



## Clinical trial results:

**A randomized, double-blinded, placebo-controlled trial that evaluates the effect of empagliflozin on oxidative stress in patients with type 2 diabetes**

### Summary

|                          |                 |
|--------------------------|-----------------|
| EudraCT number           | 2016-000370-38  |
| Trial protocol           | DK              |
| Global end of trial date | 22 January 2020 |

### Results information

|                                |                  |
|--------------------------------|------------------|
| Result version number          | v1 (current)     |
| This version publication date  | 04 February 2021 |
| First version publication date | 04 February 2021 |

### Trial information

#### Trial identification

|                       |          |
|-----------------------|----------|
| Sponsor protocol code | 2016-100 |
|-----------------------|----------|

#### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT02890745 |
| WHO universal trial number (UTN)   | -           |

Notes:

### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Department of Clinical Pharmacology, Bispebjerg-Frederiksberg Hospital - Rigshospitalet, Q7642   |
| Sponsor organisation address | Blegdamsvej 9, Copenhagen, Denmark,  |
| Public contact               | Henrik Enghusen Poulsen, Department of Clinical Pharmacology,<br>Bispebjerg-Frederiksberg Hospital,<br>Denmark, +45 35457695,<br>henrik.enghusen.poulsen.01@regionh.dk |
| Scientific contact           | Henrik Enghusen Poulsen, Department of Clinical Pharmacology,<br>Bispebjerg-Frederiksberg Hospital,<br>Denmark, +45 35457695,<br>henrik.enghusen.poulsen.01@regionh.dk |

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                       | 01 November 2020 |
| Is this the analysis of the primary completion data? | Yes              |
| Primary completion date                              | 22 January 2020  |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 22 January 2020  |
| Was the trial ended prematurely?                     | Yes              |

Notes:

## General information about the trial

Main objective of the trial:

Urinary excretion rates of 8-oxo-7,8-dihydroguanosine (8-oxoGuo) and 8-oxo-7,8-dihydro-2'-deoxyguanosine (8-oxodG) before and after treatment with empagliflozin compared to placebo treatment in addition to standard care in patients with type 2 diabetes

Protection of trial subjects:

All data was stored in accordance with the Danish Law of data protection

Background therapy: -

Evidence for comparator: -

|   |                  |
|---|------------------|
| Actual start date of recruitment                          | 23 November 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 | Denmark: 35 |
| Worldwide total number of subjects   | 35          |
| EEA total number of subjects         | 35          |

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)                      | 18 |
| From 65 to 84 years                       | 17 |

|                   |   |
|-------------------|---|
| 85 years and over | 0 |
|-------------------|---|

## Subject disposition

### Recruitment

Recruitment details:

Recruitment were done in relation to patients outpatient consultation at Gentofte Hospital and Bispebjerg Hospital as well as through advertisements at public available material.

### Pre-assignment

Screening details:

A screening visit is performed prior to enrollment in the study to ensure eligibility of study criteria with a physical examination and disease and life style history

### 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, Monitor, Data analyst, Assessor |

### Arms

|                              |              |
|------------------------------|--------------|
| Are arms mutually exclusive? | Yes          |
| <b>Arm title</b>             | Intervention |

Arm description:

Active arm. Empagliflozin 25 mg, once daily for 14 days

|  |               |
|--|---------------|
| Arm type                               | Experimental  |
| Investigational medicinal product name | empagliflozin |
| Investigational medicinal product code |               |
| Other name                             |               |
| Pharmaceutical forms                   | Tablet        |
| Routes of administration               | Oral use      |

Dosage and administration details:

25 mg, tablet, oral use

|                  |         |
|------------------|---------|
| <b>Arm title</b> | Placebo |
|------------------|---------|

Arm description:

Placebo

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

Dosage and administration details:

Placebo, tablet, oral use

| Number of subjects in period<br>1 <sup>[1]</sup> | Intervention | Placebo |
|--|--------------|---------|
|  |              |         |
| Started  | 16           | 15      |
| Completed  | 16           | 15      |

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Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: A total number of 35 participants were enrolled in the study. However, 4 participants chose to withdraw before getting trial medicine, and were thus not included in the baseline information.

## Baseline characteristics

### Reporting groups

|                                |               |
|--------------------------------|---------------|
| Reporting group title          | Overall trial |
| Reporting group description: - |               |

| Reporting group values                                | Overall trial | Total |  |
|---|---------------|-------|--|
| Number of subjects                                    | 31            | 31    |  |
| Age categorical                                       |               |       |  |
| Units: Subjects                                       |               |       |  |
| In utero  |               | 0     |  |
| Preterm newborn infants<br>(gestational age < 37 wks) |               | 0     |  |
| Newborns (0-27 days)                                  |               | 0     |  |
| Infants and toddlers (28 days-23<br>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  |               |       |  |
| Mean: 63  |               |       |  |
| SD: 7   |               |       |  |
| Units: years  |               |       |  |
| arithmetic mean                                       | 63            |       |  |
| standard deviation                                    | ± 7           | -     |  |
| Gender categorical                                    |               |       |  |
| Units: Subjects                                       |               |       |  |
| Female  | 0             | 0     |  |
| Male  | 31            | 31    |  |
| Body mass index                                       |               |       |  |
| Units: kg/m <sup>2</sup>                              |               |       |  |
| arithmetic mean                                       | 30.9          |       |  |
| standard deviation                                    | ± 4.6         | -     |  |
| HbA1c   |               |       |  |
| Units: mmol/mol                                       |               |       |  |
| arithmetic mean                                       | 56            |       |  |
| standard deviation                                    | ± 7           | -     |  |

## End points

### End points reporting groups

|   |              |
|---|--------------|
| Reporting group title                                   | Intervention |
| Reporting group description:                            |              |
| Active arm. Empagliflozin 25 mg, once daily for 14 days |              |
| Reporting group title                                   | Placebo      |
| Reporting group description:                            |              |
| Placebo   |              |

### Primary: Changes in urinary excretion of 8-oxo-7,8-dihydroguanosine

|                                       |  |
|---------------------------------------|--|
| End point title                       | Changes in urinary excretion of 8-oxo-7,8-dihydroguanosine |
| End point description:                |  |
| End point type                        | Primary  |
| End point timeframe:                  |  |
| Changes from baseline to end of study |  |

| End point values                     | Intervention    | Placebo         |  |  |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type                   | Reporting group | Reporting group |  |  |
| Number of subjects analysed          | 16              | 15              |  |  |
| Units: nmol/24h                      |                 |                 |  |  |
| arithmetic mean (standard deviation) | -0.5 (± 7.8)    | -1.8 (± 8.5)    |  |  |

### Statistical analyses

|   |  |
|---|--|
| Statistical analysis title              | Between group effects 8-oxo-7,8-dihydroguanosine |
| Comparison groups                       | Placebo v Intervention                           |
| Number of subjects included in analysis | 31   |
| Analysis specification                  | Pre-specified                                    |
| Analysis type                           | equivalence                                      |
| P-value                                 | = 0.66   |
| Method                                  | t-test, 2-sided                                  |
| Parameter estimate                      | Mean difference (final values)                   |
| Point estimate                          | 1.3  |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | -4.2   |
| upper limit                             | 4.8  |

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**Primary: Changes in urinary excretion of 8-oxo-7,8-dihydro-2'-deoxyguanosine**

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|                 |   |
|-----------------|---|
| End point title | Changes in urinary excretion of 8-oxo-7,8-dihydro-2'-deoxyguanosine |
|-----------------|---|

End point description:

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Changes from baseline to end of study

---

| End point values                     | Intervention    | Placebo         |  |  |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type                   | Reporting group | Reporting group |  |  |
| Number of subjects analysed          | 16              | 15              |  |  |
| Units: nmol/24h                      |                 |                 |  |  |
| arithmetic mean (standard deviation) | -1.1 (± 5.3)    | -1.5 (± 6.7)    |  |  |

**Statistical analyses**

|                            |  |
|----------------------------|--|
| Statistical analysis title | Between group effects 8-oxo-7,8-dihydro-2'-deoxygu |
|----------------------------|--|

|                   |                        |
|-------------------|------------------------|
| Comparison groups | Intervention v Placebo |
|-------------------|------------------------|

|   |    |
|---|----|
| Number of subjects included in analysis | 31 |
|---|----|

|                        |               |
|------------------------|---------------|
| Analysis specification | Pre-specified |
|------------------------|---------------|

|               |             |
|---------------|-------------|
| Analysis type | equivalence |
|---------------|-------------|

|         |        |
|---------|--------|
| P-value | = 0.89 |
|---------|--------|

|        |                 |
|--------|-----------------|
| Method | t-test, 2-sided |
|--------|-----------------|

|                    |                                |
|--------------------|--------------------------------|
| Parameter estimate | Mean difference (final values) |
|--------------------|--------------------------------|

|                |     |
|----------------|-----|
| Point estimate | 0.3 |
|----------------|-----|

Confidence interval

|       |      |
|-------|------|
| level | 95 % |
|-------|------|

|       |         |
|-------|---------|
| sides | 2-sided |
|-------|---------|

|             |      |
|-------------|------|
| lower limit | -4.2 |
|-------------|------|

|             |     |
|-------------|-----|
| upper limit | 4.8 |
|-------------|-----|

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**Secondary: Changes in plasma concentration of malondialdehyde**

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|                 |  |
|-----------------|--|
| End point title | Changes in plasma concentration of malondialdehyde |
|-----------------|--|

End point description:

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Changes from baseline to end of study

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| <b>End point values</b>              | Intervention        | Placebo            |  |  |
|--------------------------------------|---------------------|--------------------|--|--|
| Subject group type                   | Reporting group     | Reporting group    |  |  |
| Number of subjects analysed          | 16                  | 15                 |  |  |
| Units: nmol/mL                       |                     |                    |  |  |
| arithmetic mean (standard deviation) | -0.13 ( $\pm$ 0.67) | 0.08 ( $\pm$ 0.54) |  |  |

## Statistical analyses

| <b>Statistical analysis title</b>       | Between group effect malondialdehyde |
|---|--------------------------------------|
| Comparison groups                       | Intervention v Placebo               |
| Number of subjects included in analysis | 31                                   |
| Analysis specification                  | Pre-specified                        |
| Analysis type                           | equivalence                          |
| P-value                                 | = 0.33                               |
| Method                                  | t-test, 2-sided                      |
| Parameter estimate                      | Mean difference (final values)       |
| Point estimate                          | -0.22                                |
| Confidence interval                     |                                      |
| level                                   | 95 %                                 |
| sides                                   | 2-sided                              |
| lower limit                             | -0.66                                |
| upper limit                             | 0.23                                 |

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

During the study period (14 days) and one week afterwards

Adverse event reporting additional description:

Daily text messages and at the end of study. If any occurred the week following the study, participants contacted the investigator

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 23.1 |
|--------------------|------|

### Reporting groups

|                       |                    |
|-----------------------|--------------------|
| Reporting group title | Intervention group |
|-----------------------|--------------------|

Reporting group description:

Empagliflozin 25 mg, once daily for 14 days

|                       |         |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Placebo for 14 days

| Serious adverse events                            | Intervention group | Placebo        |  |
|---|--------------------|----------------|--|
| Total subjects affected by serious adverse events |                    |                |  |
| subjects affected / exposed                       | 0 / 16 (0.00%)     | 0 / 15 (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                            | Intervention group | Placebo         |  |
|---|--------------------|-----------------|--|
| Total subjects affected by non-serious adverse events |                    |                 |  |
| subjects affected / exposed                           | 10 / 16 (62.50%)   | 6 / 15 (40.00%) |  |
| Gastrointestinal disorders                            |                    |                 |  |
| Increased thirst                                      |                    |                 |  |
| subjects affected / exposed                           | 1 / 16 (6.25%)     | 0 / 15 (0.00%)  |  |
| occurrences (all)                                     | 1                  | 0               |  |
| Nausea or changed stool consistence                   |                    |                 |  |
| subjects affected / exposed                           | 0 / 16 (0.00%)     | 2 / 15 (13.33%) |  |
| occurrences (all)                                     | 0                  | 2               |  |
| Reproductive system and breast disorders              |                    |                 |  |

|  |                      |                      |  |
|--|----------------------|----------------------|--|
| Genital fungal infection<br>subjects affected / exposed<br>occurrences (all)   | 1 / 16 (6.25%)<br>1  | 0 / 15 (0.00%)<br>0  |  |
| Renal and urinary disorders<br>Polyuria<br>subjects affected / exposed<br>occurrences (all)                            | 9 / 16 (56.25%)<br>9 | 1 / 15 (6.67%)<br>1  |  |
| Psychiatric disorders<br>Tired<br>subjects affected / exposed<br>occurrences (all)                                     | 0 / 16 (0.00%)<br>0  | 2 / 15 (13.33%)<br>2 |  |
| Musculoskeletal and connective tissue disorders<br>Sprained finger<br>subjects affected / exposed<br>occurrences (all) | 1 / 16 (6.25%)<br>1  | 0 / 15 (0.00%)<br>0  |  |
| Infections and infestations<br>Upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all)   | 0 / 16 (0.00%)<br>0  | 2 / 15 (13.33%)<br>2 |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

|  |
|--|
| The project did not include 34 participants that successfully completed the study. 35 participants were enrolled, however, 4 participants withdrew before starting trial medicine. Thus, 31 participants successfully completed the study. |
|--|

Notes: