



Clinical trial results:

A single-dose cross-over study to assess direct and indirect effects of dapagliflozin on pancreatic alpha and beta cells in patients with type 2 diabetes

Summary

| | |
|--------------------------|------------------|
| EudraCT number | 2015-005549-30 |
| Trial protocol | SE |
| Global end of trial date | 01 December 2016 |

Results information

| | |
|-----------------------------------|--|
| Result version number | v1 (current) |
| This version publication date | 07 August 2020 |
| First version publication date | 07 August 2020 |
| Summary attachment (see zip file) | A single-dose cross-over study to assess direct and indirect effects of dapagliflozin on pancreatic alpha and beta cells in patients with type 2 diabetes (DG CSR 3.0_20180503_CLEAN.docx) |

Trial information

Trial identification

| | |
|-----------------------|--------------|
| Sponsor protocol code | ESR-15-11421 |
|-----------------------|--------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02765204 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Uppsala University |
| Sponsor organisation address | Sjukhusvägen 1, Uppsala, Sweden, 75185 |
| Public contact | Jan Eriksson, Dept of Medical Sciences, Clinical Diabetes and Metabolism, Uppsala University, 46 186114419, jan.eriksson@medsci.uu.se |
| Scientific contact | Jan Eriksson, Dept of Medical Sciences, Clinical Diabetes and Metabolism, Uppsala University, 46 186114419, jan.eriksson@medsci.uu.se |

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 | 15 June 2017 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 01 December 2016 |
| Global end of trial reached? | Yes |
| Global end of trial date | 01 December 2016 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To evaluate if Dapagliflozin has direct effect on alpha cell glucagon release.

Protection of trial subjects:

Heartrate, bloodpressure, bloodsamples taken as a standard procedure as in ordinary healthcare

Background therapy: -

Evidence for comparator: -

| | |
|---|---------------|
| Actual start date of recruitment | 01 March 2016 |
| 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 | Sweden: 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) | 4 |
| From 65 to 84 years | 11 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Advertisement, studycenter patientlist

Pre-assignment

Screening details:

Age 18-75 years, BMI 20-35, diagnosis at least 6 months of T2D, Metformin treatment with stable dos for at least 1 month, HbA1c range 55-86mmol/mol

Period 1

| | |
|----------------------------------|--------------------------------|
| Period 1 title | overall trail (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |
| Blinding implementation details: | |
| Not blinded | |

Arms

| | |
|------------------------------|------|
| Are arms mutually exclusive? | Yes |
| Arm title | Dapa |

Arm description:

D=Dapagliflozin 10mg and Salin infusion

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

Dosage and administration details:

10 mg dapagliflozin

| | |
|------------------|----------|
| Arm title | Dapa+Iso |
|------------------|----------|

Arm description:

Dapagliflozin 10mg and isoglycemicclamp

| | |
|--|-------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | Dapagliflozin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

10 mg Dapagliflozin

| | |
|------------------|-------------|
| Arm title | Dapa + Saxa |
|------------------|-------------|

Arm description:

Dapagliflozin 10mg and saxagliptin 5mg and salininfusion

| | |
|----------|-------------------|
| Arm type | Active comparator |
|----------|-------------------|

| | |
|--|-------------------------------|
| Investigational medicinal product name | Dapagliflozin and saxagliptin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

10mg Dapagliflozin

5mg saxagliptin

| Number of subjects in period 1 | Dapa | Dapa+Iso | Dapa + Saxa |
|---------------------------------------|------|----------|-------------|
| Started | 5 | 5 | 5 |
| Completed | 3 | 5 | 4 |
| Not completed | 2 | 0 | 1 |
| Consent withdrawn by subject | 1 | - | 1 |
| Adverse event, non-fatal | 1 | - | - |

Baseline characteristics

End points

End points reporting groups

| | |
|--|-------------|
| Reporting group title | Dapa |
| Reporting group description: | |
| D=Dapagliflozin 10mg and Salin infusion | |
| Reporting group title | Dapa+Iso |
| Reporting group description: | |
| Dapagliflozin 10mg and isoglycemicclamp | |
| Reporting group title | Dapa + Saxa |
| Reporting group description: | |
| Dapagliflozin 10mg and saxagliptin 5mg and salininfusion | |

Primary: Plasma glucose and glucagon levels during experimental periods. Comparing experiments with spontaneous glycemia and isoglycemia respectively.

| | |
|---|---|
| End point title | Plasma glucose and glucagon levels during experimental periods. Comparing experiments with spontaneous glycemia and isoglycemia respectively. |
| End point description: | |
| This study will provide insight into SGLT2 action in beta and alpha cells, in particular with respect to direct and indirect effects on glucagon secretion. Furthermore, it explores the mechanisms of glucose control when combining SGLT2- and DPP4 inhibitors. | |
| End point type | Primary |
| End point timeframe: | |
| 10 month | |

| End point values | Dapa | Dapa+Iso | Dapa + Saxa | |
|-----------------------------|-----------------|-----------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 3 | 5 | 4 | |
| Units: mmol/mol | | | | |
| number (not applicable) | 3 | 5 | 4 | |

| | |
|----------------------------|--------------------------------|
| Attachments (see zip file) | 2019 PL Dapa glucagon JCEM.pdf |
|----------------------------|--------------------------------|

Statistical analyses

| | |
|----------------------------|--|
| Statistical analysis title | Primary comparison: Effect of Dapagliflozin on glu |
| Comparison groups | Dapa v Dapa+Iso v Dapa + Saxa |

| | |
|---|------------------------|
| Number of subjects included in analysis | 12 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[1] |
| P-value | < 0.001 ^[2] |
| Method | Mixed models analysis |
| Parameter estimate | Hazard ratio (HR) |

Notes:

[1] - The study had 90% power to detect a 15% difference in the primary end point between the two conditions in the primary comparison. Based on previous work, this difference was judged to be clinically relevant and calculated to be 3 pmol/L (baseline level of about 20 pmol/L; SD, 3 pmol/L) (11). Thus, the sample size required for analysis of the primary end point was 12 evaluable patients. A maximum of three patients who did not complete the study (premature withdrawals) was expected. Thus, 15 patients

[2] - The study had 90% power to detect a 15% difference in the primary end point between the two conditions in the primary comparison. Based on previous work, this difference was judged to be clinically relevant and calculated to be 3 pmol/L (baseline level)

Adverse events

Adverse events information

Timeframe for reporting adverse events:

10 month

| | |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|----|
| Dictionary version | 18 |
|--------------------|----|

Reporting groups

| | |
|-----------------------|-----------|
| Reporting group title | Tiredness |
|-----------------------|-----------|

Reporting group description:

Safety In general, the study treatments were well tolerated; 19 AEs were reported in six patients. No new and unexpected AEs were observed. The most commonly reported events were headache (six events in three patients) and tiredness (five events in three patients). Fifteen events were mild and two (ureteral stone and urticaria) were moderate in intensity. One event, deep vein thrombosis of the arm, was deemed severe in intensity and resulted in the patient withdrawing from the study. The moderate and severe AEs required medication but none required hospitalization. Only one event (dizziness) was

| Serious adverse events | Tiredness | | |
|---|---------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | 0 | | |

Frequency threshold for reporting non-serious adverse events: 5 %

| Non-serious adverse events | Tiredness | | |
|---|---|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 3 / 5 (60.00%) | | |
| General disorders and administration site conditions | | | |
| Head banging | Additional description: Safety In general, the study treatments were well tolerated; 19 AEs were reported in six patients. No new and unexpected AEs were observed. The most commonly reported events were headache (six events in three patients) and tiredness (five events in three patients). Fifteen | | |
| subjects affected / exposed | 3 / 5 (60.00%) | | |
| occurrences (all) | 5 | | |

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