%) 1 1 / 25 (4.00%) 1 1 / 25 (4.00%) 1		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all) Sinusitis	 1 / 25 (4.00%) 1 1 / 25 (4.00%) 1		

subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 1		
Skin and subcutaneous tissue disorders Hyperhidrosis subjects affected / exposed occurrences (all)	 1 / 25 (4.00%) 1		
Psychiatric disorders Sleep disorder subjects affected / exposed occurrences (all)	 2 / 25 (8.00%) 3		
Renal and urinary disorders Pollakiuria subjects affected / exposed occurrences (all)	 2 / 25 (8.00%) 2		
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	 1 / 25 (4.00%) 2		
Infections and infestations Genital infection fungal subjects affected / exposed occurrences (all)	 1 / 25 (4.00%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 November 2014	The originally submitted trial protocol (Version 1.0, dated 21 Oct 2014) was updated in response to objections made by the IEC. This updated version was submitted to the Competent Authority as substantial Amendment 1: • Inclusion criterion 1 and 3 were modified (extension of stable metformin therapy from 3 to 6 months and removal of the restriction that T2DM could have been diagnosed only within 3 months prior to screening) • Withdrawal criteria 5 and 6 were added to be able to withdraw subjects with severe hypoglycaemia or any other severe complication during the clamp procedure • Due to safety objections subjects were not released immediately after the clamp but kept for another 4 hours post-clamp for stabilization and control of blood glucose values.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported