



## Clinical trial results:

### **DPP-4 inhibition with sitagliptin and the risk for hypoglycaemia in the fasting state in subjects with type 2 diabetes treated to fasting plasma glucose targets with insulin glargine and metformin**

#### **Summary**

EudraCT number	2016-004480-39
Trial protocol	DE
Global end of trial date	17 July 2019

#### **Results information**

Result version number	v1 (current)
This version publication date	15 May 2021
First version publication date	15 May 2021

#### **Trial information**

##### **Trial identification**

Sponsor protocol code	DPP4-Hypo
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##### **Additional study identifiers**

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03359590
WHO universal trial number (UTN)	-

Notes:

##### **Sponsors**

Sponsor organisation name	Profil Institut für Stoffwechselforschung GmbH
Sponsor organisation address	Hellersbergstr. 9, Neuss, Germany, 41460
Public contact	Project Development, Profil Institut für Stoffwechselforschung GmbH, +49 21314018219, eric.zijlstra@profil.com
Scientific contact	Project Development, Profil Institut für Stoffwechselforschung GmbH, +49 21314018219, eric.zijlstra@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	18 November 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 July 2019
Global end of trial reached?	Yes
Global end of trial date	17 July 2019
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

to test the influence of DPP-4 inhibition (comparing sitagliptin 100 mg per day versus placebo in a cross-over design) on

(a) the risk to develop hypoglycemia and on

(b) hormonal responses and recovery from hypoglycemia in the case that they occur

Protection of trial subjects:

Trial-related risks are mainly associated with an increased risk of hypoglycaemia due to therapy intensification with basal insulin titration. Mitigation strategies implemented in the protocol reduce the potential risks of treatment and trial-related procedures. Subjects that are required to washout oral anti-diabetes medication before starting the insulin titration period may temporarily experience more pronounced fluctuations of their plasma glucose levels, with a tendency to elevated glucose levels. As the washout period is relatively short (1 week) and is followed by an intensification of their diabetes treatment thereafter, this risk is considered low.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	21 March 2018
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: 20
Worldwide total number of subjects	20
EEA total number of subjects	20

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)	20
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

Recruitment from the own database; advertisement on homepage

### Pre-assignment

Screening details:

- HbA1c)  $\leq 8.5\%$
- Total insulin dose  $< 1.2$  U/kg/day
- on stable treatment with insulin glargine (any dose) and metformin ( $\geq 1500$  mg/day or at highest tolerated dose) for at least 3 months prior to inclusion
- All subjects underwent 1–16 weeks outpatient insulin titration during each treatment period.

### 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:

blinded dosing bottles

### Arms

Are arms mutually exclusive?	No
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<b>Arm title</b>	Sitagliptin arm
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Arm description:

Januvia 100 mg/d

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

Dosage and administration details:

50 mg tablets; 100 mg/d

<b>Arm title</b>	Placebo arm
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Arm description:

Placebo matching Januvia

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:

Placebo matching Januvia, 2 tablets (50 mg) once a day

<b>Number of subjects in period 1</b>	Sitagliptin arm	Placebo arm
Started	20	20
Completed	17	19
Not completed	3	1
Adverse event, non-fatal	1	-
Protocol deviation	2	1

## Baseline characteristics

### Reporting groups

Reporting group title	Overall trial
Reporting group description: -	

Reporting group values	Overall trial	Total	
Number of subjects	20	20	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	20	20	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous			
Units: years			
median	59.0		
standard deviation	± 6.17	-	
Gender categorical			
Units: Subjects			
Female	5	5	
Male	15	15	
Weight			
Units: kg			
arithmetic mean	92.32		
standard deviation	± 13.79	-	
Height			
Units: cm			
arithmetic mean	178.1		
standard deviation	± 9.20	-	
Waist circumference			
Units: cm			
arithmetic mean	105.9		
standard deviation	± 9.02	-	
HbA1c			
Units: percent			
arithmetic mean	7.35		
standard deviation	± 0.661	-	
BMI			
Units: kg/m2			
arithmetic mean	29.19		
standard deviation	± 4.139	-	



## End points

### End points reporting groups

Reporting group title	Sitagliptin arm
Reporting group description:	Januvia 100 mg/d
Reporting group title	Placebo arm
Reporting group description:	Placebo matching Januvia

### Primary: Hypoglycaemic episodes

End point title	Hypoglycaemic episodes
End point description:	
End point type	Primary
End point timeframe:	during in-house periods

End point values	Sitagliptin arm	Placebo arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	18		
Units: numbers	91	103		

### Statistical analyses

Statistical analysis title	Primary Endpoint
Comparison groups	Sitagliptin arm v Placebo arm
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	other <sup>[1]</sup>
P-value	= 0.389
Method	ANOVA

Notes:

[1] - Difference between sitagliptin and placebo regarding the number of chemical hypoglycaemic episodes.

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Only treatment-emergent adverse events (TEAEs) are reported, occurring after randomisation. No AEs were reported for the washout period.

Assessment type	Non-systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	22.1
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### Reporting groups

Reporting group title	Sitagliptin arm
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Reporting group description: -

Reporting group title	Placebo arm
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Reporting group description: -

<b>Serious adverse events</b>	Sitagliptin arm	Placebo arm	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 17 (0.00%)	1 / 19 (5.26%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Cardiac disorders			
Coronary heart disease			
subjects affected / exposed	0 / 17 (0.00%)	1 / 19 (5.26%)	
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: 0 %

<b>Non-serious adverse events</b>	Sitagliptin arm	Placebo arm	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 17 (70.59%)	11 / 19 (57.89%)	
Investigations			
Electrocardiogram ST segment depression			
subjects affected / exposed	0 / 17 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			

Arthropod bite subjects affected / exposed occurrences (all)	2 / 17 (11.76%) 2	1 / 19 (5.26%) 1	
Decapitation subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	1 / 19 (5.26%) 1	
Infusion site thrombosis subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1	0 / 19 (0.00%) 0	
Traumatic amputation subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1	0 / 19 (0.00%) 0	
Vascular disorders			
Orthostatic intolerance subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1	0 / 19 (0.00%) 0	
Syncope subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	1 / 19 (5.26%) 1	
Cardiac disorders			
Cardiovascular disorder subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	1 / 19 (5.26%) 1	
Coronary artery disease subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	1 / 19 (5.26%) 1	
Tachyarrhythmia subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1	0 / 19 (0.00%) 0	
Ventricular extrasystoles subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	1 / 19 (5.26%) 1	
Nervous system disorders			
Allodynia subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1	0 / 19 (0.00%) 0	
Dizziness			

subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1	1 / 19 (5.26%) 4	
Headache subjects affected / exposed occurrences (all)	6 / 17 (35.29%) 6	3 / 19 (15.79%) 3	
Ear and labyrinth disorders Ear discomfort subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	1 / 19 (5.26%) 1	
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1	4 / 19 (21.05%) 4	
Nausea subjects affected / exposed occurrences (all)	3 / 17 (17.65%) 3	1 / 19 (5.26%) 1	
Vomiting subjects affected / exposed occurrences (all)	2 / 17 (11.76%) 3	2 / 19 (10.53%) 2	
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	1 / 19 (5.26%) 1	
Nasopharyngitis subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1	1 / 19 (5.26%) 1	
Rhinitis subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	1 / 19 (5.26%) 1	
Psychiatric disorders Sleep disorder subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	1 / 19 (5.26%) 1	
Musculoskeletal and connective tissue disorders Arthralgia			

subjects affected / exposed	1 / 17 (5.88%)	2 / 19 (10.53%)
occurrences (all)	1	2
<b>Back pain</b>		
subjects affected / exposed	0 / 17 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	1
<b>Fibromyalgia</b>		
subjects affected / exposed	0 / 17 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	1
<b>Intervertebral disc displacement</b>		
subjects affected / exposed	0 / 17 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	1
<b>Muscle contractions involuntary</b>		
subjects affected / exposed	1 / 17 (5.88%)	0 / 19 (0.00%)
occurrences (all)	1	0

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 December 2017	Issued due to BfArM objections

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported