



## Clinical trial results: Oral insulin for prevention of diabetes in relatives at risk for type 1 diabetes mellitus

### Summary

|                          |                  |
|--------------------------|------------------|
| EudraCT number           | 2006-006550-96   |
| Trial protocol           | IT FI DE GB SE   |
| Global end of trial date | 01 November 2017 |

### Results information

|                                   |                                                                                                                                                                                                                                                                                                                                                                                              |
|-----------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Result version number             | v1 (current)                                                                                                                                                                                                                                                                                                                                                                                 |
| This version publication date     | 16 November 2018                                                                                                                                                                                                                                                                                                                                                                             |
| First version publication date    | 16 November 2018                                                                                                                                                                                                                                                                                                                                                                             |
| Summary attachment (see zip file) | TN07 Oral Insulin Clinical Study Report 20180501 (TN07 Oral Insulin Clinical Study Report 20180501.pdf)<br>Appendix 16.2.6 Clinical Laboratory Values_Response Data_by Patient (Appendix 16.2.6 Clinical Laboratory Values_Response Data_by Patient.xls)<br>declaration of late submission signed (declaration of late submission signed.pdf)<br>TN-07 Oral Insulin (TN-07 Oral Insulin.pdf) |

### Trial information

#### Trial identification

|                       |          |
|-----------------------|----------|
| Sponsor protocol code | 80804005 |
|-----------------------|----------|

#### Additional study identifiers

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

Notes:

### Sponsors

|                              |                                                                                                          |
|------------------------------|----------------------------------------------------------------------------------------------------------|
| Sponsor organisation name    | TrialNet Coordinating Center                                                                             |
| Sponsor organisation address | 3650 Spectrum Boulevard, Suite 100, Tampa, United States, FL 33612                                       |
| Public contact               | Courtney Henderson, TrialNet Coordinating Center, +1 8133969183, courtney.henderson@epi.usf.edu          |
| Scientific contact           | Desmond Schatz, TrialNet Coordinating Center<br>University of Florida,<br>Gainesville FL, +1 8133969183, |

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? | Yes |

Notes:

## Results analysis stage

|                                                      |                  |
|------------------------------------------------------|------------------|
| Analysis stage                                       | Final            |
| Date of interim/final analysis                       | 01 November 2017 |
| Is this the analysis of the primary completion data? | No               |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 01 November 2017 |
| Was the trial ended prematurely?                     | No               |

Notes:

## General information about the trial

Main objective of the trial:

determine whether intervention with repeated oral administration of recombinant human insulin will prevent or delay the development of clinical type 1 Diabetes Mellitus (T1DM) in non diabetic relatives of patients with T1DM who are positive for insulin autoantibodies but who do not have a metabolic defect. This intervention will be compared with placebo given in a double-masked fashion.

Secondary objectives included the description of the effects of treatment with oral insulin versus placebo in other categories of subjects defined using different combinations of autoantibodies and metabolic status (the Secondary Analysis Strata) and an assessment of the consistency of treatment effect among strata. Secondary objectives also included the assessment of the effects of treatment on immunologic and metabolic markers, and the association of these markers with the risk of diabetes onset, among other possible risk factors.

Protection of trial subjects:

In what concerns Protecting Against or Minimizing Potential Treatment Risks subjects will not be enrolled who have other active serious medical problems. Regular monitoring of subjects and active inquiry will allow for early identification of adverse events.

Adverse events were assessed and adjudicated, if required, by the TrialNet Medical Monitor. The DSMB conducted regular safety reviews approximately every three to six months (and, as needed) of adverse events by treatment group assignment. Serious adverse events, as well as adverse events leading to study discontinuation, were reviewed by the DSMB as needed.

Background therapy: -

Evidence for comparator: -

|                                                           |               |
|-----------------------------------------------------------|---------------|
| Actual start date of recruitment                          | 02 March 2007 |
| 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 | Australia: 11      |
| Country: Number of subjects enrolled | New Zealand: 8     |
| Country: Number of subjects enrolled | United States: 485 |
| Country: Number of subjects enrolled | Sweden: 8          |
| Country: Number of subjects enrolled | United Kingdom: 12 |
| Country: Number of subjects enrolled | Finland: 9         |
| Country: Number of subjects enrolled | Germany: 15        |
| Country: Number of subjects enrolled | Italy: 14          |

|                                    |     |
|------------------------------------|-----|
| Worldwide total number of subjects | 562 |
| EEA total number of subjects       | 58  |

Notes:

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**Subjects enrolled per age group**

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|                                           |     |
|-------------------------------------------|-----|
| 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)                     | 418 |
| Adolescents (12-17 years)                 | 119 |
| Adults (18-64 years)                      | 25  |
| From 65 to 84 years                       | 0   |
| 85 years and over                         | 0   |

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## Subject disposition

### Recruitment

Recruitment details:

Of a total of 560 randomized participants (median enrollment age, 8.2 years; interquartile range [IQR], 5.7-12.1 years; 170 boys [60%]; 90.7% white non-Hispanic; 57.6% with a sibling with type 1 diabetes), 550 completed the trial including 389 participants (median age, 8.4 years; 245 boys [63%]), 382 (96%) in the main study group.

### Pre-assignment

Screening details:

Eligible subjects were non-diabetic relatives of patients with T1DM, who had normal glucose tolerance on an OGTT, who were confirmed to be mIAA positive on two samples (collections), and who also met the criteria for the following primary and secondary study strata based on other autoantibodies and metabolic characteristics

### Pre-assignment period milestones

|                              |     |
|------------------------------|-----|
| Number of subjects started   | 562 |
| Number of subjects completed | 560 |

### Pre-assignment subject non-completion reasons

|                            |                       |
|----------------------------|-----------------------|
| Reason: Number of subjects | Protocol deviation: 2 |
|----------------------------|-----------------------|

### Period 1

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

### Arms

|                                        |                               |
|----------------------------------------|-------------------------------|
| Are arms mutually exclusive?           | Yes                           |
| <b>Arm title</b>                       | Oral Insulin                  |
| Arm description: -                     |                               |
| Arm type                               | Experimental                  |
| Investigational medicinal product name | 7.5 mg of recombinant insulin |
| Investigational medicinal product code |                               |
| Other name                             |                               |
| Pharmaceutical forms                   | Capsule                       |
| Routes of administration               | Oral use                      |

Dosage and administration details:

All subjects took one capsule of study medication (7.5 mg of recombinant insulin or placebo) daily by mouth for the duration of the study. Study medication was dispensed at each 6-month visit. Subjects remained on the same dose of insulin/placebo throughout the trial. Participants were assigned to receive capsules of either oral insulin, 7.5 mg of recombinant human insulin crystals (Eli Lilly, Indianapolis, IN), or matched placebo.

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

Arm description:

All subjects took one capsule of study medication (7.5 mg of recombinant insulin or placebo) daily by mouth for the duration of the study. Study medication was dispensed at each 6-month visit. Subjects remained on the same dose of insulin/placebo throughout the trial.

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

All subjects took one capsule of study medication (7.5 mg of recombinant insulin or placebo) daily by mouth for the duration of the study. Study medication was dispensed at each 6-month visit. Subjects remained on the same dose of insulin/placebo throughout the trial. Participants were assigned to receive capsules of either oral insulin, 7.5 mg of recombinant human insulin crystals (Eli Lilly, Indianapolis, IN), or matched placebo.

| <b>Number of subjects in period 1<sup>[1]</sup></b> | Oral Insulin | Placebo |
|-----------------------------------------------------|--------------|---------|
| Started                                             | 283          | 277     |
| Completed                                           | 276          | 274     |
| Not completed                                       | 7            | 3       |
| reasons not reported                                | 7            | -       |
| reasons not specified                               | -            | 3       |

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: The total worldwide for the actual number of subjects enrolled is 562. However, 560 subjects were randomized in this clinical trial.

## Baseline characteristics

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### Reporting groups

|                       |                                |
|-----------------------|--------------------------------|
| Reporting group title | Overall Study (overall period) |
|-----------------------|--------------------------------|

Reporting group description: -

| Reporting group values                                                            | Overall Study<br>(overall period) | Total |  |
|-----------------------------------------------------------------------------------|-----------------------------------|-------|--|
| Number of subjects                                                                | 560                               | 560   |  |
| Age categorical<br>Units: Subjects                                                |                                   |       |  |
| Age continuous<br>Units: years<br>arithmetic mean<br>inter-quartile range (Q1-Q3) | 8.2<br>5.7 to 12.1                | -     |  |
| Gender categorical<br>Units: Subjects                                             |                                   |       |  |
| Female                                                                            | 220                               | 220   |  |
| Male                                                                              | 340                               | 340   |  |

## End points

### End points reporting groups

|                                                                                                                                                                                                                                                                                                              |              |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------|
| Reporting group title                                                                                                                                                                                                                                                                                        | Oral Insulin |
| Reporting group description: -                                                                                                                                                                                                                                                                               |              |
| Reporting group title                                                                                                                                                                                                                                                                                        | Placebo      |
| Reporting group description:<br>All subjects took one capsule of study medication (7.5 mg of recombinant insulin or placebo) daily by mouth for the duration of the study. Study medication was dispensed at each 6-month visit. Subjects remained on the same dose of insulin/placebo throughout the trial. |              |

### Primary: Number of subjects with serious adverse events (SAEs)

|                                                                                                                                                                                                                                                                                 |                                                                      |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                 | Number of subjects with serious adverse events (SAEs) <sup>[1]</sup> |
| End point description:<br>The primary outcome was the elapsed time from random treatment assignment to the development of diabetes among those enrolled in the primary analysis cohort consisting of subjects with insulin autoimmunity and absence of metabolic abnormalities. |                                                                      |
| End point type                                                                                                                                                                                                                                                                  | Primary                                                              |
| End point timeframe:<br>None                                                                                                                                                                                                                                                    |                                                                      |

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical analyses were performed using TIBCO Spotfire S+8.2 (PerkinElmer). Data on adverse events and efficacy were evaluated twice yearly by an independent data and safety monitoring board with predefined stopping rules.

| End point values            | Oral Insulin    | Placebo         |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 283             | 277             |  |  |
| Units: mg/dL                |                 |                 |  |  |
| number (not applicable)     | 283             | 277             |  |  |

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse event reporting by the investigator to the sponsor was done in 24 hours after the receipt of the event as there were no SUSARs identified during the trial hence no reporting to the competent authorities and ethics committees was required

Adverse event reporting additional description:

There were no serious adverse events and no reported episodes of severe hypoglycaemia. There were no deaths during this study. The most common adverse event was categorized as infection, with 134 and 120 events reported in this category in the oral insulin and placebo groups, respectively, over the duration of the study.

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

### Dictionary used

|                    |        |
|--------------------|--------|
| Dictionary name    | MedDRA |
| Dictionary version | 20.1   |

### Reporting groups

|                       |              |
|-----------------------|--------------|
| Reporting group title | Oral Insulin |
|-----------------------|--------------|

Reporting group description:

There were no serious adverse events. There were no reported episodes of severe hypoglycemia. The most common adverse event was categorized as infection, with 134 and 120 events reported in this category in the oral insulin and placebo arms, respectively, over the duration of the study.

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

Reporting group description: -

| Serious adverse events                            | Oral Insulin    | Placebo         |  |
|---------------------------------------------------|-----------------|-----------------|--|
| Total subjects affected by serious adverse events |                 |                 |  |
| subjects affected / exposed                       | 0 / 294 (0.00%) | 0 / 278 (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: 0 %

| Non-serious adverse events                            | Oral Insulin      | Placebo           |  |
|-------------------------------------------------------|-------------------|-------------------|--|
| Total subjects affected by non-serious adverse events |                   |                   |  |
| subjects affected / exposed                           | 67 / 294 (22.79%) | 62 / 278 (22.30%) |  |
| Vascular disorders                                    |                   |                   |  |
| Hemorrhage/Bleeding                                   |                   |                   |  |
| subjects affected / exposed                           | 2 / 294 (0.68%)   | 1 / 278 (0.36%)   |  |
| occurrences (all)                                     | 2                 | 1                 |  |
| Surgical and medical procedures                       |                   |                   |  |

|                                                                                    |                         |                         |  |
|------------------------------------------------------------------------------------|-------------------------|-------------------------|--|
| Surgery/Intra-Operative Injury<br>subjects affected / exposed<br>occurrences (all) | 7 / 294 (2.38%)<br>7    | 3 / 278 (1.08%)<br>3    |  |
| General disorders and administration<br>site conditions                            |                         |                         |  |
| Lymphatics<br>subjects affected / exposed<br>occurrences (all)                     | 1 / 294 (0.34%)<br>1    | 1 / 278 (0.36%)<br>1    |  |
| Constitutional symptoms<br>subjects affected / exposed<br>occurrences (all)        | 10 / 294 (3.40%)<br>13  | 12 / 278 (4.32%)<br>18  |  |
| Pain<br>subjects affected / exposed<br>occurrences (all)                           | 11 / 294 (3.74%)<br>14  | 11 / 278 (3.96%)<br>11  |  |
| Syndromes<br>subjects affected / exposed<br>occurrences (all)                      | 4 / 294 (1.36%)<br>4    | 2 / 278 (0.72%)<br>2    |  |
| Immune system disorders                                                            |                         |                         |  |
| Allergy/Immunology<br>subjects affected / exposed<br>occurrences (all)             | 17 / 294 (5.78%)<br>18  | 11 / 278 (3.96%)<br>11  |  |
| Reproductive system and breast<br>disorders                                        |                         |                         |  |
| Sexual/Reproductive Function<br>subjects affected / exposed<br>occurrences (all)   | 1 / 294 (0.34%)<br>1    | 2 / 278 (0.72%)<br>2    |  |
| Respiratory, thoracic and mediastinal<br>disorders                                 |                         |                         |  |
| Pulmonary/Upper Respiratory<br>subjects affected / exposed<br>occurrences (all)    | 30 / 294 (10.20%)<br>51 | 30 / 278 (10.79%)<br>37 |  |
| Cardiac disorders                                                                  |                         |                         |  |
| Cardiac Arrhythmia<br>subjects affected / exposed<br>occurrences (all)             | 2 / 294 (0.68%)<br>2    | 1 / 278 (0.36%)<br>1    |  |
| Nervous system disorders                                                           |                         |                         |  |
| Neurology<br>subjects affected / exposed<br>occurrences (all)                      | 13 / 294 (4.42%)<br>15  | 12 / 278 (4.32%)<br>17  |  |

|                                                                                                                                    |                         |                        |  |
|------------------------------------------------------------------------------------------------------------------------------------|-------------------------|------------------------|--|
| Blood and lymphatic system disorders<br>Blood/Bone Marrow<br>subjects affected / exposed<br>occurrences (all)                      | 1 / 294 (0.34%)<br>1    | 2 / 278 (0.72%)<br>2   |  |
| Ear and labyrinth disorders<br>Auditory/Ear<br>subjects affected / exposed<br>occurrences (all)                                    | 12 / 294 (4.08%)<br>14  | 11 / 278 (3.96%)<br>15 |  |
| Eye disorders<br>Ocular/Visual<br>subjects affected / exposed<br>occurrences (all)                                                 | 4 / 294 (1.36%)<br>4    | 4 / 278 (1.44%)<br>4   |  |
| Gastrointestinal disorders<br>Gastrointestinal<br>subjects affected / exposed<br>occurrences (all)                                 | 28 / 294 (9.52%)<br>30  | 25 / 278 (8.99%)<br>34 |  |
| Hepatobiliary disorders<br>Hepatobiliary/Pancreas<br>subjects affected / exposed<br>occurrences (all)                              | 2 / 294 (0.68%)<br>3    | 0 / 278 (0.00%)<br>0   |  |
| Skin and subcutaneous tissue disorders<br>Dermatology/Skin<br>subjects affected / exposed<br>occurrences (all)                     | 25 / 294 (8.50%)<br>29  | 18 / 278 (6.47%)<br>20 |  |
| Renal and urinary disorders<br>Renal/Genitourinary<br>subjects affected / exposed<br>occurrences (all)                             | 1 / 294 (0.34%)<br>1    | 3 / 278 (1.08%)<br>5   |  |
| Endocrine disorders<br>Endocrine<br>subjects affected / exposed<br>occurrences (all)                                               | 18 / 294 (6.12%)<br>18  | 12 / 278 (4.32%)<br>12 |  |
| Musculoskeletal and connective tissue disorders<br>Musculoskeletal/Soft Tissue<br>subjects affected / exposed<br>occurrences (all) | 38 / 294 (12.93%)<br>45 | 18 / 278 (6.47%)<br>20 |  |
| Infections and infestations                                                                                                        |                         |                        |  |

|                                    |                                                                                                                                                                                                                         |                   |  |
|------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|--|
| Infection                          | Additional description: The most common adverse event was infection (n = 254), with 134 events in the oral insulin group and 120 events in the placebo group, but no significant study-related adverse events occurred. |                   |  |
| subjects affected / exposed        | 67 / 294 (22.79%)                                                                                                                                                                                                       | 62 / 278 (22.30%) |  |
| occurrences (all)                  | 134                                                                                                                                                                                                                     | 120               |  |
| Metabolism and nutrition disorders |                                                                                                                                                                                                                         |                   |  |
| Metabolic/Laboratory               |                                                                                                                                                                                                                         |                   |  |
| subjects affected / exposed        | 0 / 294 (0.00%)                                                                                                                                                                                                         | 4 / 278 (1.44%)   |  |
| occurrences (all)                  | 0                                                                                                                                                                                                                       | 4                 |  |

## 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

None reported