



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

| | | | |
|--|-------------------------|-------------------------|--|
| Blood and lymphatic system disorders Blood and lymphatic system disorders subjects affected / exposed occurrences (all) | 3 / 101 (2.97%) 3 | 7 / 111 (6.31%) 7 | |
| Ear and labyrinth disorders Ear and labyrinth disorders subjects affected / exposed occurrences (all) | 2 / 101 (1.98%) 2 | 2 / 111 (1.80%) 2 | |
| Eye disorders Eye disorders subjects affected / exposed occurrences (all) | 5 / 101 (4.95%) 6 | 45 / 111 (40.54%) 5 | |
| Gastrointestinal disorders Gastrointestinal disorders subjects affected / exposed occurrences (all) | 22 / 101 (21.78%) 34 | 21 / 111 (18.92%) 29 | |
| Hepatobiliary disorders Hepatobiliary disorders subjects affected / exposed occurrences (all) | 2 / 101 (1.98%) 2 | 0 / 111 (0.00%) 0 | |
| Skin and subcutaneous tissue disorders Skin and subcutaneous tissue disorders subjects affected / exposed occurrences (all) | 17 / 101 (16.83%) 22 | 10 / 111 (9.01%) 15 | |
| Renal and urinary disorders Renal and urinary disorders subjects affected / exposed occurrences (all) | 3 / 101 (2.97%) 3 | 1 / 111 (0.90%) 1 | |
| Endocrine disorders Endocrine disorders subjects affected / exposed occurrences (all) | 3 / 101 (2.97%) 4 | 2 / 111 (1.80%) 2 | |
| Musculoskeletal and connective tissue disorders Musculoskeletal and connective tissue disorders subjects affected / exposed occurrences (all) | 19 / 101 (18.81%) 25 | 15 / 111 (13.51%) 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 | <p>Amendment made to clarify eligibility, refine outcome measurements, and expand the scope of the study's safety and funding considerations.</p> <p>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).</p> <p>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.</p> <p>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.</p> <p>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).</p> <p>Funding Sources: Updated to reflect expanded financial support, including the NIAID, NIDDK, and NICHD. Bristol-Myers Squibb continues to provide the abatacept medication.</p> |
| 25 July 2019 | <p>Amendment to focus on extending follow-up procedures, refining study power estimates, closing enrollment, and outlining interim analysis protocols to assess effectiveness and safety.</p> <p>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.</p> <p>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.</p> <p>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.</p> |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported