Clinical trial results:
PINIT Study - An immune efficacy study for primary prevention using intranasal insulin therapy in islet autoantibody negative children at high risk for type 1 diabetes

Summary

EudraCT number	2015-003379-31
Trial protocol	DE
Global end of trial date	07 June 2021

Results information

Result version number	v1 (current)
This version publication date	02 April 2022
First version publication date	02 April 2022

Trial information

Trial identification

Sponsor protocol code	808040015

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03182322
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Technical University Munich, represented by the School of Medicine
Sponsor organisation address	Ismaninger Str. 22, München, Germany, 81675
Public contact	Prof. Dr. med. Peter Achenbach, Forschergruppe Diabetes, Klinikum Rechts der Isar, Technische Universität München, 0049 8931872896, peter.achenbach@helmholtz-muenchen.de
Scientific contact	Prof. Dr. med. Peter Achenbach, Forschergruppe Diabetes, Klinikum Rechts der Isar, Technische Universität München, 0049 8931872896, peter.achenbach@helmholtz-muenchen.de

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	25 February 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 June 2021
Global end of trial reached?	Yes
Global end of trial date	07 June 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine whether intranasal administration of 440 IU insulin to children with high genetic risk for T1D will induce likely protective IgG or IgA antibody responses to insulin, and/or T-cell responses to insulin and/or proinsulin.

Protection of trial subjects:

Local anesthetics (EMLA) to reduce pain during blood draws

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	25 May 2018
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	Germany: 38
Worldwide total number of subjects	38
EEA total number of subjects	38

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)	12
Children (2-11 years)	26
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were recruited through a (at that time) newly launched newborn T1D risk screening program in Saxony and by study team making contact with T1D families through clinics/diabetes educators/diabetologists.

Pre-assignment

Screening details:

Autoantibody negative children, aged 1 year to 7 years, with the HLA DR3/4-DQ8 genotype or with a first degree relative with T1D and at least one HLA DR4-DQ8 haplotype and no protective HLA DR-DQ alleles or haplotypes.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Intranasal Insulin

Arm description:

IMP: Recombinant Human Insulin, 1100IU/ml (40mg/ml manufacturing formulation)
Application: intranasal
Dosing: once daily for 7 consecutive days, and one day per week thereafter for a period of 6-month.

Arm type	Experimental
Investigational medicinal product name	Recombinant Human Insulin, 1100IU/ml
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Nasal spray
Routes of administration	Nasal use

Dosage and administration details:

Recombinant human insulin provided as bulk crystals (28.7 IU/mg) formulated in a carrier solution of water with 0.072 mg/ml benzalkonium chloride and 16 mg/ml glycerol.
Insulin at a dose of 1100 IU/ml, which equals 40 mg/ml manufacturing formulation, was administered intranasally as four 50 µl spray doses per nostril equivalent to a total dose of 440 IU.
Multi-dose nasal spray with actuator was used.

Arm title	Placebo

Arm description:

Placebo will be the insulin carrier solution
Water with 0.072 mg/ml benzalkonium chloride and 16 mg/ml glycerol

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Nasal spray
Routes of administration	Nasal use

Dosage and administration details:

Reference placebo will be the insulin carrier solution (water with 0.072 mg/ml benzalkonium chloride and 16 mg/ml glycerol).
Placebo was administered intranasally as four 50 µl spray doses per nostril.
Multi-dose nasal spray with actuator was used.

Number of subjects in period 1	Intranasal Insulin	Placebo
Started	18	20
Completed	18	18
Not completed	0	2
Adverse event, non-fatal	-	2

Baseline characteristics

Reporting groups	
Reporting group title	Intranasal Insulin
Reporting group description:	
IMP: Recombinant Human Insulin, 1100IU/ml (40mg/ml manufacturing formulation) Application: intranasal Dosing: once daily for 7 consecutive days, and one day per week thereafter for a period of 6-month.	
Reporting group title	Placebo
Reporting group description:	
Placebo will be the insulin carrier solution Water with 0.072 mg/ml benzalkonium chloride and 16 mg/ml glycerol	

Reporting group values	Intranasal Insulin	Placebo	Total
Number of subjects	18	20	38
Age categorical Units: Subjects			
Infants and toddlers (28 days-23 months)	7	5	12
Children (2-11 years)	11	15	26
Gender categorical Units: Subjects			
Female	9	7	16
Male	9	13	22

End points

End points reporting groups

Reporting group title	Intranasal Insulin
Reporting group description:	
IMP: Recombinant Human Insulin, 1100IU/ml (40mg/ml manufacturing formulation) Application: intranasal Dosing: once daily for 7 consecutive days, and one day per week thereafter for a period of 6-month.	
Reporting group title	Placebo
Reporting group description:	
Placebo will be the insulin carrier solution Water with 0.072 mg/ml benzalkonium chloride and 16 mg/ml glycerol	

Primary: Primary Outcome: Primary Immune Efficacy

End point title	Primary Outcome: Primary Immune Efficacy
End point description:	
End point type	Primary
End point timeframe:	
Baseline, 3 months or 6 months' visits	

End point values	Intranasal Insulin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	20		
Units: Subjects	18	20		

Statistical analyses

Statistical analysis title	Full Analysis
Comparison groups	Placebo v Intranasal Insulin
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3201 [1]
Method	Fisher exact
Parameter estimate	CI

Notes:

[1] - The difference in the frequency of observed positive outcomes between the two treatment arms was not significant.

Statistical analysis title	Sensitivity Analysis

Statistical analysis description:

After excluding one child who experienced positive GAD autoantibodies (The child was in the placebo

group), the primary efficacy analysis was also conducted separately in the 37 children that did not show signs of treatment failure.

Comparison groups	Intranasal Insulin v Placebo
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1837 [2]
Method	Fisher exact
Parameter estimate	CI

Notes:

[2] - A comparison between both arms did not show any significant difference regarding immune response.

Primary: Primary Outcome: Additional Analysis on Primary Immune Efficacy / Serum IgG Response to Insulin

End point title	Primary Outcome: Additional Analysis on Primary Immune Efficacy / Serum IgG Response to Insulin

End point description:

Serum IgG binding to insulin.
A positive response was defined as a >10 counts per minute (cpm) increase over the baseline value at any of the 3 months or 6 months' visits.

End point type	Primary

End point timeframe:

Baseline, 3 months or 6 months' visits

End point values	Intranasal Insulin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	20		
Units: Subjects	18	20		

Statistical analyses

Statistical analysis title	Full Analysis
Comparison groups	Intranasal Insulin v Placebo
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.224 [3]
Method	Fisher exact
Parameter estimate	CI

Notes:

[3] - The difference in the frequency of observed positive outcomes between the two treatment arms was not significant.

Primary: Primary Outcome: Additional Analysis on Primary Immune Efficacy / Salivary IgA Response to Insulin

End point title	Primary Outcome: Additional Analysis on Primary Immune Efficacy / Salivary IgA Response to Insulin

End point description:

Salivary IgA binding to insulin.
Results were expressed as background - corrected cpm and then as a ratio to the baseline value. A saliva sample from a control subject was used to define the background cpm in the saliva IgA-insulin assay. A positive response was defined as a background - corrected cpm value that is > (mean + 2SD) of untreated children with a >3-fold increase over the background-corrected cpm baseline value (ratio >3) at any of the 3 months or 6 months' visits.

End point type	Primary

End point timeframe:

Baseline, 3 months or 6 months' visits

End point values	Intranasal Insulin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	19		
Units: Subjects	18	20		

Statistical analyses

Statistical analysis title	Subset Analysis
Comparison groups	Intranasal Insulin v Placebo
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6843 [4]
Method	Fisher exact
Parameter estimate	CI

Notes:

[4] - The difference in the frequency of observed positive outcomes between the two treatment arms was not significant.

Primary: Primary Outcome: Additional Analysis on Primary Immune Efficacy / CD4 T-Cell Response to Insulin

End point title	Primary Outcome: Additional Analysis on Primary Immune Efficacy / CD4 T-Cell Response to Insulin

End point description:

CD4+ T cell response to insulin.
A positive response was defined as a stimulation index (SI) >3 and a >2-fold increase over the baseline SI value at any of the 3 months or 6 months' visits.

End point type	Primary

End point timeframe:

Baseline, 3 months or 6 months' visits

End point values	Intranasal Insulin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	18		
Units: Subjects	18	20		

Statistical analyses

Statistical analysis title	Subset Analysis
Comparison groups	Intranasal Insulin v Placebo
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≥ 0.9999 [5]
Method	Fisher exact
Parameter estimate	CI

Notes:

[5] - The difference in the frequency of observed positive outcomes between the two treatment arms was not significant.

Other pre-specified: Safety and Tolerability

End point title	Safety and Tolerability

End point description:

End point type	Other pre-specified

End point timeframe:

Complete study duration

End point values	Intranasal Insulin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	20		
Units: Subjects	18	20		

Statistical analyses

Statistical analysis title	Safety Analysis
Comparison groups	Intranasal Insulin v Placebo
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1673 [6]
Method	Kaplan-Meier Method

Notes:
[6] - Comparing the event probabilities between the two groups resulted in non-significant

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were recorded throughout the study in which the study participants received the treatment ; documentation and assessment of AEs and SAEs occurred during 3 monthly visits (Baseline Visit / 3 Month Visit / 6 Month Visit).

Adverse event reporting additional description:

AEs were collected via eCRF
SAEs were collected via paper form

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	14.1

Reporting groups

Reporting group title	Verum

Reporting group description:

IMP: Recombinant Human Insulin, 1100IU/ml (40mg/ml manufacturing formulation)
Application: intranasal
Dosing: once daily for 7 consecutive days, and one day per week thereafter for a period of 6-month.

Reporting group title	Placebo

Reporting group description:

Reference Placebo: Insulin carrier solution (water with 0.072 mg/ml benzalkonium chloride and 16 mg/ml glycerol)
Application: intranasal
Dosing: once daily for 7 consecutive days, and one day per week thereafter for a period of 6-month.

Serious adverse events	Verum	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
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: 0 %

Non-serious adverse events	Verum	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	17 / 18 (94.44%)	17 / 20 (85.00%)	
Injury, poisoning and procedural complications			
Forearm fracture			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Arm fracture			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Scar			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Injury NOS			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Lymphadenitis			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Thrombocytosis			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Fever			
subjects affected / exposed	7 / 18 (38.89%)	7 / 20 (35.00%)	
occurrences (all)	12	12	
Fever of unknown origin			
subjects affected / exposed	1 / 18 (5.56%)	1 / 20 (5.00%)	
occurrences (all)	1	1	

Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Diarrhea			
subjects affected / exposed	2 / 18 (11.11%)	1 / 20 (5.00%)	
occurrences (all)	3	1	
Vomiting			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	3	
Stomach function disorder			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorder NOS			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Allergic asthma			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Bleeding nose			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Cough			
subjects affected / exposed	2 / 18 (11.11%)	3 / 20 (15.00%)	
occurrences (all)	9	10	
Epistaxis			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	
occurrences (all)	3	0	
Sore nose			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	
occurrences (all)	1	0	

Musculoskeletal and connective tissue disorders			
Leg pain			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 18 (5.56%)	3 / 20 (15.00%)	
occurrences (all)	2	4	
Cercarial dermatitis			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Cold			
subjects affected / exposed	4 / 18 (22.22%)	1 / 20 (5.00%)	
occurrences (all)	7	1	
Common cold			
subjects affected / exposed	8 / 18 (44.44%)	7 / 20 (35.00%)	
occurrences (all)	14	15	
Conjunctivitis			
subjects affected / exposed	0 / 18 (0.00%)	5 / 20 (25.00%)	
occurrences (all)	0	5	
Croup			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Exanthema subitum			
subjects affected / exposed	2 / 18 (11.11%)	0 / 20 (0.00%)	
occurrences (all)	2	0	
Gastroenteritis			
subjects affected / exposed	0 / 18 (0.00%)	3 / 20 (15.00%)	
occurrences (all)	0	4	
Gastrointestinal infection			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Glue ear			
subjects affected / exposed	0 / 18 (0.00%)	3 / 20 (15.00%)	
occurrences (all)	0	3	
Hand-foot-and-mouth disease			

subjects affected / exposed	2 / 18 (11.11%)	0 / 20 (0.00%)	
occurrences (all)	2	0	
Influenza			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Otitis			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Otitis media			
subjects affected / exposed	4 / 18 (22.22%)	1 / 20 (5.00%)	
occurrences (all)	4	1	
Pneumonia			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Respiratory infection			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	
occurrences (all)	2	0	
Rhinitis			
subjects affected / exposed	1 / 18 (5.56%)	4 / 20 (20.00%)	
occurrences (all)	1	5	
Scarlet fever			
subjects affected / exposed	1 / 18 (5.56%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Sinusitis			
subjects affected / exposed	1 / 18 (5.56%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Streptococcal infection NOS			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Tonsillitis			
subjects affected / exposed	0 / 18 (0.00%)	2 / 20 (10.00%)	
occurrences (all)	0	3	
Upper respiratory infection			
subjects affected / exposed	1 / 18 (5.56%)	3 / 20 (15.00%)	
occurrences (all)	2	6	
Upper respiratory tract infection			

subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Viral infection			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Hypoglycemia			
subjects affected / exposed	2 / 18 (11.11%)	0 / 20 (0.00%)	
occurrences (all)	3	0	
Iron deficiency			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 September 2020	Substancial Amendments to Protocol / Version 2.2 to 2.3 New definition of study end (updated to reflect real dates for FPFV and LPLV and change of definition of end of study) A redefinition of the end of the study was necessary because the performance of the required mechanistic assays could only be started after the LPLV. The measurement of all laboratory values relevant for the evaluation, including the very complex T-cell stimulation assay, took some time. Thus, the study could not be considered complete until the above measurements were completed and the results were available to be entered into the database. Therefore, the end of the study was redefined accordingly.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported