



## Clinical trial results:

**A 24 week monocentric prospective randomized, placebo-controlled trial to evaluate Efficacy of combination of Exenatide and Dapagliflozin compared to Dapagliflozin and Placebo and its effects on hepatic, myocardial and pancreatic fat distribution in patients with uncontrolled type 2 diabetes mellitus.**

### Summary

|                          |                  |
|--------------------------|------------------|
| EudraCT number           | 2016-000574-38   |
| Trial protocol           | AT               |
| Global end of trial date | 27 November 2019 |

### Results information

|                                   |  |
|-----------------------------------|--|
| Result version number             | v1 (current)   |
| This version publication date     | 03 March 2021  |
| First version publication date    | 03 March 2021  |
| Summary attachment (see zip file) | Diabetes_Obesity_ and _Metabolism_2021 (dom.14319-1.pdf) |

### Trial information

#### Trial identification

|                       |              |
|-----------------------|--------------|
| Sponsor protocol code | ESR-15-10882 |
|-----------------------|--------------|

#### Additional study identifiers

|                                    |                 |
|------------------------------------|-----------------|
| ISRCTN number                      | -               |
| ClinicalTrials.gov id (NCT number) | NCT03007329     |
| WHO universal trial number (UTN)   | U1111-1179-3250 |

Notes:

### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Medical University Vienna  |
| Sponsor organisation address | Spitalgasse 23, Wien, Austria, 1090  |
| Public contact               | Medical University Vienna, Medical University Vienna, +43 140400 21260, juergen.harreiter@meduniwien.ac.at |
| Scientific contact           | Medical University Vienna, Medical University Vienna, +43 140400 21260, juergen.harreiter@meduniwien.ac.at |

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:

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**Results analysis stage**

|  |                   |
|--|-------------------|
| Analysis stage                                       | Final             |
| Date of interim/final analysis                       | 01 September 2020 |
| Is this the analysis of the primary completion data? | No                |
| Global end of trial reached?                         | Yes               |
| Global end of trial date                             | 27 November 2019  |
| Was the trial ended prematurely?                     | No                |

Notes:

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**General information about the trial**

Main objective of the trial:

to investigate the effects on hepatic lipid content reduction of combination therapy with dapagliflozin (10mg daily) and exenatide (2mg weekly) compared to dapagliflozin (10mg daily) and placebo given for 24 weeks in patients with type 2 diabetes mellitus and insufficient glycaemic control.

Protection of trial subjects:

not applicable

Background therapy: -

Evidence for comparator: -

|   |                  |
|---|------------------|
| Actual start date of recruitment                          | 01 February 2017 |
| Long term follow-up planned                               | No               |
| Independent data monitoring committee (IDMC) involvement? | No               |

Notes:

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**Population of trial subjects****Subjects enrolled per country**

|                                      |             |
|--------------------------------------|-------------|
| Country: Number of subjects enrolled | Austria: 30 |
| Worldwide total number of subjects   | 30          |
| EEA total number of subjects         | 30          |

Notes:

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**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                       | 12 |
| 85 years and over                         | 0  |

## Subject disposition

### Recruitment

Recruitment details:

recruitment was conducted between June 2017 to May 2019. In total 7 study visits were conducted during the study, which was a screening visit (week -4 to 0) followed by the randomization visit at baseline (week 0), study visits at 4,8,16,24 weeks and a follow-up visit at week 28.

### Pre-assignment

Screening details:

Screening window was 4 weeks, in these 4 weeks all necessary examinations were performed. In total 563 were screened/prescreened of whom 533 were excluded.

- Not meeting inclusion criteria (n=481)
- Declined to participate (n=52)

### Period 1

|                              |                                       |
|------------------------------|---------------------------------------|
| Period 1 title               | baseline (overall period)             |
| Is this the baseline period? | Yes                                   |
| Allocation method            | Randomised - controlled               |
| Blinding used                | Double blind                          |
| Roles blinded                | Investigator, Monitor, Subject, Carer |

### Arms

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

Arm description:

placebo + dapagliflozin 10mg once daily

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

Dosage and administration details:

10mg once daily

|                  |                    |
|------------------|--------------------|
| <b>Arm title</b> | combined treatment |
|------------------|--------------------|

Arm description:

exenatide 2mg + dapagliflozin 10mg

|  |                   |
|--|-------------------|
| 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:

10mg once daily

|  |                  |
|--|------------------|
| Investigational medicinal product name | exenatide        |
| Investigational medicinal product code |                  |
| Other name                             |                  |
| Pharmaceutical forms                   | Injection        |
| Routes of administration               | Subcutaneous use |

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Dosage and administration details:

2mg once weekly

| <b>Number of subjects in period 1</b> | placebo | combined treatment |
|---------------------------------------|---------|--------------------|
| Started                               | 14      | 16                 |
| Completed                             | 13      | 16                 |
| Not completed                         | 1       | 0                  |
| Lost to follow-up                     | 1       | -                  |

## Baseline characteristics

### Reporting groups

|                       |         |
|-----------------------|---------|
| Reporting group title | placebo |
|-----------------------|---------|

Reporting group description:

placebo + dapagliflozin 10mg once daily

|                       |                    |
|-----------------------|--------------------|
| Reporting group title | combined treatment |
|-----------------------|--------------------|

Reporting group description:

exenatide 2mg + dapagliflozin 10mg

| Reporting group values                                | placebo | combined treatment | Total |
|---|---------|--------------------|-------|
| Number of subjects                                    | 14      | 16                 | 30    |
| Age categorical<br>Units: Subjects                    |         |                    |       |
| In utero  | 0       | 0                  | 0     |
| Preterm newborn infants<br>(gestational age < 37 wks) | 0       | 0                  | 0     |
| Newborns (0-27 days)                                  | 0       | 0                  | 0     |
| Infants and toddlers (28 days-23<br>months)           | 0       | 0                  | 0     |
| Children (2-11 years)                                 | 0       | 0                  | 0     |
| Adolescents (12-17 years)                             | 0       | 0                  | 0     |
| Adults (18-64 years)                                  | 7       | 11                 | 18    |
| From 65-84 years                                      | 7       | 5                  | 12    |
| 85 years and over                                     | 0       | 0                  | 0     |
| 18  | 0       | 0                  | 0     |
| 12  | 0       | 0                  | 0     |
| Age continuous<br>Units: years                        |         |                    |       |
| arithmetic mean                                       | 60.9    | 59.4               |       |
| standard deviation                                    | ± 7.4   | ± 8.5              | -     |
| Gender categorical<br>Units: Subjects                 |         |                    |       |
| Female  | 4       | 6                  | 10    |
| Male  | 10      | 10                 | 20    |
| liver fat content<br>Units: 12.85 %                   |         |                    |       |
| arithmetic mean                                       | 13.17   | 12.85              |       |
| standard deviation                                    | ± 8.91  | ± 9.26             | -     |

## End points

### End points reporting groups

|   |                    |
|---|--------------------|
| Reporting group title   | placebo            |
| Reporting group description:<br>placebo + dapagliflozin 10mg once daily |                    |
| Reporting group title   | combined treatment |
| Reporting group description:<br>exenatide 2mg + dapagliflozin 10mg      |                    |

### Primary: liver fat content

|                                  |                   |
|----------------------------------|-------------------|
| End point title                  | liver fat content |
| End point description:           |                   |
| End point type                   | Primary           |
| End point timeframe:<br>24 weeks |                   |

| End point values                     | placebo            | combined treatment |  |  |
|--------------------------------------|--------------------|--------------------|--|--|
| Subject group type                   | Reporting group    | Reporting group    |  |  |
| Number of subjects analysed          | 14                 | 16                 |  |  |
| Units: percentage                    |                    |                    |  |  |
| arithmetic mean (standard deviation) | 9.30 ( $\pm$ 8.43) | 8.43 ( $\pm$ 8.00) |  |  |

### Statistical analyses

|   |                              |
|---|------------------------------|
| Statistical analysis title              | statistical analysis         |
| Comparison groups                       | placebo v combined treatment |
| Number of subjects included in analysis | 30                           |
| Analysis specification                  | Pre-specified                |
| Analysis type                           | superiority                  |
| P-value                                 | < 0.05                       |
| Method                                  | ANCOVA                       |

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

screening - to follow up visit after 28 weeks

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

### Dictionary used

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

|                    |    |
|--------------------|----|
| Dictionary version | 23 |
|--------------------|----|

### Reporting groups

|                       |         |
|-----------------------|---------|
| Reporting group title | placebo |
|-----------------------|---------|

Reporting group description:

placebo + dapagliflozin 10mg once daily

|                       |                    |
|-----------------------|--------------------|
| Reporting group title | combined treatment |
|-----------------------|--------------------|

Reporting group description:

exenatide 2mg + dapagliflozin 10mg

| Serious adverse events                            | placebo        | combined treatment |  |
|---|----------------|--------------------|--|
| Total subjects affected by serious adverse events |                |                    |  |
| subjects affected / exposed                       | 0 / 14 (0.00%) | 1 / 16 (6.25%)     |  |
| number of deaths (all causes)                     | 0              | 0                  |  |
| number of deaths resulting from adverse events    | 0              | 0                  |  |
| Cardiac disorders                                 |                |                    |  |
| Hypertensive crisis                               |                |                    |  |
| subjects affected / exposed                       | 0 / 14 (0.00%) | 1 / 16 (6.25%)     |  |
| occurrences causally related to treatment / all   | 0 / 0          | 0 / 1              |  |
| deaths causally related to treatment / all        | 0 / 0          | 0 / 0              |  |
| Ear and labyrinth disorders                       |                |                    |  |
| Otitis media acute                                |                |                    |  |
| subjects affected / exposed                       | 0 / 14 (0.00%) | 1 / 16 (6.25%)     |  |
| occurrences causally related to treatment / all   | 0 / 0          | 0 / 1              |  |
| deaths causally related to treatment / all        | 0 / 0          | 0 / 0              |  |
| Vertigo   |                |                    |  |
| subjects affected / exposed                       | 0 / 14 (0.00%) | 1 / 16 (6.25%)     |  |
| occurrences causally related to treatment / all   | 0 / 0          | 0 / 1              |  |
| deaths causally related to treatment / all        | 0 / 0          | 0 / 0              |  |

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

| <b>Non-serious adverse events</b>                     | placebo          | combined treatment |  |
|---|------------------|--------------------|--|
| Total subjects affected by non-serious adverse events |                  |                    |  |
| subjects affected / exposed                           | 12 / 14 (85.71%) | 12 / 16 (75.00%)   |  |
| Gastrointestinal disorders                            |                  |                    |  |
| Gastrointestinal Side Effects                         |                  |                    |  |
| subjects affected / exposed                           | 1 / 14 (7.14%)   | 4 / 16 (25.00%)    |  |
| occurrences (all)                                     | 1                | 4                  |  |
| Skin and subcutaneous tissue disorders                |                  |                    |  |
| Skin reaction   |                  |                    |  |
| subjects affected / exposed                           | 1 / 14 (7.14%)   | 2 / 16 (12.50%)    |  |
| occurrences (all)                                     | 1                | 2                  |  |
| Musculoskeletal and connective tissue disorders       |                  |                    |  |
| Pain  |                  |                    |  |
| subjects affected / exposed                           | 8 / 14 (57.14%)  | 2 / 16 (12.50%)    |  |
| occurrences (all)                                     | 8                | 2                  |  |
| Infections and infestations                           |                  |                    |  |
| Mycosis   |                  |                    |  |
| subjects affected / exposed                           | 2 / 14 (14.29%)  | 5 / 16 (31.25%)    |  |
| occurrences (all)                                     | 2                | 5                  |  |



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment  |
|------------------|--|
| 06 February 2018 | Inclusion criteria were adapted: inclusion criteria was changed from HbA1c 7.0-11.0% to 6.5-11.0%. |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported

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### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/33464703>