Clinical trial results:
Effect of the SGLT-2 inhibitor dapagliflozin on impaired awareness of hypoglycemia in type 1 diabetes

Summary

EudraCT number	2018-001569-17
Trial protocol	NL
Global end of trial date	20 December 2019

Results information

Result version number	v1 (current)
This version publication date	12 December 2020
First version publication date	12 December 2020
Summary attachment (see zip file)	Endresults trial (Eindresultaat trial NL65635.091.18.pdf)

Trial information

Trial identification

Sponsor protocol code	T1DM_IAH_dapa

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03556033
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Radboud university medical center
Sponsor organisation address	PO box 9101, Nijmegen, Netherlands,
Public contact	Lian van Meijel, Radboud university medical center, 31 243610846, Lian.vanMeijel@radboudumc.nl
Scientific contact	Lian van Meijel, Radboud university medical center, 31 243610846, Lian.vanMeijel@radboudumc.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	26 November 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 December 2019
Global end of trial reached?	Yes
Global end of trial date	20 December 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate the effect of treatment with the SGLT-2 inhibitor dapagliflozin on the awareness of and counterregulatory hormone responses to hypoglycemia in people with type 1 diabetes and impaired hypoglycemic awareness

Protection of trial subjects:

We did not use specific measures to protect trial subjects.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 August 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	Netherlands: 15
Worldwide total number of subjects	15
EEA total number of subjects	15

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	2
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were included between November 2018 and August 2019.
Last patient visit was 20th of December 2019.

Pre-assignment

Screening details:

We included 15 participants, 2 withdrew consent before start of the study. They were replaced by 2 other participants, so in total 15 people completed the study.
There were 2 treatment periods of both 8 weeks, with a washout period of 2 weeks in between.

Period 1

Period 1 title	Baseline
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Baseline
Arm description: -	
Arm type	baseline
Investigational medicinal product name	dapagliflozin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

10 mg once daily

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

one capsule once daily

Number of subjects in period 1	Baseline
Started	15
Completed	15

Period 2

Period 2 title	Dapagliflozin first, then placebo
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Subject

Arms

Arm title	Dapagliflozin first, then placebo

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	dapagliflozin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

10 mg once daily

Number of subjects in period 2[1]	Dapagliflozin first, then placebo
Started	8
Completed	8

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: starting number is 15, this is a cross-over trial, so 8 patients started with dapagliflozin first and then placebo, and 7 patients started with placebo first and then dapagliflozin

Period 3

Period 3 title	Placebo first, then dapagliflozin
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Arm title	Placebo first, then dapagliflozin

Arm description: -

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

one capsule once daily

Number of subjects in period 3[2]	Placebo first, then dapagliflozin
Started	7
Completed	7

Notes:

[2] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: starting number is 15, this is a cross-over trial, so 8 patients started with dapagliflozin first and then placebo, and 7 patients started with placebo first and then dapagliflozin

Baseline characteristics

Reporting groups

Reporting group title	Baseline

Reporting group description: -

Reporting group values	Baseline	Total	
Number of subjects	15	15	
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)	13	13	
From 65-84 years	2	2	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	9	9	
Male	6	6	

Subject analysis sets

Subject analysis set title	Primary outcome
Subject analysis set type	Full analysis

Subject analysis set description:

Symptom scores in response to hypoglycemia

Reporting group values	Primary outcome		
Number of subjects	15		
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)	13		
From 65-84 years	2		
85 years and over	0		

Gender categorical Units: Subjects			
Female	9		
Male	6		

End points

End points reporting groups

Reporting group title	Baseline
Reporting group description: -	
Reporting group title	Dapagliflozin first, then placebo
Reporting group description: -	
Reporting group title	Placebo first, then dapagliflozin
Reporting group description: -	
Subject analysis set title	Primary outcome
Subject analysis set type	Full analysis
Subject analysis set description: Symptom scores in response to hypoglycemia	

Primary: Symptom scores in response to hypoglycemia

End point title	Symptom scores in response to hypoglycemia
End point description: Symptom scores in response to hypoglycemia during the clamps	
End point type	Primary
End point timeframe: 45 minutes	

End point values	Dapagliflozin first, then placebo	Placebo first, then dapagliflozin	Primary outcome	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	8	7	15	
Units: points				
number (not applicable)	8.0	5.2	15	

Statistical analyses

Statistical analysis title	Paired t-test
Comparison groups	Dapagliflozin first, then placebo v Placebo first, then dapagliflozin
Number of subjects included in analysis	15
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	≤ 0.05
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard error of the mean

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Two treatment periods of both 8 weeks	
Assessment type	Systematic
Dictionary used	
Dictionary name	unknown
Dictionary version	1
Reporting groups	
Reporting group title	Dapagliflozin first, then placebo
Reporting group description: Subgroup that received dapagliflozin first and then placebo	
Reporting group title	Placebo first, then dapagliflozin
Reporting group description: Subgroup that received placebo first for 8 weeks and then dapagliflozin	

Serious adverse events	Dapagliflozin first, then placebo	Placebo first, then dapagliflozin	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 8 (0.00%)	0 / 7 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Dapagliflozin first, then placebo	Placebo first, then dapagliflozin	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 8 (62.50%)	0 / 7 (0.00%)	
Gastrointestinal disorders			
Food poisoning			
subjects affected / exposed	1 / 8 (12.50%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Reproductive system and breast disorders			
Genital infection			
subjects affected / exposed	1 / 8 (12.50%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			

Urinary tract infection			
subjects affected / exposed	1 / 8 (12.50%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Ankle fracture			
subjects affected / exposed	1 / 8 (12.50%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Bursitis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
flu			
subjects affected / exposed	1 / 8 (12.50%)	0 / 7 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 October 2018	Include patients using antihypertensive drugs (This was an exclusion criterium first)
20 March 2019	HbA1c<75 mmol/mol

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported