Clinical trial results:
Fr1da Insulin Intervention - Mechanistic study using oral insulin for immune and treatment efficacy in secondary prevention of type 1 diabetes

Summary

EudraCT number	2015-003028-30
Trial protocol	DE
Global end of trial date	30 September 2024

Results information

Result version number	v1 (current)
This version publication date	11 February 2026
First version publication date	11 February 2026

Trial information

Trial identification

Sponsor protocol code	808040019

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02620072
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Technical University Munich, School of Medicine
Sponsor organisation address	Ismaninger Str. 22, Munich, Germany, 81675
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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	22 May 2025
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 September 2024
Global end of trial reached?	Yes
Global end of trial date	30 September 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the immune efficacy, and treatment efficacy of daily high dose oral insulin (up to 67.5 mg) in children aged 2 years to 12 years with multiple islet autoantibodies in a secondary intervention study. Immune efficacy is defined as a change in the immune response to the treatment, which is associated with a reduction in the progression to dysglycemia or diabetes. Treatment efficacy is a treatment related reduction in the rate of progression to dysglycemia or diabetes.

Protection of trial subjects:

- Blood glucose, insulin and c-peptide values were measured before and 30, 60, and 120 minutes after
study drug was administered during the baseline and 3 montsh visit. Capillary blood glucose was measured with a glucose meter. Families were instructed to report suspected hypoglycemic events
- Systematic adverse event (AE) assessment at all study visits
- Allergy surveillance: parents instructed to monitor and report signs of allergic reactions (e.g. conjunctivitis, rhinitis, urticaria, anaphylaxis).
- Blood sampling: safety blood draw at visit 1 and visit 5

Background therapy:

no background therapy

Evidence for comparator: -

Actual start date of recruitment	11 December 2015
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: 220
Worldwide total number of subjects	220
EEA total number of subjects	220

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	0

months)	
Children (2-11 years)	220
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:

Potential trial participants have been identified through screening for islet auto-antibodies in the Fr1da study (majority) or in any other screening program in Germany (i.e. Munich Cohort Studies). Recruitment started in December 2015 and lasted until June 2021.

Pre-assignment

Screening details:

The Fr1da study offers islet auto-antibody testing to all children in Bavaria at the age of 2 - 10 years in the context of compulsory medical preventive check-ups. The Fr1da screening enables detection of type 1 diabetes at an early stage and is conducted by Helmholtz Munich in cooperation with the association of pediatricians.

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	Oral Insulin

Arm description:

Children in the oral insulin group received increasing dose of daily oral insulin: 7.5 mg (3 months), rising to 67.5 mg (9 months).

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

Dosage and administration details:

Children received increasing dose of daily oral insulin: 7.5 mg (3 months), rising to 67.5 mg (9 months). The insulin crystals (7.5 mg rH-insulin crystals or 67.5 mg rH-insulin crystals) are formulated together with filling substance (microcrystalline cellulose to a total weight of 200 mg) and contained in hard gelatine capsules.
The study treatment was self-administered by participants or by the child’s parents or guardians as content of one capsule per day. The study treatment will be given orally as a powder spread on a small quantity meal serving e.g. with yoghurt, tea spoon of water etc.
Treatment was administered daily preferably in the morning (7-10am) after feeding for 12 months.

Arm title	Placebo

Arm description:

Children in the placebo group will receive 12 months of daily oral placebo.

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:

Placebo was the filling substance microcrystalline cellulose (200 mg) contained in hard gelatine capsules. The study treatment was be self-administered by participants or by the child’s parents or guardians as

content of one capsule per day. The study treatment was given orally as a powder spread on a small quantity meal serving e.g. with yoghurt, tea spoon of water etc. Treatment was administered daily preferably in the morning (7-10am) after feeding for 12 months.

Number of subjects in period 1	Oral Insulin	Placebo
Started	110	110
Completed	90	89
Not completed	20	21
Consent withdrawn by subject	4	7
other reason & non-compliance	13	11
Lost to follow-up	3	3

Baseline characteristics

Reporting groups	
Reporting group title	Oral Insulin
Reporting group description:	
Children in the oral insulin group received increasing dose of daily oral insulin: 7.5 mg (3 months), rising to 67.5 mg (9 months).	
Reporting group title	Placebo
Reporting group description:	
Children in the placebo group will receive 12 months of daily oral placebo.	

Reporting group values	Oral Insulin	Placebo	Total
Number of subjects	110	110	220
Age categorical			
children at median age 4.8 years			
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)	110	110	220
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	59	53	112
Male	51	57	108

Subject analysis sets	
Subject analysis set title	Full Analysis Set (Intention-to-treat)
Subject analysis set type	Full analysis
Subject analysis set description:	
All randomised children who received ≥1 dose of study medication	
Subject analysis set title	Safety analysis set
Subject analysis set type	Safety analysis
Subject analysis set description:	
All children who received ≥1 dose, analyzed per actual treatment	

Reporting group values	Full Analysis Set (Intention-to-treat)	Safety analysis set	
Number of subjects	220	220	
Age categorical			
children at median age 4.8 years			
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)	220	220	
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	Oral Insulin
Reporting group description:	
Children in the oral insulin group received increasing dose of daily oral insulin: 7.5 mg (3 months), rising to 67.5 mg (9 months).	
Reporting group title	Placebo
Reporting group description:	
Children in the placebo group will receive 12 months of daily oral placebo.	
Subject analysis set title	Full Analysis Set (Intention-to-treat)
Subject analysis set type	Full analysis
Subject analysis set description:	
All randomised children who received ≥1 dose of study medication	
Subject analysis set title	Safety analysis set
Subject analysis set type	Safety analysis
Subject analysis set description:	
All children who received ≥1 dose, analyzed per actual treatment	

Primary: Primary: Immune Response (efficacy)

End point title	Primary: Immune Response (efficacy)
End point description:	
Of the first 90 randomised children, 86 received at least one dose of treatment or placebo and their immune response results were recorded, therefore they are considered as part of the full analysis sample for the primary endpoint analysis.	
End point type	Primary
End point timeframe:	
From baseline, children were monitored for a minimum of 36 months and up to approximately 90 months or until diagnosis of diabetes	

End point values	Oral Insulin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	42		
Units: Subjects	11	13		

Statistical analyses

Statistical analysis title	Primary Immune Response per Treatment Arm
Comparison groups	Placebo v Oral Insulin

Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.63
Method	Fisher exact
Parameter estimate	Hazard ratio (HR)
Confidence interval	
level	95 %
Variability estimate	Standard deviation

Primary: Co-primary: Treatment efficacy

End point title	Co-primary: Treatment efficacy

End point description:

The co-primary outcome was the elapsed time from randomisation treatment assignment to the developement of persistent dysgycemia or diabetes onset.
Dysglycemia was determined based on abnormal glucose values during oral glucose tolerance tests (OGTT), while diabetes onset followed ADA diagnostic criteria. The analysis was conducted in the full intention-to-treat (ITT) population (n = 220) and evaluated using time-to-event methods, with participants censored at their last assessment if no event occurred.

End point type	Primary

End point timeframe:

From baseline, children were monitored for a minimum of 36 months and up to approximately 90 months or until diagnosis of diabetes

End point values	Oral Insulin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	110	110		
Units: Subjects	46	41		

Statistical analyses

Statistical analysis title	Time to dysglycemia or diabetes progression
Comparison groups	Oral Insulin v Placebo
Number of subjects included in analysis	220
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.74
Method	Wald-Test
Parameter estimate	Hazard ratio (HR)
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.66
upper limit	1.73

Variability estimate	Standard deviation

Secondary: Type 1 Diabetes (T1D)

End point title	Type 1 Diabetes (T1D)

End point description:

Time to onset of clinical type 1 diabetes, defined according to ADA criteria. Diagnosis requires confirmation on two separate occasions (≥1 day apart) based on one or more of the following:

Fasting plasma glucose ≥126 mg/dL (7.0 mmol/L),
2-hour plasma glucose ≥200 mg/dL (11.1 mmol/L) during OGTT,
Random plasma glucose ≥200 mg/dL (11.1 mmol/L) with classic symptoms (polyuria, polydipsia, weight loss).

Participants were followed from randomisation until diagnosis or last contact with the trial center.

End point type	Secondary

End point timeframe:

From baseline, children were monitored for a minimum of 36 months and up to approximately 90 months or until diagnosis of diabetes

End point values	Oral Insulin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	110	110		
Units: Subjects	38	36		

Statistical analyses

Statistical analysis title	Time to T1D progression
Comparison groups	Oral Insulin v Placebo
Number of subjects included in analysis	220
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9182
Method	Wald-test
Parameter estimate	Cox proportional hazard
Point estimate	1.024
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.649
upper limit	1.616

Secondary: Immune response outcomes -IAA

End point title	Immune response outcomes -IAA

End point description:

End point type	Secondary

End point timeframe:

From baseline, children were monitored for a minimum of 36 months and up to approximately 90 months or until diagnosis of diabetes

End point values	Oral Insulin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	42		
Units: subjects	9	9		

Statistical analyses

Statistical analysis title	Insulin auto-antibodies response analysis
Comparison groups	Oral Insulin v Placebo
Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9558
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.974
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.387
upper limit	2.455
Variability estimate	Standard deviation

Secondary: Immune reponse outcome: Salivary IgA

End point title	Immune reponse outcome: Salivary IgA

End point description:

End point type	Secondary

End point timeframe:

From baseline, children were monitored for a minimum of 36 months and up to approximately 90 months or until diagnosis of diabetes

End point values	Oral Insulin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	42		
Units: Subjects	2	2		

Statistical analyses

Statistical analysis title	Salivary IgA Response analysis
Comparison groups	Oral Insulin v Placebo
Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9338
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.087
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.153
upper limit	7.715
Variability estimate	Standard deviation

Secondary: Immune response outcome: CD4+ T-cell

End point title	Immune response outcome: CD4+ T-cell

End point description:

End point type	Secondary

End point timeframe:

From baseline, children were monitored for a minimum of 36 months and up to approximately 90 months or until diagnosis of diabetes

End point values	Oral Insulin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	38		
Units: subjects	2	3		

Statistical analyses

Statistical analysis title	CD4+ T-cell response analysis
Comparison groups	Placebo v Oral Insulin

Number of subjects included in analysis	76
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6587
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.112
upper limit	4.01
Variability estimate	Standard deviation

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were assessed every three months during the 12-month treatment phase and subsequently at 6-month intervals until 90 months after baseline or until the development of type 1 diabetes.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	14.1

Reporting groups

Reporting group title	Oral Insulin
Reporting group description: -	
Reporting group title	Placebo

Reporting group description: -

Serious adverse events	Oral Insulin	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 110 (3.64%)	1 / 110 (0.91%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Injury, poisoning and procedural complications			
subjects affected / exposed	1 / 110 (0.91%)	0 / 110 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac disorder			
subjects affected / exposed	1 / 110 (0.91%)	0 / 110 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastrointestinal disorder			
subjects affected / exposed	1 / 110 (0.91%)	0 / 110 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			

Respiratory, thoracic and meidatinal disorder			
subjects affected / exposed	1 / 110 (0.91%)	1 / 110 (0.91%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Infection and infestation			
subjects affected / exposed	4 / 110 (3.64%)	1 / 110 (0.91%)	
occurrences causally related to treatment / all	0 / 4	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	Oral Insulin	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	98 / 110 (89.09%)	96 / 110 (87.27%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasms benign, malignant and unspecified			
subjects affected / exposed	2 / 110 (1.82%)	0 / 110 (0.00%)	
occurrences (all)	2	0	
Surgical and medical procedures			
Surgical and medical procedures			
subjects affected / exposed	2 / 110 (1.82%)	0 / 110 (0.00%)	
occurrences (all)	2	0	
General disorders and administration site conditions			
General disorders ans administration site conditions			
subjects affected / exposed	35 / 110 (31.82%)	35 / 110 (31.82%)	
occurrences (all)	63	50	
Immune system disorders			
Immune system disorders			
subjects affected / exposed	5 / 110 (4.55%)	3 / 110 (2.73%)	
occurrences (all)	5	3	
Respiratory, thoracic and mediastinal disorders			
Respiratory, thoracic and mediastinal disorders			

subjects affected / exposed	25 / 110 (22.73%)	32 / 110 (29.09%)	
occurrences (all)	72	71	
Investigations			
Investigations			
subjects affected / exposed	1 / 110 (0.91%)	1 / 110 (0.91%)	
occurrences (all)	1	1	
Injury, poisoning and procedural complications			
Imjury, poisoning and procedural complications			
subjects affected / exposed	8 / 110 (7.27%)	6 / 110 (5.45%)	
occurrences (all)	13	6	
Congenital, familial and genetic disorders			
Congenital, familial and genetic disorders			
subjects affected / exposed	1 / 110 (0.91%)	1 / 110 (0.91%)	
occurrences (all)	1	1	
Cardiac disorders			
Cardiac disorder			
subjects affected / exposed	1 / 110 (0.91%)	0 / 110 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Nervous system disorders			
subjects affected / exposed	5 / 110 (4.55%)	7 / 110 (6.36%)	
occurrences (all)	7	9	
Blood and lymphatic system disorders			
Blood and lymphatic system disorders			
subjects affected / exposed	3 / 110 (2.73%)	0 / 110 (0.00%)	
occurrences (all)	4	0	
Ear and labyrinth disorders			
Ear and labyrinth disorders			
subjects affected / exposed	0 / 110 (0.00%)	4 / 110 (3.64%)	
occurrences (all)	0	5	
Gastrointestinal disorders			
Gastrointestinal disorders			
subjects affected / exposed	39 / 110 (35.45%)	26 / 110 (23.64%)	
occurrences (all)	59	47	
Skin and subcutaneous tissue disorders			

Skin and subcutaneous tissue disorders			
subjects affected / exposed	6 / 110 (5.45%)	6 / 110 (5.45%)	
occurrences (all)	8	8	
Endocrine disorders			
Endocrine disorders			
subjects affected / exposed	0 / 110 (0.00%)	1 / 110 (0.91%)	
occurrences (all)	0	2	
Musculoskeletal and connective tissue disorders			
Musculosceletal and connective tissue disorders			
subjects affected / exposed	3 / 110 (2.73%)	3 / 110 (2.73%)	
occurrences (all)	4	4	
Infections and infestations			
Infections and infestations			
subjects affected / exposed	86 / 110 (78.18%)	78 / 110 (70.91%)	
occurrences (all)	252	202	
Metabolism and nutrition disorders			
Metabolism and nutrition disorders			
subjects affected / exposed	2 / 110 (1.82%)	0 / 110 (0.00%)	
occurrences (all)	2	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 December 2015	Shelf life extension of IMP
22 September 2016	Protocol Version 3.0: additional endpoint dysglycemia and Increase in the number of participants from 62 to 220
22 February 2018	Shelf life extension of IMP
22 May 2019	Protocol Version 4.1 -Extension of recruitment period from 30 months to 56 months -Extension of study duration -new definition of AE-reporting timelines -Changes in study objective and primary /secondary outcome -Modifications to the statistical rationale for sample size calculation.
15 April 2020	Update IB Version 2.0 Protocol Version 5.0
15 January 2021	Protocol Version 6 -Revision of inconsistencies regarding the objective and outcomes -Update timelines for end of study
07 September 2021	Protocol Version 7 -Interim analysis for first 90 study participants

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

A limitation of the design is the short treatment duration, which prevents conclusions regarding potential long-term therapeutic effects. Since treatment was largely in individuals while they had stage 1 type 1 diabetes, it is unknown whether hig

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/41563349