



## Clinical trial results:

### Effect of Intervention with DMR, GLP-1 and lifestyle intensification -in Subjects with insulin dePendent type 2 diabetes- on Insulin Requirement and mEtabolic parameters

#### Summary

|                          |                  |
|--------------------------|------------------|
| EudraCT number           | 2017-000349-30   |
| Trial protocol           | NL               |
| Global end of trial date | 16 December 2020 |

#### Results information

|                                   |                                                                     |
|-----------------------------------|---------------------------------------------------------------------|
| Result version number             | v1 (current)                                                        |
| This version publication date     | 18 April 2022                                                       |
| First version publication date    | 18 April 2022                                                       |
| Summary attachment (see zip file) | Published results INSPIRE<br>(INSPIRE_manuscript_published_GIE.pdf) |

#### Trial information

##### Trial identification

|                       |         |
|-----------------------|---------|
| Sponsor protocol code | NL60669 |
|-----------------------|---------|

##### Additional study identifiers

|                                    |                     |
|------------------------------------|---------------------|
| ISRCTN number                      | -                   |
| ClinicalTrials.gov id (NCT number) | -                   |
| WHO universal trial number (UTN)   | -                   |
| Other trial identifiers            | ABR nummer: NL60669 |

Notes:

#### Sponsors

|                              |                                                                                      |
|------------------------------|--------------------------------------------------------------------------------------|
| Sponsor organisation name    | Amsterdam UMC                                                                        |
| Sponsor organisation address | Meibergdreef 9 , Amsterdam , Netherlands, 1105 AZ                                    |
| Public contact               | Suzanne Meiring, Academic Medical Center, +31 21357593,<br>s.meiring@amsterdamumc.nl |
| Scientific contact           | Annieke van Baar, Academic Medical Center, +31 205661613,<br>a.c.vanbaar@amc.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                       | 16 December 2020  |
| Is this the analysis of the primary completion data? | Yes               |
| Primary completion date                              | 01 September 2020 |
| Global end of trial reached?                         | Yes               |
| Global end of trial date                             | 16 December 2020  |
| Was the trial ended prematurely?                     | No                |

Notes:

## General information about the trial

Main objective of the trial:

The main objective of this pilot study is to evaluate the efficacy of the Duodenal Mucosal Resurfacing procedure combined with GLP-1 administration and lifestyle intervention in subjects with insulindependent type 2 diabetes. Study success is defined as insulin independence at 6 months after DMR with an HbA1c level of  $\leq 7.5\%$ .

Protection of trial subjects:

Liraglutide is already approved for the treatment of type 2 diabetes. We used this medication in the same patient population and the same dosage as is registered.

Because side effects are minimal and mostly self-limiting, there were no additional measures taken for protection, because it was not necessary.

Background therapy: -

Evidence for comparator: -

|                                                           |                   |
|-----------------------------------------------------------|-------------------|
| Actual start date of recruitment                          | 01 September 2017 |
| Long term follow-up planned                               | Yes               |
| Long term follow-up rationale                             | Safety, Efficacy  |
| Long term follow-up duration                              | 2 Years           |
| Independent data monitoring committee (IDMC) involvement? | Yes               |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                 |
|--------------------------------------|-----------------|
| Country: Number of subjects enrolled | Netherlands: 16 |
| Worldwide total number of subjects   | 16              |
| EEA total number of subjects         | 16              |

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)      | 12 |
| From 65 to 84 years       | 4  |
| 85 years and over         | 0  |

## Subject disposition

### Recruitment

Recruitment details:

#### 3.1 Subject Recruitment

The investigational site (AMC) may utilize a number of methods to recruit potential subjects into the study including evaluation of existing subjects from their clinical practice, referrals from other physicians and recruitment via external advertising. Advertising materials need to be reviewed and approved by the Independent

### Pre-assignment

Screening details:

1. Diagnosed with Type 2 Diabetes
2. 28 -75 years of age
3. Treatment with long acting insulin  $\leq$  5 years
4. On daily long acting insulin dose  $\leq$  1 U/kg
5. BMI  $\geq$  24 and  $\leq$  40 kg/m<sup>2</sup>
6. HbA1c  $\leq$  8.0% (64 mmol/mol)
7. Fasting C-peptide  $\geq$  0.5 nmol/L (1.5 ng/ml)

### Period 1

|                              |                                |
|------------------------------|--------------------------------|
| Period 1 title               | Overall trial (overall period) |
| Is this the baseline period? | Yes                            |
| Allocation method            | Not applicable                 |
| Blinding used                | Not blinded                    |

### Arms

|                                        |                                     |
|----------------------------------------|-------------------------------------|
| Arm title                              | Overall trial                       |
| Arm description: -                     |                                     |
| Arm type                               | Experimental                        |
| Investigational medicinal product name | Liraglutide                         |
| Investigational medicinal product code |                                     |
| Other name                             |                                     |
| Pharmaceutical forms                   | Solution for solution for injection |
| Routes of administration               | Subcutaneous use                    |

Dosage and administration details:

1.8mg once daily

| Number of subjects in period 1 | Overall trial |
|--------------------------------|---------------|
| Started                        | 16            |
| Completed                      | 16            |

## Baseline characteristics

### Reporting groups

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

| Reporting group values                                | Overall trial | Total |  |
|-------------------------------------------------------|---------------|-------|--|
| Number of subjects                                    | 16            | 16    |  |
| 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                                        |               |       |  |
| Units: years                                          |               |       |  |
| median                                                | 61            |       |  |
| inter-quartile range (Q1-Q3)                          | 55 to 67      | -     |  |
| Gender categorical                                    |               |       |  |
| Units: Subjects                                       |               |       |  |
| Female                                                | 6             | 6     |  |
| Male                                                  | 10            | 10    |  |
| Duration of type 2 diabetes                           |               |       |  |
| Units: years                                          |               |       |  |
| median                                                | 11            |       |  |
| inter-quartile range (Q1-Q3)                          | 8 to 15       | -     |  |
| BMI                                                   |               |       |  |
| Units: kg/m2                                          |               |       |  |
| median                                                | 28.8          |       |  |
| inter-quartile range (Q1-Q3)                          | 26.5 to 31.7  | -     |  |
| HbA1c                                                 |               |       |  |
| Units: percent                                        |               |       |  |
| median                                                | 7.5           |       |  |
| inter-quartile range (Q1-Q3)                          | 7.1 to 7.9    | -     |  |
| Fasting Plasma Glucose                                |               |       |  |
| Units: mmol/l                                         |               |       |  |
| median                                                | 10.1          |       |  |
| inter-quartile range (Q1-Q3)                          | 8.9 to 12     | -     |  |

## Subject analysis sets

|                            |                                    |
|----------------------------|------------------------------------|
| Subject analysis set title | Analysis complete trial population |
| Subject analysis set type  | Full analysis                      |

Subject analysis set description:

Complete patient population analysis. All patient were included in the analysis. All patients underwent DMR and started with liraglutide.

| Reporting group values                                                                                                                                                                                                                                    | Analysis complete trial population |  |  |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------|--|--|
| Number of subjects                                                                                                                                                                                                                                        | 16                                 |  |  |
| Age categorical<br>Units: Subjects                                                                                                                                                                                                                        |                                    |  |  |
| In utero<br>Preterm newborn infants (gestational age < 37 wks)<br>Newborns (0-27 days)<br>Infants and toddlers (28 days-23 months)<br>Children (2-11 years)<br>Adolescents (12-17 years)<br>Adults (18-64 years)<br>From 65-84 years<br>85 years and over |                                    |  |  |
| Age continuous<br>Units: years<br>median<br>inter-quartile range (Q1-Q3)                                                                                                                                                                                  |                                    |  |  |
| Gender categorical<br>Units: Subjects                                                                                                                                                                                                                     |                                    |  |  |
| Female                                                                                                                                                                                                                                                    | 6                                  |  |  |
| Male                                                                                                                                                                                                                                                      | 10                                 |  |  |
| Duration of type 2 diabetes<br>Units: years<br>median<br>inter-quartile range (Q1-Q3)                                                                                                                                                                     |                                    |  |  |
| BMI<br>Units: kg/m2<br>median<br>inter-quartile range (Q1-Q3)                                                                                                                                                                                             |                                    |  |  |
| HbA1c<br>Units: percent<br>median<br>inter-quartile range (Q1-Q3)                                                                                                                                                                                         |                                    |  |  |
| Fasting Plasma Glucose<br>Units: mmol/l<br>median<br>inter-quartile range (Q1-Q3)                                                                                                                                                                         |                                    |  |  |

