

**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) Appendix 16.2.6 Clinical Laboratory Values_Response Data_by Patient (Appendix 16.2.6 Clinical Laboratory Values_Response Data_by Patient.xls) declaration of late submission signed (declaration of late submission signed.pdf) TN-07 Oral Insulin (TN-07 Oral Insulin.pdf)

**Trial information****Trial identification**

Sponsor protocol code	80804005
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**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 University of Florida, 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:

<b>Subjects enrolled per age group</b>	
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

## 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
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### 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
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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
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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)
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Reporting group description: -

Reporting group values	Overall Study (overall period)	Total	
Number of subjects	560	560	
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean inter-quartile range (Q1-Q3)	8.2 5.7 to 12.1	-	
Gender categorical 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: 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: 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: 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
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### Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

### Reporting groups

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

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