Clinical trial results:
CTLA-4Ig (Abatacept) for Prevention of Abnormal Glucose Tolerance and Diabetes in Relatives at Risk for Type 1 Diabetes Mellitus

Summary

EudraCT number	2013-002249-13
Trial protocol	GB DE FI IT SE
Global end of trial date	14 December 2022

Results information

Result version number	v1 (current)
This version publication date	23 November 2024
First version publication date	23 November 2024
Summary attachment (see zip file)	TN18 Final Study Report (TN18 Final Study Report.pdf)

Trial information

Trial identification

Sponsor protocol code	TN-18

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01773707
WHO universal trial number (UTN)	-
Other trial identifiers	IND: 117,208

Notes:

Sponsors

Sponsor organisation name	TrialNet
Sponsor organisation address	3650 Spectrum Blvd Ste 100, Tampa, United States, 33620
Public contact	Erica Perri, TrialNet Coordinating Center, 1 8133969543, Erica.Perri@epi.usf.edu
Scientific contact	EricaPerri, TrialNet Coordinating Center, 1 813396 9543, Erica.Perri@epi.usf.edu

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	14 December 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 December 2021
Global end of trial reached?	Yes
Global end of trial date	14 December 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study is to determine whether treatment of subjects at risk for diabetes with Abatacept results in delay or prevention of abnormal glucose tolerance.

Protection of trial subjects:

The DSMB met regularly during the study and reviewed safety and related information.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 March 2013
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	Sweden: 1
Country: Number of subjects enrolled	United Kingdom: 14
Country: Number of subjects enrolled	Finland: 2
Country: Number of subjects enrolled	Germany: 7
Country: Number of subjects enrolled	Italy: 1
Country: Number of subjects enrolled	Australia: 7
Country: Number of subjects enrolled	Canada: 14
Country: Number of subjects enrolled	United States: 166
Worldwide total number of subjects	212
EEA total number of subjects	11

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)	59

Adolescents (12-17 years)	75
Adults (18-64 years)	78
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participant in TrialNet Natural History/Pathway to Prevention Study (TN01) and thus, a relative of a proband with T1DM.

Pre-assignment

Screening details:

Initial testing for autoantibodies, HLA type, and Oral Glucose Tolerance Test (OGTT) is done in the Natural History/Pathway to Prevention Study. Participants in the Abatacept trial must have two confirmed diabetes-related autoantibodies (excluding mIAA) and normal OGTT results within 52 days of randomization to be eligible.

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
Arm title	Abatacept IV Infusion

Arm description:

CTLA4-Ig (Abatacept) will be administered as 14 (30 minute) infusions over one year (3 infusions every other week the first month; monthly for the following 11 months)

CTLA4-Ig (Abatacept): Given as 30-minute IV infusion.

Arm type	Experimental
Investigational medicinal product name	Abatacept
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Infusion

Dosage and administration details:

The dose was chosen based on demonstrated safety and efficacy in children and adults with type 1 diabetes as well as in other human autoimmune diseases. Dosing was according to the individual's weight during the previous visit unless the previous visit was more than three months prior. In that case, dosing was according to the individual's weight on the day of the visit.

Arm title	Placebo

Arm description:

The placebo arm will receive 14 (30 minute) IV infusions (containing saline) given 3 times (every other week) the first month and monthly for the following 11 months.

Placebo: Saline given as 30-minute IV infusion

Arm type	Placebo
Investigational medicinal product name	Saline
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Infusion

Dosage and administration details:

The dose was chosen based on demonstrated safety and efficacy in children and adults with type 1 diabetes as well as in other human autoimmune diseases. Dosing was according to the individual's weight during the previous visit unless the previous visit was more than three months prior. In that

case, dosing was according to the individual’s weight on the day of the visit.

Number of subjects in period 1	Abatacept IV Infusion	Placebo
Started	101	111
Completed	99	108
Not completed	2	3
Consent withdrawn by subject	-	2
Lost to follow-up	2	1

Baseline characteristics

Reporting groups	
Reporting group title	Abatacept IV Infusion

Reporting group description:

CTLA4-Ig (Abatacept) will be administered as 14 (30 minute) infusions over one year (3 infusions every other week the first month; monthly for the following 11 months)

CTLA4-Ig (Abatacept): Given as 30-minute IV infusion.

Reporting group title	Placebo

Reporting group description:

The placebo arm will receive 14 (30 minute) IV infusions (containing saline) given 3 times (every other week) the first month and monthly for the following 11 months.

Placebo: Saline given as 30-minute IV infusion

Reporting group values	Abatacept IV Infusion	Placebo	Total
Number of subjects	101	111	212
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
median	16.3	14.9	
inter-quartile range (Q1-Q3)	11.9 to 27.5	11.4 to 22.0	-
Gender categorical Units: Subjects			
Female	50	57	107
Male	51	54	105

End points

End points reporting groups

Reporting group title	Abatacept IV Infusion

Reporting group description:

CTLA4-Ig (Abatacept) will be administered as 14 (30 minute) infusions over one year (3 infusions every other week the first month; monthly for the following 11 months)

CTLA4-Ig (Abatacept): Given as 30-minute IV infusion.

Reporting group title	Placebo

Reporting group description:

The placebo arm will receive 14 (30 minute) IV infusions (containing saline) given 3 times (every other week) the first month and monthly for the following 11 months.

Placebo: Saline given as 30-minute IV infusion

Primary: Time From Randomization to Confirmed Abnormal Glucose Tolerance Test

End point title	Time From Randomization to Confirmed Abnormal Glucose Tolerance Test

End point description:

Measured by Oral Glucose Tolerance Test (OGTT):

Abnormal Glucose Tolerance is primary endpoint and defined as:
1. Fasting plasma glucose ≥ 110 mg/dL (6.1 mmol/L) and < 126 mg/dL (7 mmol/L), or
2. 2 hour plasma glucose ≥ 140 mg/dL (7.8 mmol/L) and < 200 (11.1 mmol/L), or
3. 30, 60, 90 minute plasma glucose during OGTT ≥ 200 mg/dL (11.1 mmol/L)

End point type	Primary

End point timeframe:

96 months

End point values	Abatacept IV Infusion	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	101[1]	111[2]		
Units: Months				
number (not applicable)	89.2	71.6		

Notes:

[1] - Number = Median
Inter-quartile Range: 41.1 to N/A (upper quartile range has not been reached)
[2] - Number = Median
Inter-quartile Range: 23.7 to N/A (upper quartile range has not been reached)

Statistical analyses

Statistical analysis title	Primary Analysis

Statistical analysis description:

Time From Randomization to Confirmed Abnormal Glucose Tolerance Test

Comparison groups	Placebo v Abatacept IV Infusion

Number of subjects included in analysis	212
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.11
Method	t-test, 2-sided
Parameter estimate	Cox proportional hazard
Point estimate	0.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.452
upper limit	1.09

Secondary: Change in C-Peptide Concentration to Oral Glucose Tolerance Test (OGTT)

End point title	Change in C-Peptide Concentration to Oral Glucose Tolerance Test (OGTT)

End point description:

End point type	Secondary

End point timeframe:

0 time to 30 months

End point values	Abatacept IV Infusion	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	101	111		
Units: Unit of Measure: nmol/L				
log mean (inter-quartile range (Q1-Q3))	2.16 (1.61 to 2.50)	2.07 (1.51 to 2.74)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline Visit through study endpoint, up to 6 years

Adverse event reporting additional description:

CTCAE; Adverse events were analyzed and published based on organ system class without regard to the specific Adverse Event Term.

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	3

Reporting groups

Reporting group title	Abatacept IV Infusion

Reporting group description:

CTLA4-Ig (Abatacept) will be administered as 14 (30 minute) infusions over one year (3 infusions every other week the first month; monthly for the following 11 months)

CTLA4-Ig (Abatacept): Given as 30-minute IV infusion.

Reporting group title	Placebo

Reporting group description:

The placebo arm will receive 14 (30 minute) IV infusions (containing saline) given 3 times (every other week) the first month and monthly for the following 11 months.

Placebo: Saline given as 30-minute IV infusion

Serious adverse events	Abatacept IV Infusion	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 101 (1.98%)	3 / 111 (2.70%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other, specify			
subjects affected / exposed	2 / 101 (1.98%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Surgical and medical procedures - Other			
subjects affected / exposed	0 / 101 (0.00%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Nervous system disorders			
Stroke			
subjects affected / exposed	0 / 101 (0.00%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 101 (0.00%)	1 / 111 (0.90%)	
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	Abatacept IV Infusion	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	63 / 101 (62.38%)	77 / 111 (69.37%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasms benign, malignant and unspecified (including cysts and polyps cysts and polyps)			
subjects affected / exposed	4 / 101 (3.96%)	2 / 111 (1.80%)	
occurrences (all)	4	2	
Vascular disorders			
Vascular disorders			
subjects affected / exposed	2 / 101 (1.98%)	45 / 111 (40.54%)	
occurrences (all)	2	4	
Surgical and medical procedures			
Surgical and medical procedures			
subjects affected / exposed	9 / 101 (8.91%)	9 / 111 (8.11%)	
occurrences (all)	9	9	
Pregnancy, puerperium and perinatal conditions			
Pregnancy, puerperium and perinatal condition			
subjects affected / exposed	2 / 101 (1.98%)	0 / 111 (0.00%)	
occurrences (all)	5	0	
General disorders and administration site conditions			

General disorders and administration site conditions			
subjects affected / exposed	14 / 101 (13.86%)	20 / 111 (18.02%)	
occurrences (all)	17	24	
Immune system disorders			
Immune system disorders			
subjects affected / exposed	2 / 101 (1.98%)	3 / 111 (2.70%)	
occurrences (all)	2	3	
Reproductive system and breast disorders			
Reproductive system and breast disorders			
subjects affected / exposed	3 / 101 (2.97%)	3 / 111 (2.70%)	
occurrences (all)	7	3	
Respiratory, thoracic and mediastinal disorders			
Respiratory, thoracic and mediastinal disorders			
subjects affected / exposed	16 / 101 (15.84%)	15 / 111 (13.51%)	
occurrences (all)	25	22	
Psychiatric disorders			
Psychiatric disorders			
subjects affected / exposed	7 / 101 (6.93%)	9 / 111 (8.11%)	
occurrences (all)	82	13	
Investigations			
Investigations			
subjects affected / exposed	3 / 101 (2.97%)	10 / 111 (9.01%)	
occurrences (all)	5	12	
Injury, poisoning and procedural complications			
Injury, poisoning and procedural complications*			
subjects affected / exposed	15 / 101 (14.85%)	8 / 111 (7.21%)	
occurrences (all)	19	12	
Cardiac disorders			
Cardiac disorders			
subjects affected / exposed	3 / 101 (2.97%)	3 / 111 (2.70%)	
occurrences (all)	5	3	
Nervous system disorders			
Nervous system disorders			
subjects affected / exposed	13 / 101 (12.87%)	13 / 111 (11.71%)	
occurrences (all)	19	8	