## End points

### End points reporting groups

|                                                                                                                                           |                                    |
|-------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------|
| Reporting group title                                                                                                                     | Overall trial                      |
| Reporting group description: -                                                                                                            |                                    |
| Subject analysis set title                                                                                                                | Analysis complete trial population |
| Subject analysis set type                                                                                                                 | Full analysis                      |
| Subject analysis set description:                                                                                                         |                                    |
| Complete patient population analysis. All patient were included in the analysis. All patients underwent DMR and started with liraglutide. |                                    |

### Primary: % of patients HbA1c <7.6% at 6 months

|                        |                                       |
|------------------------|---------------------------------------|
| End point title        | % of patients HbA1c <7.6% at 6 months |
| End point description: |                                       |
| End point type         | Primary                               |
| End point timeframe:   |                                       |
| 6 months after DMR     |                                       |

| End point values            | Overall trial   | Analysis complete trial population |  |  |
|-----------------------------|-----------------|------------------------------------|--|--|
| Subject group type          | Reporting group | Subject analysis set               |  |  |
| Number of subjects analysed | 16              | 16                                 |  |  |
| Units: number of patients   |                 |                                    |  |  |
| number (not applicable)     | 16              | 16                                 |  |  |

### Statistical analyses

|                                         |                                                    |
|-----------------------------------------|----------------------------------------------------|
| Statistical analysis title              | Analysis complete trial                            |
| Comparison groups                       | Overall trial v Analysis complete trial population |
| Number of subjects included in analysis | 32                                                 |
| Analysis specification                  | Pre-specified                                      |
| Analysis type                           | non-inferiority                                    |
| P-value                                 | < 0.05                                             |
| Method                                  | Wilcoxon (Mann-Whitney)                            |
| Parameter estimate                      | Median difference (final values)                   |

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

18 months

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

### Dictionary used

|                 |                |
|-----------------|----------------|
| Dictionary name | Toetsingonline |
|-----------------|----------------|

|                    |   |
|--------------------|---|
| Dictionary version | 1 |
|--------------------|---|

### Reporting groups

|                       |                           |
|-----------------------|---------------------------|
| Reporting group title | Complete study population |
|-----------------------|---------------------------|

Reporting group description: -

| Serious adverse events                            | Complete study population                                                 |  |  |
|---------------------------------------------------|---------------------------------------------------------------------------|--|--|
| Total subjects affected by serious adverse events |                                                                           |  |  |
| subjects affected / exposed                       | 3 / 16 (18.75%)                                                           |  |  |
| number of deaths (all causes)                     | 0                                                                         |  |  |
| number of deaths resulting from adverse events    | 0                                                                         |  |  |
| Vascular disorders                                |                                                                           |  |  |
| Deep venous thrombosis                            |                                                                           |  |  |
| subjects affected / exposed                       | 1 / 16 (6.25%)                                                            |  |  |
| occurrences causally related to treatment / all   | 0 / 1                                                                     |  |  |
| deaths causally related to treatment / all        | 0 / 0                                                                     |  |  |
| Respiratory, thoracic and mediastinal disorders   |                                                                           |  |  |
| Asthma exacerbation                               | Additional description: For which ER presentation/admission was necessary |  |  |
| subjects affected / exposed                       | 1 / 16 (6.25%)                                                            |  |  |
| occurrences causally related to treatment / all   | 0 / 1                                                                     |  |  |
| deaths causally related to treatment / all        | 0 / 0                                                                     |  |  |
| Musculoskeletal and connective tissue disorders   |                                                                           |  |  |
| Ankle fracture                                    |                                                                           |  |  |
| subjects affected / exposed                       | 1 / 16 (6.25%)                                                            |  |  |
| occurrences causally related to treatment / all   | 0 / 1                                                                     |  |  |
| deaths causally related to treatment / all        | 0 / 0                                                                     |  |  |
| Infections and infestations                       |                                                                           |  |  |
| Pneumonia                                         | Additional description: For which hospital admission was necessary        |  |  |

|                                                 |                |  |  |
|-------------------------------------------------|----------------|--|--|
| subjects affected / exposed                     | 1 / 16 (6.25%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |

Frequency threshold for reporting non-serious adverse events: 0 %

| <b>Non-serious adverse events</b>                     | Complete study population |  |  |
|-------------------------------------------------------|---------------------------|--|--|
| Total subjects affected by non-serious adverse events |                           |  |  |
| subjects affected / exposed                           | 15 / 16 (93.75%)          |  |  |
| Vascular disorders                                    |                           |  |  |
| Ulcer dig II left                                     |                           |  |  |
| subjects affected / exposed                           | 1 / 16 (6.25%)            |  |  |
| occurrences (all)                                     | 1                         |  |  |
| Orthostatic hypotension                               |                           |  |  |
| subjects affected / exposed                           | 1 / 16 (6.25%)            |  |  |
| occurrences (all)                                     | 1                         |  |  |
| Blood and lymphatic system disorders                  |                           |  |  |
| Iron deficiency anemia                                |                           |  |  |
| subjects affected / exposed                           | 1 / 16 (6.25%)            |  |  |
| occurrences (all)                                     | 1                         |  |  |
| Ear and labyrinth disorders                           |                           |  |  |
| Dizziness                                             |                           |  |  |
| subjects affected / exposed                           | 1 / 16 (6.25%)            |  |  |
| occurrences (all)                                     | 1                         |  |  |
| Immune system disorders                               |                           |  |  |
| Hay fever                                             |                           |  |  |
| subjects affected / exposed                           | 1 / 16 (6.25%)            |  |  |
| occurrences (all)                                     | 1                         |  |  |
| Gastrointestinal disorders                            |                           |  |  |
| Nausea                                                |                           |  |  |
| subjects affected / exposed                           | 5 / 16 (31.25%)           |  |  |
| occurrences (all)                                     | 5                         |  |  |
| Abdominal pain                                        |                           |  |  |
| subjects affected / exposed                           | 7 / 16 (43.75%)           |  |  |
| occurrences (all)                                     | 9                         |  |  |
| Diarrhea                                              |                           |  |  |

|                                                 |                                                                       |  |  |
|-------------------------------------------------|-----------------------------------------------------------------------|--|--|
| subjects affected / exposed                     | 7 / 16 (43.75%)                                                       |  |  |
| occurrences (all)                               | 8                                                                     |  |  |
| Superficial duodenal mucosal laesions           | Additional description: prior to procedure and start medication       |  |  |
| subjects affected / exposed                     | 2 / 16 (12.50%)                                                       |  |  |
| occurrences (all)                               | 2                                                                     |  |  |
| Obstipation                                     |                                                                       |  |  |
| subjects affected / exposed                     | 2 / 16 (12.50%)                                                       |  |  |
| occurrences (all)                               | 2                                                                     |  |  |
| Loss of appetite                                |                                                                       |  |  |
| subjects affected / exposed                     | 1 / 16 (6.25%)                                                        |  |  |
| occurrences (all)                               | 1                                                                     |  |  |
| Dysphagia                                       |                                                                       |  |  |
| subjects affected / exposed                     | 1 / 16 (6.25%)                                                        |  |  |
| occurrences (all)                               | 1                                                                     |  |  |
| Mild esofagitis                                 | Additional description: Found during follow-up endoscopy              |  |  |
| subjects affected / exposed                     | 1 / 16 (6.25%)                                                        |  |  |
| occurrences (all)                               | 1                                                                     |  |  |
| Barrett segment                                 | Additional description: Found during DMR procedure, follow-up planned |  |  |
| subjects affected / exposed                     | 1 / 16 (6.25%)                                                        |  |  |
| occurrences (all)                               | 1                                                                     |  |  |
| Reflux                                          |                                                                       |  |  |
| subjects affected / exposed                     | 2 / 16 (12.50%)                                                       |  |  |
| occurrences (all)                               | 2                                                                     |  |  |
| Dark stool                                      | Additional description: without alarm symptoms                        |  |  |
| subjects affected / exposed                     | 1 / 16 (6.25%)                                                        |  |  |
| occurrences (all)                               | 1                                                                     |  |  |
| Reproductive system and breast disorders        |                                                                       |  |  |
| Asthma exacerbation                             |                                                                       |  |  |
| subjects affected / exposed                     | 1 / 16 (6.25%)                                                        |  |  |
| occurrences (all)                               | 1                                                                     |  |  |
| Respiratory, thoracic and mediastinal disorders |                                                                       |  |  |
| Throat infection                                |                                                                       |  |  |
| subjects affected / exposed                     | 2 / 16 (12.50%)                                                       |  |  |
| occurrences (all)                               | 2                                                                     |  |  |
| Renal and urinary disorders                     |                                                                       |  |  |

|                                                                                          |                      |                                                |  |
|------------------------------------------------------------------------------------------|----------------------|------------------------------------------------|--|
| Benign cystic and prostate polyps<br>subjects affected / exposed<br>occurrences (all)    | 1 / 16 (6.25%)<br>2  |                                                |  |
| Endocrine disorders<br>Hyperglycemia<br>subjects affected / exposed<br>occurrences (all) | 1 / 16 (6.25%)<br>1  |                                                |  |
| Musculoskeletal and connective tissue disorders                                          |                      |                                                |  |
| Rotatorcuff rupture<br>subjects affected / exposed<br>occurrences (all)                  | 1 / 16 (6.25%)<br>1  | Additional description: After cycling accident |  |
| Dumbness en tingling limbs<br>subjects affected / exposed<br>occurrences (all)           | 2 / 16 (12.50%)<br>2 |                                                |  |
| Myalgia shoulders legs<br>subjects affected / exposed<br>occurrences (all)               | 1 / 16 (6.25%)<br>1  |                                                |  |
| Muscle ache<br>subjects affected / exposed<br>occurrences (all)                          | 1 / 16 (6.25%)<br>1  |                                                |  |
| Infections and infestations                                                              |                      |                                                |  |
| Flu with flu-like symptoms<br>subjects affected / exposed<br>occurrences (all)           | 5 / 16 (31.25%)<br>6 |                                                |  |
| Testicular infection<br>subjects affected / exposed<br>occurrences (all)                 | 1 / 16 (6.25%)<br>1  |                                                |  |
| Conjunctivitis<br>subjects affected / exposed<br>occurrences (all)                       | 1 / 16 (6.25%)<br>1  |                                                |  |
| Fungal infection vagina<br>subjects affected / exposed<br>occurrences (all)              | 1 / 16 (6.25%)<br>1  |                                                |  |
| Face infection<br>subjects affected / exposed<br>occurrences (all)                       | 1 / 16 (6.25%)<br>1  |                                                |  |

|                                    |                 |  |  |
|------------------------------------|-----------------|--|--|
| Metabolism and nutrition disorders |                 |  |  |
| Low energy level                   |                 |  |  |
| subjects affected / exposed        | 3 / 16 (18.75%) |  |  |
| occurrences (all)                  | 3               |  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment                                                                            |
|------------------|--------------------------------------------------------------------------------------|
| 15 March 2018    | Change in patient information sheet, regarding body material collection and storage. |
| 14 December 2018 | Addition of extra MRI assessment.                                                    |
| 18 March 2019    | Prolongation of the follow-up from 1 year to 2 years                                 |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported