



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 | Subject, Investigator |

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