Clinical trial results:
HYDROXYCHLOROQUINE FOR PREVENTION OF ABNORMAL GLUCOSE TOLERANCE AND DIABETES IN INDIVIDUALS AT-RISK FOR TYPE 1 DIABETES MELLITUS

Summary

EudraCT number	2018-000659-42
Trial protocol	SE GB IT FI
Global end of trial date	01 November 2022

Results information

Result version number	v1 (current)
This version publication date	03 August 2024
First version publication date	03 August 2024
Summary attachment (see zip file)	TN-22 Hydroxychloroquine in Stage 1 Type 1 Diabetes Final Study Report (TN22 Final Study Report.pdf)

Trial information

Trial identification

Sponsor protocol code	TN-22

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	TrialNet
Sponsor organisation address	3650 Spectrum Blvd , Tampa, United States, 33612
Public contact	Erica Perri, TrialNet Coordinating Center, 1 8133969543, Erica.Perri@epi.usf.edu
Scientific contact	Dr. Kevan Herold, Yale University , 1 203-785-6507, Kevan.Herold@yale.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	15 March 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 November 2022
Global end of trial reached?	Yes
Global end of trial date	01 November 2022
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy, safety and mode of action of hydroxychloroquine to prevent progression from Stage 1 to Stage 2 or Stage 3 of T1D. The primary objective is to determine whether intervention with hydroxychloroquine will prevent or delay the progression from Stage 1 (normal glucose tolerance) to Stage 2 (abnormal glucose tolerance) or Stage 3 (clinically overt T1D).

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	15 August 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	Australia: 20
Country: Number of subjects enrolled	Canada: 16
Country: Number of subjects enrolled	United States: 227
Country: Number of subjects enrolled	Sweden: 1
Country: Number of subjects enrolled	United Kingdom: 4
Country: Number of subjects enrolled	Finland: 3
Country: Number of subjects enrolled	Italy: 2
Worldwide total number of subjects	273
EEA total number of subjects	6

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)	147

Adolescents (12-17 years)	95
Adults (18-64 years)	31
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Potential study participants may be identified through the TrialNet Pathway to Prevention Study, although prior participation is not required.

Pre-assignment

Screening details:

A pre-screening visit may be required if diabetes-related autoantibody status needs to be assessed by a TrialNet contracted laboratory. Autoantibody-positive individuals are then further evaluated with the performance of OGTTs, additional blood tests, detailed medical history, and physical exam.

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	Hydroxychloroquine

Arm description: -

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

Dosage and administration details:

The target dose is 5 mg/kg/day (actual body weight), up to a maximum of 400mg/day, of hydroxychloroquine. The dose was chosen based on demonstrated safety and efficacy in other human autoimmune diseases. Dose by body weight will be calculated in 100mg increments and will be equivalent to ≤ 5 mg/kg/day averaged over a one-week period.

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 target dose is 5 mg/kg/day (actual body weight), up to a maximum of 400mg/day, of placebo. The dose was chosen based on demonstrated safety and efficacy in other human autoimmune diseases. Dose by body weight will be calculated in 100mg increments and will be equivalent to ≤ 5 mg/kg/day averaged over a one-week period.

Number of subjects in period 1	Hydroxychloroquine	Placebo
Started	183	90
Completed	168	77
Not completed	15	13
Consent withdrawn by subject	10	10
Lost to follow-up	5	3

Baseline characteristics

Reporting groups	
Reporting group title	Hydroxychloroquine
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Reporting group values	Hydroxychloroquine	Placebo	Total
Number of subjects	183	90	273
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)	96	51	147
Adolescents (12-17 years)	69	26	95
Adults (18-64 years)	18	13	31
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
median	11.7	10.9	
inter-quartile range (Q1-Q3)	8.3 to 15.6	8.2 to 15.7	-
Gender categorical Units: Subjects			
Female	61	33	94
Male	122	57	179

End points

End points reporting groups	
Reporting group title	Hydroxychloroquine
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Primary: Change From Treatment Assignment Glucose Tolerance to Abnormal Glucose Tolerance or Diabetes	
End point title	Change From Treatment Assignment Glucose Tolerance to Abnormal Glucose Tolerance or Diabetes
End point description:	
The primary outcome is the time in months from random treatment assignment to the development of confirmed abnormal glucose tolerance or clinical diabetes.	
End point type	Primary
End point timeframe:	
Glucose tolerance is measured every 6 months for up to 4 years	

End point values	Hydroxychloroquine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	168	83		
Units: Number of Subjects Analyzed				
number (not applicable)	168	83		

Statistical analyses

Statistical analysis title	Primary Analysis
Statistical analysis description:	
The primary outcome is the time in months from random treatment assignment to the development of confirmed abnormal glucose tolerance or clinical diabetes.	
Comparison groups	Hydroxychloroquine v Placebo
Number of subjects included in analysis	251
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.032 [1]
Method	t-test, 2-sided
Parameter estimate	Cox proportional hazard
Point estimate	0.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.56
upper limit	1.61

Notes:

[1] - The hazard ratio for the time development of AGT (Hydroxychloroquine vs. placebo) was 0.95 in two years (95% confidence interval, 0.56 to 1.61; P = non-significant by adjusted Cox proportional-hazards model).

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Duration of study from screening to last visit encompassing each participant's duration of time in the study no more than 4 years with an average duration prior to study termination of 23.9 months.

Adverse event reporting additional description:

Adverse Events were defined using the Common Terminology Criteria for Adverse Events (CTCAE)

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	3

Reporting groups

Reporting group title	Hydroxychloroquine

Reporting group description: -

Reporting group title	Placebo

Reporting group description: -

Serious adverse events	Hydroxychloroquine	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 183 (2.73%)	1 / 90 (1.11%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
General disorders and administration site conditions			
General disorders and administration site conditions			
subjects affected / exposed	1 / 183 (0.55%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylaxis			
subjects affected / exposed	1 / 183 (0.55%)	0 / 90 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	2 / 183 (1.09%)	0 / 90 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 183 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide attempt			
subjects affected / exposed	0 / 183 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychosis			
subjects affected / exposed	0 / 183 (0.00%)	1 / 90 (1.11%)	
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	1 / 183 (0.55%)	0 / 90 (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: 0 %

Non-serious adverse events	Hydroxychloroquine	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	125 / 183 (68.31%)	61 / 90 (67.78%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other			
subjects affected / exposed	1 / 183 (0.55%)	1 / 90 (1.11%)	
occurrences (all)	1	1	
Skin papilloma			
subjects affected / exposed	0 / 183 (0.00%)	3 / 90 (3.33%)	
occurrences (all)	0	3	
Surgical and medical procedures			
Surgical and medical procedures - Other			

subjects affected / exposed	10 / 183 (5.46%)	3 / 90 (3.33%)	
occurrences (all)	12	4	
General disorders and administration site conditions			
Fever hallucinations			
subjects affected / exposed	5 / 183 (2.73%)	0 / 90 (0.00%)	
occurrences (all)	7	0	
Flu like symptoms			
subjects affected / exposed	2 / 183 (1.09%)	1 / 90 (1.11%)	
occurrences (all)	2	1	
General disorders and administration site conditions			
subjects affected / exposed	3 / 183 (1.64%)	4 / 90 (4.44%)	
occurrences (all)	3	5	
Pain			
subjects affected / exposed	2 / 183 (1.09%)	0 / 90 (0.00%)	
occurrences (all)	2	0	
Immune system disorders			
Allergic reaction			
subjects affected / exposed	2 / 183 (1.09%)	2 / 90 (2.22%)	
occurrences (all)	2	2	
Anaphylaxis			
subjects affected / exposed	1 / 183 (0.55%)	0 / 90 (0.00%)	
occurrences (all)	1	0	
Autoimmune disorder			
subjects affected / exposed	1 / 183 (0.55%)	0 / 90 (0.00%)	
occurrences (all)	1	0	
Immune system disorders - Other			
subjects affected / exposed	0 / 183 (0.00%)	1 / 90 (1.11%)	
occurrences (all)	0	1	
Reproductive system and breast disorders			
Dysmenorrhea			
subjects affected / exposed	1 / 183 (0.55%)	1 / 90 (1.11%)	
occurrences (all)	1	1	
Respiratory, thoracic and mediastinal disorders			

Allergic Rhinitis				
subjects affected / exposed	5 / 183 (2.73%)	2 / 90 (2.22%)		
occurrences (all)	5	2		
Bronchospasm				
subjects affected / exposed	1 / 183 (0.55%)	0 / 90 (0.00%)		
occurrences (all)	1	0		
Cough				
subjects affected / exposed	6 / 183 (3.28%)	2 / 90 (2.22%)		
occurrences (all)	6	2		
Dyspnea				
subjects affected / exposed	1 / 183 (0.55%)	0 / 90 (0.00%)		
occurrences (all)	1	0		
Epistaxis				
subjects affected / exposed	3 / 183 (1.64%)	0 / 90 (0.00%)		
occurrences (all)	4	0		
Nasal congestion				
subjects affected / exposed	2 / 183 (1.09%)	1 / 90 (1.11%)		
occurrences (all)	2	1		
Pleuritic pain				
subjects affected / exposed	0 / 183 (0.00%)	1 / 90 (1.11%)		
occurrences (all)	0	1		
Respiratory, thoracic and mediastinal disorders - Other				
subjects affected / exposed	6 / 183 (3.28%)	3 / 90 (3.33%)		
occurrences (all)	6	6		
Sinus disorder				
subjects affected / exposed	1 / 183 (0.55%)	0 / 90 (0.00%)		
occurrences (all)	1	0		
Sleep apnea				
subjects affected / exposed	1 / 183 (0.55%)	0 / 90 (0.00%)		
occurrences (all)	1	0		
Sore throat				
subjects affected / exposed	2 / 183 (1.09%)	3 / 90 (3.33%)		
occurrences (all)	2	4		
Wheezing				

subjects affected / exposed	3 / 183 (1.64%)	1 / 90 (1.11%)	
occurrences (all)	4	1	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	3 / 183 (1.64%)	0 / 90 (0.00%)	
occurrences (all)	3	0	
Insomnia			
subjects affected / exposed	0 / 183 (0.00%)	1 / 90 (1.11%)	
occurrences (all)	0	1	
Psychiatric disorders - Other			
subjects affected / exposed	4 / 183 (2.19%)	9 / 90 (10.00%)	
occurrences (all)	5	4	
Depression			
subjects affected / exposed	0 / 183 (0.00%)	1 / 90 (1.11%)	
occurrences (all)	0	1	
Psychosis			
subjects affected / exposed	0 / 183 (0.00%)	1 / 90 (1.11%)	
occurrences (all)	0	1	
Suicide attempt			
subjects affected / exposed	0 / 183 (0.00%)	1 / 90 (1.11%)	
occurrences (all)	0	1	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 183 (1.09%)	0 / 90 (0.00%)	
occurrences (all)	2	0	
Aspartate aminotransferase increased			
subjects affected / exposed	3 / 183 (1.64%)	0 / 90 (0.00%)	
occurrences (all)	4	0	
Creatine increased			
subjects affected / exposed	4 / 183 (2.19%)	0 / 90 (0.00%)	
occurrences (all)	4	0	
Investigations - Other			
subjects affected / exposed	6 / 183 (3.28%)	3 / 90 (3.33%)	
occurrences (all)	6	3	
Lymphocyte count decreased			

subjects affected / exposed	1 / 183 (0.55%)	0 / 90 (0.00%)	
occurrences (all)	1	0	
Neutrophil count decreased			
subjects affected / exposed	32 / 183 (17.49%)	26 / 90 (28.89%)	
occurrences (all)	56	41	
Weight gain			
subjects affected / exposed	0 / 183 (0.00%)	1 / 90 (1.11%)	
occurrences (all)	0	1	
Weight loss			
subjects affected / exposed	3 / 183 (1.64%)	1 / 90 (1.11%)	
occurrences (all)	3	1	
White blood cell decreased			
subjects affected / exposed	4 / 183 (2.19%)	4 / 90 (4.44%)	
occurrences (all)	4	5	
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	1 / 183 (0.55%)	1 / 90 (1.11%)	
occurrences (all)	1	1	
Fall			
subjects affected / exposed	3 / 183 (1.64%)	0 / 90 (0.00%)	
occurrences (all)	4	0	
Fracture			
subjects affected / exposed	8 / 183 (4.37%)	3 / 90 (3.33%)	
occurrences (all)	8	3	
Injury, poisoning and procedural complications - Other			
subjects affected / exposed	8 / 183 (4.37%)	5 / 90 (5.56%)	
occurrences (all)	19	5	
Venous injury			
subjects affected / exposed	0 / 183 (0.00%)	1 / 90 (1.11%)	
occurrences (all)	0	1	
Cardiac disorders			
Cardiac Disorders			
subjects affected / exposed	1 / 183 (0.55%)	0 / 90 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			

Concentration impairment			
subjects affected / exposed	1 / 183 (0.55%)	0 / 90 (0.00%)	
occurrences (all)	1	0	
Headache			
subjects affected / exposed	5 / 183 (2.73%)	3 / 90 (3.33%)	
occurrences (all)	7	4	
Nervous system disorders - Other			
subjects affected / exposed	2 / 183 (1.09%)	0 / 90 (0.00%)	
occurrences (all)	2	0	
Paresthesia			
subjects affected / exposed	1 / 183 (0.55%)	0 / 90 (0.00%)	
occurrences (all)	1	0	
Presyncope			
subjects affected / exposed	2 / 183 (1.09%)	0 / 90 (0.00%)	
occurrences (all)	2	0	
Syncope			
subjects affected / exposed	2 / 183 (1.09%)	0 / 90 (0.00%)	
occurrences (all)	2	0	
Vasovagal reaction			
subjects affected / exposed	4 / 183 (2.19%)	1 / 90 (1.11%)	
occurrences (all)	6	0	
Blood and lymphatic system disorders			
Blood and lymphatic system disorders			
subjects affected / exposed	4 / 183 (2.19%)	0 / 90 (0.00%)	
occurrences (all)	5	0	
Lymph node pain			
subjects affected / exposed	1 / 183 (0.55%)	3 / 90 (3.33%)	
occurrences (all)	1	0	
Ear and labyrinth disorders			
Ear and labyrinth disorders			
subjects affected / exposed	1 / 183 (0.55%)	0 / 90 (0.00%)	
occurrences (all)	1	0	
ear pain			
subjects affected / exposed	1 / 183 (0.55%)	0 / 90 (0.00%)	
occurrences (all)	1	0	
hearing impaired			

subjects affected / exposed	1 / 183 (0.55%)	0 / 90 (0.00%)	
occurrences (all)	1	0	
Middle ear inflammation			
subjects affected / exposed	1 / 183 (0.55%)	0 / 90 (0.00%)	
occurrences (all)	1	0	
vertigo			
subjects affected / exposed	1 / 183 (0.55%)	0 / 90 (0.00%)	
occurrences (all)	2	0	
Eye disorders			
Blurred vision			
subjects affected / exposed	1 / 183 (0.55%)	0 / 90 (0.00%)	
occurrences (all)	1	0	
Eye Disorders			
subjects affected / exposed	2 / 183 (1.09%)	1 / 90 (1.11%)	
occurrences (all)	6	1	
Vision decreased			
subjects affected / exposed	1 / 183 (0.55%)	0 / 90 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 183 (1.09%)	2 / 90 (2.22%)	
occurrences (all)	2	2	
Bloating			
subjects affected / exposed	1 / 183 (0.55%)	0 / 90 (0.00%)	
occurrences (all)	1	0	
Constipation			
subjects affected / exposed	1 / 183 (0.55%)	0 / 90 (0.00%)	
occurrences (all)	1	1	
Diarrhea			
subjects affected / exposed	5 / 183 (2.73%)	1 / 90 (1.11%)	
occurrences (all)	5	1	
Esophagitis			
subjects affected / exposed	0 / 183 (0.00%)	2 / 90 (2.22%)	
occurrences (all)	0	0	
Flatulence			

subjects affected / exposed	2 / 183 (1.09%)	0 / 90 (0.00%)	
occurrences (all)	2	0	
Gastritis			
subjects affected / exposed	1 / 183 (0.55%)	0 / 90 (0.00%)	
occurrences (all)	1	0	
Gastroesophageal reflux disease			
subjects affected / exposed	1 / 183 (0.55%)	0 / 90 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
subjects affected / exposed	3 / 183 (1.64%)	4 / 90 (4.44%)	
occurrences (all)	3	5	
Nausea			
subjects affected / exposed	3 / 183 (1.64%)	0 / 90 (0.00%)	
occurrences (all)	3	0	
Toothache			
subjects affected / exposed	0 / 183 (0.00%)	1 / 90 (1.11%)	
occurrences (all)	1	1	
Vomiting			
subjects affected / exposed	6 / 183 (3.28%)	0 / 90 (0.00%)	
occurrences (all)	6	0	
Skin and subcutaneous tissue disorders			
Eczema			
subjects affected / exposed	3 / 183 (1.64%)	2 / 90 (2.22%)	
occurrences (all)	3	2	
Rash acneiform			
subjects affected / exposed	1 / 183 (0.55%)	0 / 90 (0.00%)	
occurrences (all)	5	0	
Rash maculo-papular			
subjects affected / exposed	5 / 183 (2.73%)	0 / 90 (0.00%)	
occurrences (all)	5	0	
kin and subcutaneous tissue disorders - Other			
subjects affected / exposed	16 / 183 (8.74%)	5 / 90 (5.56%)	
occurrences (all)	19	7	
Skin hyperpigmentation			

subjects affected / exposed	1 / 183 (0.55%)	0 / 90 (0.00%)	
occurrences (all)	1	0	
Urticaria			
subjects affected / exposed	0 / 183 (0.00%)	1 / 90 (1.11%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Renal and urinary disorders - Other			
subjects affected / exposed	0 / 183 (0.00%)	1 / 90 (1.11%)	
occurrences (all)	0	1	
Urinary frequency			
subjects affected / exposed	1 / 183 (0.55%)	0 / 90 (0.00%)	
occurrences (all)	1	0	
Endocrine disorders			
Endocrine disorders			
subjects affected / exposed	1 / 183 (0.55%)	1 / 90 (1.11%)	
occurrences (all)	1	1	
Musculoskeletal and connective tissue disorders			
Avascular necrosis			
subjects affected / exposed	1 / 183 (0.55%)	0 / 90 (0.00%)	
occurrences (all)	1	0	
Back pain			
subjects affected / exposed	0 / 183 (0.00%)	2 / 90 (2.22%)	
occurrences (all)	0	2	
Bone pain			
subjects affected / exposed	1 / 183 (0.55%)	1 / 90 (1.11%)	
occurrences (all)	1	1	
Musculoskeletal and connective tissue disorder - Other			
subjects affected / exposed	6 / 183 (3.28%)	1 / 90 (1.11%)	
occurrences (all)	8	1	
Neck pain			
subjects affected / exposed	1 / 183 (0.55%)	0 / 90 (0.00%)	
occurrences (all)	1	0	
Pain in extremity			
subjects affected / exposed	1 / 183 (0.55%)	1 / 90 (1.11%)	
occurrences (all)	1	1	
Infections and infestations			

Appendicitis			
subjects affected / exposed	1 / 183 (0.55%)	0 / 90 (0.00%)	
occurrences (all)	1	0	
Bronchial infection			
subjects affected / exposed	2 / 183 (1.09%)	0 / 90 (0.00%)	
occurrences (all)	1	0	
Enterocolitis infectious			
subjects affected / exposed	0 / 183 (0.00%)	1 / 90 (1.11%)	
occurrences (all)	0	1	
Esophageal infection			
subjects affected / exposed	1 / 183 (0.55%)	0 / 90 (0.00%)	
occurrences (all)	1	0	
Eye infection			
subjects affected / exposed	1 / 183 (0.55%)	0 / 90 (0.00%)	
occurrences (all)	1	0	
Gum infection			
subjects affected / exposed	1 / 183 (0.55%)	0 / 90 (0.00%)	
occurrences (all)	1	0	
Herpes simplex reactivation			
subjects affected / exposed	3 / 183 (1.64%)	0 / 90 (0.00%)	
occurrences (all)	4	0	
Infections and infestations - Other			
subjects affected / exposed	29 / 183 (15.85%)	13 / 90 (14.44%)	
occurrences (all)	33	14	
Nail infection			
subjects affected / exposed	1 / 183 (0.55%)	0 / 90 (0.00%)	
occurrences (all)	1	0	
Otitis media			
subjects affected / exposed	4 / 183 (2.19%)	5 / 90 (5.56%)	
occurrences (all)	4	5	
Penile infection			
subjects affected / exposed	0 / 183 (0.00%)	2 / 90 (2.22%)	
occurrences (all)	0	2	
Pharyngitis			
subjects affected / exposed	3 / 183 (1.64%)	4 / 90 (4.44%)	
occurrences (all)	3	4	

Sinusitis			
subjects affected / exposed	11 / 183 (6.01%)	5 / 90 (5.56%)	
occurrences (all)	13	5	
Skin infection			
subjects affected / exposed	3 / 183 (1.64%)	1 / 90 (1.11%)	
occurrences (all)	3	1	
Soft tissue infection			
subjects affected / exposed	0 / 183 (0.00%)	1 / 90 (1.11%)	
occurrences (all)	0	1	
Tooth infection			
subjects affected / exposed	1 / 183 (0.55%)	1 / 90 (1.11%)	
occurrences (all)	1	1	
Upper respiratory infection			
subjects affected / exposed	16 / 183 (8.74%)	7 / 90 (7.78%)	
occurrences (all)	21	10	
Wound infection			
subjects affected / exposed	0 / 183 (0.00%)	1 / 90 (1.11%)	
occurrences (all)	0	1	
Blood bilirubin increased			
subjects affected / exposed	3 / 183 (1.64%)	3 / 90 (3.33%)	
occurrences (all)	3	6	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 183 (0.55%)	0 / 90 (0.00%)	
occurrences (all)	1	0	
Hyponatremia			
subjects affected / exposed	4 / 183 (2.19%)	3 / 90 (3.33%)	
occurrences (all)	4	3	
Metabolism and nutrition disorders - Other			
subjects affected / exposed	1 / 183 (0.55%)	0 / 90 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 February 2019	Investigator emergent unmasking is permitted without the need for approval by TrialNet administration. Inclusion of lang auge that permits different consenting requirements based off of local regulatory requirements.
22 March 2021	Removal of TN01 participation as entry criteria. Addition of pregnancy or breastfeeding exclusion criteria for clarity. OGTT window correction for clarity. Change in stopping criteria was implemented and implemented site-wide for consistency across all sites. Addition of a -2 pre-screening visit for those needing testing for autoantibodies.

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.

Interim analysis completed prompted the DSMB's decision to terminate the protocol early limiting the originally planned follow up period for participants.

Notes: