Clinical trial results:
Pre-POINT (Primary Oral INsulin Trial) study
A dose finding safety and immune efficacy study for primary mucosal insulin therapy in islet autoantibody negative children at high genetic risk for type 1 diabetes

Summary

EudraCT number	2005-001621-29
Trial protocol	DE AT GB
Global end of trial date	15 September 2013

Results information

Result version number	v1 (current)
This version publication date	03 January 2024
First version publication date	03 January 2024

Trial information

Trial identification

Sponsor protocol code	80804002

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Technische Universität Dresden
Sponsor organisation address	Helmholtzstraße 10, Dresden, Germany, 01069
Public contact	Koordinierungszentrum für Klinische Studien, Medizinische Fakultät C. G. Carus, kontakt@kksdresden.de
Scientific contact	Koordinierungszentrum für Klinische Studien, Medizinische Fakultät C. G. Carus, kontakt@kksdresden.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	15 September 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 September 2013
Global end of trial reached?	Yes
Global end of trial date	15 September 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objective of this study is to determine the feasibility, safety and bioavailability of oral insulin administration in children with high genetic risk for type 1 diabetes (T1DM) in a dose escalation primary intervention pilot study.

To find a dose with proven drug bioavailability to the immune system for use in a phase II/III primary T1DM vaccination trial (POINT study) in genetically at risk subjects.

Protection of trial subjects:

Only subjects who met all of the study's inclusion criteria and none of the exclusion criteria were enrolled in the study. The occurrence of adverse events was closely monitored.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	23 October 2009
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	United Kingdom: 1
Country: Number of subjects enrolled	Austria: 2
Country: Number of subjects enrolled	Germany: 17
Country: Number of subjects enrolled	United States: 5
Worldwide total number of subjects	25
EEA total number of subjects	19

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)	25
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: -

Pre-assignment

Screening details:

All subjects were screened for eligibility prior to enrollment in the clinical trial.

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Insulin

Arm description:

The study randomized in study blocks of 5 participants. Children randomized in the first block received placebo or 2.5 milligrams insulin dose for 6 months followed by a dose escalation to placebo or 7.5 mg insulin for 3 to 12 months. Children randomized in the second block received placebo or 2.5 milligrams insulin dose for 6 months followed by a dose escalation to placebo or 22.5 mg insulin for 3 to 12 months. Children randomized in the third block received placebo or 7.5 milligrams insulin dose for 6 months followed by a dose escalation to placebo or 67.5 mg insulin for 3 to 12 months. Children randomized in the fourth block received placebo or 22.5 milligrams insulin dose for 3 to 12 months. Children randomized in the fifth block received placebo or 67.5 milligrams insulin dose for 3 to 12 months.

Arm type	Experimental
Investigational medicinal product name	Recombinant human insulin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

The IMP was administered to the children in the following doses: 2.5 mg, 7.5 mg, 22.5 mg and 67.5 mg. The contents of one capsule were administered once a day, recommended at breakfast.

Arm title	Placebo

Arm description: -

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:

The contents of one capsule were administered once a day, recommended at breakfast.

Number of subjects in period 1	Insulin	Placebo
Started	15	10
Completed	14	9
Not completed	1	1
Consent withdrawn by subject	1	1

Baseline characteristics

Reporting groups

Reporting group title	Insulin

Reporting group description:

The study randomized in study blocks of 5 participants. Children randomized in the first block received placebo or 2.5 milligrams insulin dose for 6 months followed by a dose escalation to placebo or 7.5 mg insulin for 3 to 12 months. Children randomized in the second block received placebo or 2.5 milligrams insulin dose for 6 months followed by a dose escalation to placebo or 22.5 mg insulin for 3 to 12 months. Children randomized in the third block received placebo or 7.5 milligrams insulin dose for 6 months followed by a dose escalation to placebo or 67.5 mg insulin for 3 to 12 months. Children randomized in the fourth block received placebo or 22.5 milligrams insulin dose for 3 to 12 months. Children randomized in the fifth block received placebo or 67.5 milligrams insulin dose for 3 to 12 months.

Reporting group title	Placebo

Reporting group description: -

Reporting group values	Insulin	Placebo	Total
Number of subjects	15	10	25
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	15	10	25
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	7	8	15
Male	8	2	10

Subject analysis sets

Subject analysis set title	Insulin 2.5 mg
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Subjects receiving insulin at a dose of 2.5 mg.

Subject analysis set title	Insulin 7.5 mg
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Subjects receiving insulin at a dose of 7.5 mg.

Subject analysis set title	Insulin 22.5 mg
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Subjects receiving insulin at a dose of 22.5 mg.

Subject analysis set title	Insulin 67.5 mg

Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Subjects receiving insulin at a dose of 67.5 mg.	
Subject analysis set title	Placebo
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Subjects receiving placebo.	

Reporting group values	Insulin 2.5 mg	Insulin 7.5 mg	Insulin 22.5 mg
Number of subjects	6	6	6
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	6	6	6
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female			
Male			

Reporting group values	Insulin 67.5 mg	Placebo	
Number of subjects	6	10	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	6	10	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female			
Male			

End points

End points reporting groups

Reporting group title	Insulin
Reporting group description:	
The study randomized in study blocks of 5 participants. Children randomized in the first block received placebo or 2.5 milligrams insulin dose for 6 months followed by a dose escalation to placebo or 7.5 mg insulin for 3 to 12 months. Children randomized in the second block received placebo or 2.5 milligrams insulin dose for 6 months followed by a dose escalation to placebo or 22.5 mg insulin for 3 to 12 months. Children randomized in the third block received placebo or 7.5 milligrams insulin dose for 6 months followed by a dose escalation to placebo or 67.5 mg insulin for 3 to 12 months. Children randomized in the fourth block received placebo or 22.5 milligrams insulin dose for 3 to 12 months. Children randomized in the fifth block received placebo or 67.5 milligrams insulin dose for 3 to 12 months.	
Reporting group title	Placebo
Reporting group description: -	
Subject analysis set title	Insulin 2.5 mg
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Subjects receiving insulin at a dose of 2.5 mg.	
Subject analysis set title	Insulin 7.5 mg
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Subjects receiving insulin at a dose of 7.5 mg.	
Subject analysis set title	Insulin 22.5 mg
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Subjects receiving insulin at a dose of 22.5 mg.	
Subject analysis set title	Insulin 67.5 mg
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Subjects receiving insulin at a dose of 67.5 mg.	
Subject analysis set title	Placebo
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Subjects receiving placebo.	

Primary: Development of immunity to insulin

End point title	Development of immunity to insulin
End point description:	
Antibody or T cell responses to insulin were observed during treatment.	
End point type	Primary
End point timeframe:	
From baseline to a maximum of 18 months of treatment	

End point values	Insulin 2.5 mg	Insulin 7.5 mg	Insulin 22.5 mg	Insulin 67.5 mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	6	6	6	6
Units: subject	1	1	2	5

End point values	Placebo			
Subject group type	Subject analysis set			
Number of subjects analysed	10			
Units: subject	2			

Statistical analyses

Statistical analysis title	Test for trend
Comparison groups	Insulin 2.5 mg v Insulin 7.5 mg v Insulin 22.5 mg v Insulin 67.5 mg v Placebo
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.017
Method	Chi-squared test for trend

Adverse events

Adverse events information

Timeframe for reporting adverse events:

18 months

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17

Reporting groups

Reporting group title	Insulin

Reporting group description:

The study randomized in study blocks of 5 participants. Children randomized in the first block received placebo or 2.5 milligrams insulin dose for 6 months followed by a dose escalation to placebo or 7.5 mg insulin for 3 to 12 months. Children randomized in the second block received placebo or 2.5 milligrams insulin dose for 6 months followed by a dose escalation to placebo or 22.5 mg insulin for 3 to 12 months. Children randomized in the third block received placebo or 7.5 milligrams insulin dose for 6 months followed by a dose escalation to placebo or 67.5 mg insulin for 3 to 12 months. Children randomized in the fourth block received placebo or 22.5 milligrams insulin dose for 3 to 12 months. Children randomized in the fifth block received placebo or 67.5 milligrams insulin dose for 3 to 12 months.

Reporting group title	Placebo

Reporting group description: -

Serious adverse events	Insulin	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 15 (13.33%)	0 / 10 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Surgical and medical procedures			
Otitis media	Additional description: The subject has had recurring events of otits media in the context of common colds with effusion (OME). The proband underwent surgery for 1. tonsillectomy, 2. adenoidectomy, 3. paracentesis with insertion of tympanostomy tubes.		
subjects affected / exposed	1 / 15 (6.67%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Forearm fracture			
subjects affected / exposed	1 / 15 (6.67%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Insulin	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 15 (80.00%)	10 / 10 (100.00%)	
General disorders and administration site conditions			
Common cold			
subjects affected / exposed	6 / 15 (40.00%)	3 / 10 (30.00%)	
occurrences (all)	31	6	
Immune system disorders			
Allergy symptoms			
subjects affected / exposed	1 / 15 (6.67%)	2 / 10 (20.00%)	
occurrences (all)	2	2	
Eye disorders			
Conjunctivitis			
subjects affected / exposed	1 / 15 (6.67%)	1 / 10 (10.00%)	
occurrences (all)	1	1	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	4 / 15 (26.67%)	1 / 10 (10.00%)	
occurrences (all)	7	2	
Nausea			
subjects affected / exposed	1 / 15 (6.67%)	1 / 10 (10.00%)	
occurrences (all)	1	2	
Gastroenteritis			
subjects affected / exposed	1 / 15 (6.67%)	2 / 10 (20.00%)	
occurrences (all)	1	2	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 15 (13.33%)	2 / 10 (20.00%)	
occurrences (all)	2	2	
Infections and infestations			
Rhinitis			
subjects affected / exposed	1 / 15 (6.67%)	1 / 10 (10.00%)	
occurrences (all)	3	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 February 2009	Change of sponsor
27 May 2009	Expansion of inclusion age
18 December 2009	primary oral insulin use; change of randomisation 3:1 to 3:2 (active to control arm(s)); deletion of active and control arm B; reduction of planned participant number from 40 to 25
12 December 2012	Removal of Canadian and of Italian trial sites; less restricted HLA genotype criteria for eligibility

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/18445349

http://www.ncbi.nlm.nih.gov/pubmed/18777449