Blood and lymphatic system disorders			
Blood and lymphatic system disorders			
subjects affected / exposed	3 / 101 (2.97%)	7 / 111 (6.31%)	
occurrences (all)	3	7	
Ear and labyrinth disorders			
Ear and labyrinth disorders			
subjects affected / exposed	2 / 101 (1.98%)	2 / 111 (1.80%)	
occurrences (all)	2	2	
Eye disorders			
Eye disorders			
subjects affected / exposed	5 / 101 (4.95%)	45 / 111 (40.54%)	
occurrences (all)	6	5	
Gastrointestinal disorders			
Gastrointestinal disorders			
subjects affected / exposed	22 / 101 (21.78%)	21 / 111 (18.92%)	
occurrences (all)	34	29	
Hepatobiliary disorders			
Hepatobiliary disorders			
subjects affected / exposed	2 / 101 (1.98%)	0 / 111 (0.00%)	
occurrences (all)	2	0	
Skin and subcutaneous tissue disorders			
Skin and subcutaneous tissue disorders			
subjects affected / exposed	17 / 101 (16.83%)	10 / 111 (9.01%)	
occurrences (all)	22	15	
Renal and urinary disorders			
Renal and urinary disorders			
subjects affected / exposed	3 / 101 (2.97%)	1 / 111 (0.90%)	
occurrences (all)	3	1	
Endocrine disorders			
Endocrine disorders			
subjects affected / exposed	3 / 101 (2.97%)	2 / 111 (1.80%)	
occurrences (all)	4	2	
Musculoskeletal and connective tissue disorders			
Musculoskeletal and connective tissue disorders			
subjects affected / exposed	19 / 101 (18.81%)	15 / 111 (13.51%)	
occurrences (all)	25	26	
Infections and infestations			

Infections and infestations subjects affected / exposed occurrences (all)	38 / 101 (37.62%) 82	45 / 111 (40.54%) 21	
Metabolism and nutrition disorders Metabolism and nutrition disorders subjects affected / exposed occurrences (all)	5 / 101 (4.95%) 6	45 / 111 (40.54%) 6	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 June 2017	Amendment made to clarify eligibility, refine outcome measurements, and expand the scope of the study's safety and funding considerations. Administrative Changes: Protocol title updated from version 5.0 (Feb 2016) to version 6.0 (June 2017). Expanded sponsor list, adding the National Institute of Allergy and Infectious Diseases (NIAID), National Institute of Child Health and Human Development (NICHD), and American Diabetes Association (ADA). Inclusion/Exclusion Criteria: Weight eligibility changed from ≥20 kg to ≥16 kg. Pregnancy exclusion criteria adjusted from "within 3 months" to "14 weeks" post-treatment for consistency. Primary Outcome Clarification: OGTT timing for diagnosing abnormal glucose tolerance (AGT) or diabetes updated. AGT or diabetes onset is now defined by the date of the confirmatory abnormal OGTT. Side Effects: Common: Infusion-related reactions (e.g., nausea, dizziness), respiratory and urinary infections. Uncommon: Immune system effects, such as increased risk of infections, low white blood cell counts, changes in heart rate, gastrointestinal irritation, and mood changes. Rare: Severe allergic reactions, possible increased infection risk, and potential long-term risks like cancer (though not observed in previous studies). Funding Sources: Updated to reflect expanded financial support, including the NIAID, NIDDK, and NICHD. Bristol-Myers Squibb continues to provide the abatacept medication.
25 July 2019	Amendment to focus on extending follow-up procedures, refining study power estimates, closing enrollment, and outlining interim analysis protocols to assess effectiveness and safety. Follow-up Studies: Subjects with confirmed abnormal glucose tolerance (AGT) will continue to be monitored for diabetes development and safety, even after the study concludes. Non-diabetic subjects will either be monitored through the TN01 study or offered follow-up in the TrialNet LIFT Study if diagnosed with diabetes. Study Power and Enrollment: The study is designed to have 80% power to detect a 40% risk reduction in AGT over six years. A total of 206 participants will be enrolled in a 1:1 ratio between groups. Enrollment closed on July 31, 2019, with follow-up continuing for two more years. Adjusted estimates suggest 64-70 AGT events will occur by study end, enabling hazard ratios between 0.496 to 0.512. Interim Monitoring Plan: Interim analyses will be conducted at equal intervals and reviewed by the Data and Safety Monitoring Board (DSMB). The first interim analysis is planned after 50% of events are observed. The trial could be prematurely terminated if significant effects are detected.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported