



Clinical trial results: Rotation for Optimal Targeting of Albuminuria and Treatment Evaluation Summary

EudraCT number	2015-005691-26
Trial protocol	NL DK
Global end of trial date	19 May 2021

Results information

Result version number	v1 (current)
This version publication date	29 July 2023
First version publication date	29 July 2023

Trial information

Trial identification

Sponsor protocol code	26201501252
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	Dutch Trial Register (LTR): NL5458

Notes:

Sponsors

Sponsor organisation name	University Medical Center Groningen
Sponsor organisation address	Hanzeplein 1, Groningen, Netherlands,
Public contact	N/A, University Medical Center Groningen, h.j.lambers.heerspink@umcg.nl
Scientific contact	N/A, University Medical Center Groningen, h.j.lambers.heerspink@umcg.nl

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 January 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 May 2021
Global end of trial reached?	Yes
Global end of trial date	19 May 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

A better understanding on the individual response to different albuminuria lowering drugs and a better understanding why these drugs, of which some are developed for another indication, may help to tailor optimal therapy. Therefore in this study individual patients will be subjected to four different drug classes that have all been shown to reduce albuminuria on a group level. The drug that induces the strongest albuminuria-lowering response will be repeated in a fifth treatment period to assess whether the albuminuria lowering effect can be confirmed in a second treatment period to ascertain the consistency of the individual response.

Protection of trial subjects:

ETHICAL CONSIDERATIONS

Regulation statement:

The study was conducted in accordance with the Declaration of Helsinki (latest version adopted by the 64th WMA General Assembly in Fortaleza, Brazil, October 2013) and the Medical Research Involving Human Subjects Act (WMO). The Medical Ethical Committee of the University Medical Center in Groningen and of the Capital Region in Denmark, approved the study for initiation in The Netherlands and in Denmark, respectively.

Benefits and risks assessment, group relatedness:

There was no direct benefit to the patient's health be expected from this study. Participation in the study is on a free-will base. Patients will receive restitution of all costs of transportation. Patients will not receive priority for treatment of other diseases in the clinic during this study. Participation in the proposed study was accompanied with only minor risks, if any at all.

Compensation for injury:

The patients were covered by the existing law of product liability insurance for the study medication as well as the law of patient insurance. All patients received written information about this insurance.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 February 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Denmark: 25
Country: Number of subjects enrolled	Netherlands: 1
Worldwide total number of subjects	26
EEA total number of subjects	26

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)	17
From 65 to 84 years	9
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

26 participants with type 1 diabetes and albuminuria were recruited from Steno Diabetes Center Copenhagen, Denmark and Ziekenhuis Groep Twente, Almelo, Netherlands. Coordination of the study centers were performed by the University Medical Center Groningen, Netherlands.

Pre-assignment

Screening details:

Adult participants with type 1 or type 2 diabetes with a urinary albumin to creatinine ratio (UACR) between 30 and 500 mg/g and estimated glomerular filtration rate ≥ 45 mL/min/1.73 m² were eligible.

Period 1

Period 1 title	First treatment
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Not blinded

Arms

Are arms mutually exclusive?	No
Arm title	Telmisartan

Arm description:

4-week open label treatment with telmisartan 80 mg, before crossing over to next arm, in random order.

Arm type	Active comparator
Investigational medicinal product name	Micardis
Investigational medicinal product code	
Other name	TELMISARTAN
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

80 mg, once daily

Arm title	Empagliflozin
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Arm description:

4-week treatment with empagliflozin 25 mg, before crossing over to next arm, in random order.

Arm type	Active comparator
Investigational medicinal product name	Jardiance
Investigational medicinal product code	
Other name	EMPAGLIFLOZIN
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

25 MG, ONCE daily

Arm title	Baricitinib
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Arm description:

4-week treatment with baricitinib 2 mg, before crossing over to next arm, in random order.

Arm type	Active comparator
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Investigational medicinal product name	Olumiant
Investigational medicinal product code	
Other name	Baricitinib
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
2 mg, once daily	
Arm title	Linagliptin

Arm description:

4-week treatment with linagliptin 5 mg, before crossing over to next arm, in random order.

Arm type	Active comparator
Investigational medicinal product name	Trajenta
Investigational medicinal product code	
Other name	LINAGLIPTIN
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

5 mg, once daily

Number of subjects in period 1	Telmisartan	Empagliflozin	Baricitinib
Started	26	26	26
Completed	26	26	26

Number of subjects in period 1	Linagliptin
Started	26
Completed	26

Period 2

Period 2 title	Confirmation
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Not blinded

Arms

Arm title	Confirmation
Arm description: -	
Arm type	Active comparator
Investigational medicinal product name	Micardis
Investigational medicinal product code	
Other name	TELMISARTAN
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
80 mg, once daily	
Investigational medicinal product name	Jardiance
Investigational medicinal product code	
Other name	EMPAGLIFLOZIN
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
25 MG, ONCE daily	
Investigational medicinal product name	Olumiant
Investigational medicinal product code	
Other name	Baricitinib
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
2 mg, once daily	
Investigational medicinal product name	Trajenta
Investigational medicinal product code	
Other name	LINAGLIPTIN
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
5 mg, once daily	

Number of subjects in period 2	Confirmation
Started	26
Completed	26

Baseline characteristics

Reporting groups

Reporting group title	First treatment
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Reporting group description: -

Reporting group values	First treatment	Total	
Number of subjects	26	26	
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	60		
standard deviation	± 12	-	
Gender categorical			
Units: Subjects			
Female	7	7	
Male	19	19	
Race			
Units: Subjects			
White	26	26	
Non-white	0	0	
Current smokers			
Units: Subjects			
Smoker	3	3	
Non-smoker	23	23	
Diuretics treatment			
Units: Subjects			
Thiazide	10	10	
Loop	15	15	
No diuretics	1	1	
Metformin treatment			
Units: Subjects			
Metformin	2	2	
No metformin	24	24	
Insulin treatment			
Units: Subjects			
Insulin	26	26	

No insulin	0	0	
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HbA1c			
Glycated hemoglobin			
Units: mmol/mol			
arithmetic mean	60		
standard deviation	± 7	-	
UACR			
Urinary albumin/creatinine ratio			
Units: mg/g			
median	92		
inter-quartile range (Q1-Q3)	65 to 282	-	
BMI			
Body mass index			
Units: kg/m ²			
arithmetic mean	29		
standard deviation	± 5	-	
Serum creatinine			
Units: µmol/l			
arithmetic mean	88		
standard deviation	± 23	-	
eGFR			
Estimated creatinine-derived glomerular filtration rate			
Units: ml/min/1.73m ²			
arithmetic mean	79		
standard deviation	± 18	-	
Systolic blood pressure			
Units: mmHg			
arithmetic mean	138		
standard deviation	± 13	-	
Diastolic blood pressure			
Units: mmHg			
arithmetic mean	79		
standard deviation	± 18	-	

End points

End points reporting groups

Reporting group title	Telmisartan
Reporting group description: 4-week open label treatment with telmisartan 80 mg, before crossing over to next arm, in random order.	
Reporting group title	Empagliflozin
Reporting group description: 4-week treatment with empagliflozin 25 mg, before crossing over to next arm, in random order.	
Reporting group title	Baricitinib
Reporting group description: 4-week treatment with baricitinib 2 mg, before crossing over to next arm, in random order.	
Reporting group title	Linagliptin
Reporting group description: 4-week treatment with linagliptin 5 mg, before crossing over to next arm, in random order.	
Reporting group title	Confirmation
Reporting group description: -	

Primary: Change in UACR across 4 weeks of treatment

End point title	Change in UACR across 4 weeks of treatment
End point description: The study comprised four consecutive crossover treatment periods of 4 weeks, in random order, each with 4-week washout periods in between. At the end of the 4-week rotation schedule, participants proceeded to a 4-week confirmatory treatment period during which they were treated with their individual best UACR-lowering drug.	
End point type	Primary
End point timeframe: Change across 4 weeks	

End point values	Telmisartan	Empagliflozin	Baricitinib	Linagliptin
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	26	26	26	26
Units: percent				
arithmetic mean (confidence interval 95%)	-22.6 (-32.5 to -11.4)	4.7 (-9.7 to 21.4)	-6.5 (-19.1 to 8.1)	-9.5 (-21.4 to 4.3)

End point values	Confirmation			
Subject group type	Reporting group			
Number of subjects analysed	26			
Units: percent				
arithmetic mean (confidence interval 95%)	-15.0 (-26.7 to -1.4)			

Statistical analyses

Statistical analysis title	Primary analysis
Comparison groups	Telmisartan v Empagliflozin v Baricitinib v Linagliptin v Confirmation
Number of subjects included in analysis	130
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.05
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Confidence interval	
level	95 %
sides	2-sided

Adverse events

Adverse events information

Timeframe for reporting adverse events:

14 months

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	2.1
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Reporting groups

Reporting group title	Full dataset
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Reporting group description: -

Serious adverse events	Full dataset		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 26 (15.38%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Eye disorders			
Vitreous haemorrhage			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
COVID-19			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Full dataset		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	26 / 26 (100.00%)		
Vascular disorders			
Foot ulcer			
subjects affected / exposed	2 / 26 (7.69%)		
occurrences (all)	2		
Hypertension			
subjects affected / exposed	2 / 26 (7.69%)		
occurrences (all)	2		
Orthostatic hypotension			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
Vertigo			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
Intermittent lower limb paresthesia			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
Neuropathy peripheral			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
General disorders and administration site conditions			

Peripheral edema subjects affected / exposed occurrences (all)	4 / 26 (15.38%) 4		
Thirst subjects affected / exposed occurrences (all)	2 / 26 (7.69%) 2		
Dry mouth subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 1		
Eye disorders Iritis subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 1		
Glaucoma subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 1		
Retinopathy subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 1		
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 1		
Nausea subjects affected / exposed occurrences (all)	3 / 26 (11.54%) 3		
Constipation subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 1		
Colorectal polype subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 1		
Respiratory, thoracic and mediastinal disorders Epistaxis subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 1		

Dyspnoea subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 1		
Cough subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 1		
Skin and subcutaneous tissue disorders Pruritus subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 1		
Irritated foreskin subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 1		
Eczema subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 1		
Insulin pump failure subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 1		
Psychiatric disorders Depression subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 1		
Renal and urinary disorders Polyuria subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 1		
Musculoskeletal and connective tissue disorders Muscular pain subjects affected / exposed occurrences (all)	2 / 26 (7.69%) 2		
Arthralgia subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 1		
Exacerbation of arthritic pains			

subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
Dislocation of clavicle			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
Infections and infestations			
Cystitis bacterial			
subjects affected / exposed	2 / 26 (7.69%)		
occurrences (all)	2		
Influenza like illness			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
Foot wart			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
Gastroenteritis			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
Borrelia infection			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
Hypoglycaemia			
subjects affected / exposed	4 / 26 (15.38%)		
occurrences (all)	4		
Blood glucose fluctuation			
subjects affected / exposed	3 / 26 (11.54%)		
occurrences (all)	3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/36657986>