



## Clinical trial results:

### Anti-CD3 mAb (teplizumab) for prevention of diabetes in relatives at-risk for Type 1 diabetes mellitus

#### Summary

EudraCT number	2013-002248-98
Trial protocol	DE GB IT
Global end of trial date	30 June 2019

#### Results information

Result version number	v1 (current)
This version publication date	15 December 2022
First version publication date	15 December 2022
Summary attachment (see zip file)	TN10 End of Study Report (TN10 Final Study Report 27Aug2019.docx)

#### Trial information

##### Trial identification

Sponsor protocol code	TN-10
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01030861
WHO universal trial number (UTN)	-
Other trial identifiers	IND: 102,629

Notes:

##### Sponsors

Sponsor organisation name	TrialNet
Sponsor organisation address	3650 Spectrum Boulevard, Suite 100, Tampa, United States, 33612
Public contact	Erica Perri, TrialNet Coordinating Center, 1 813396-9543, Erica.Perri@epi.usf.edu
Scientific contact	Erica Perri, 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	13 November 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	13 November 2018
Global end of trial reached?	Yes
Global end of trial date	30 June 2019
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 at-risk subjects with teplizumab results in a delay or prevention of type 1 diabetes mellitus (T1DM).

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 August 2010
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: 3
Country: Number of subjects enrolled	United States: 69
Country: Number of subjects enrolled	Canada: 4
Worldwide total number of subjects	76
EEA total number of subjects	3

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)	24
Adolescents (12-17 years)	31
Adults (18-64 years)	21
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

Participants were recruited from the TrialNet Natural History Study (TN01) and thus a relative of a proband with T1D.

### Pre-assignment

Screening details:

This study included participants, age 8 and older, with (1) Relatives of T1DM proband, (2) two or more diabetes-related autoantibodies present, and (3) Abnormal OGTT performed within 7 weeks prior to randomization.

### 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
<b>Arm title</b>	Teplizumab
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Teplizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Infusion

Dosage and administration details:

Participants received a 14-day course of teplizumab consisting of daily IV doses of 51 micrograms/meter squared ( $\mu\text{g}/\text{m}^2$ ), 103  $\mu\text{g}/\text{m}^2$ , 207  $\mu\text{g}/\text{m}^2$ , and 413  $\mu\text{g}/\text{m}^2$  on Study Days 0–3, respectively, and one dose of 826  $\mu\text{g}/\text{m}^2$  on each of Study Days 4–13. The total dose for a 14-day course is approximately 9034  $\mu\text{g}/\text{m}^2$ . For subjects weighing 70 kg and having a body surface area (BSA) of 1.92  $\text{m}^2$ , this dosing schedule delivers ~18 milligrams (mg) of teplizumab.

<b>Arm title</b>	Placebo
Arm description: -	
Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Infusion

Dosage and administration details:

Participants received a 14-day course of IV placebo only.

<b>Number of subjects in period 1</b>	Teplizumab	Placebo
Started	44	32
Completed	44	32

## Baseline characteristics

### Reporting groups

Reporting group title	Teplizumab
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Reporting group values	Teplizumab	Placebo	Total
Number of subjects	44	32	76
Age categorical Units: Subjects			
Age continuous Units: years median inter-quartile range (Q1-Q3)	44 8.5 to 49.5	32 8.6 to 45.0	-
Gender categorical Units: Subjects			
Female	19	15	34
Male	25	17	42

## End points

### End points reporting groups

Reporting group title	Teplizumab
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

### Primary: Rate of New Diabetes Per Year

End point title	Rate of New Diabetes Per Year
End point description: Rate at which criteria are met for diabetes onset as defined by the American Diabetes Association (ADA) based on glucose testing or the presence of unequivocal hyperglycemia with acute metabolic decompensation. Relatives of patients with type 1 diabetes who did not have diabetes but were at high risk for development of clinical disease.	
End point type	Primary
End point timeframe: During follow-up, median 745 days, range 74 to 2683.	

End point values	Teplizumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	32		
Units: N diabetes per 100 participant years				
number (not applicable)	43	32		

### Statistical analyses

Statistical analysis title	Primary Analysis
Statistical analysis description: Analyses of study data were conducted to address the primary and secondary objectives of the trial, other stated objectives, and other interrelationships among elements of study data of interest to the investigators and of relevance to the objectives of the study. Additional analyses may also entail the use of data from other studies in combination with data from this study. Likewise, data from this study may be used in combination with data from another study to address objectives of that study	
Comparison groups	Teplizumab v Placebo
Number of subjects included in analysis	76
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.006 <sup>[1]</sup>
Method	t-test, 2-sided
Parameter estimate	Cox proportional hazard
Point estimate	0.41

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.22
upper limit	0.78

Notes:

[1] - The hazard ratio for the diagnosis of type 1 diabetes (teplizumab vs. placebo) was 0.41 (95% confidence interval, 0.22 to 0.78; P = 0.006 by adjusted Cox proportional-hazards model).

### Secondary: Number of Participants With Adverse Events

End point title	Number of Participants With Adverse Events
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End point description:

End point type	Secondary
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End point timeframe:

Baseline Visit to Diagnosis of Type 1 Diabetes median 745 days, range 74 to 2683

End point values	Teplizumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	32		
Units: 76	43	23		

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse Event data were collected for individual participants, beginning with the Baseline Visit and ending with the documented Diagnosis of Type 1 Diabetes (the primary study endpoint), median 745 days, range 74 to 2683.

Adverse event reporting additional description:

All adverse event information can be found in the attached TN10 Final Study Report.

Assessment type	Systematic
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### Dictionary used

Dictionary name	CTCAE
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Dictionary version	3
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### Reporting groups

Reporting group title	Teplizumab
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Reporting group description: -	
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Reporting group title	Placebo
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Reporting group description: -	
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Serious adverse events	Teplizumab	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 44 (18.18%)	1 / 32 (3.13%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 44 (2.27%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastroenteritis			
subjects affected / exposed	1 / 44 (2.27%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstruction gastric			
subjects affected / exposed	1 / 44 (2.27%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstruction, GU			



subjects affected / exposed	0 / 44 (0.00%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Infection - Skin			
subjects affected / exposed	1 / 44 (2.27%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Fracture			
subjects affected / exposed	1 / 44 (2.27%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest Wall Pain			
subjects affected / exposed	1 / 44 (2.27%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	1 / 44 (2.27%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Infection with normal ANC or Grade 1 or 2 neutrophils			
subjects affected / exposed	1 / 44 (2.27%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection with unknown ANC			
subjects affected / exposed	1 / 44 (2.27%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

<b>Non-serious adverse events</b>	Teplizumab	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	43 / 44 (97.73%)	23 / 32 (71.88%)	
Vascular disorders			
Thrombosis			
subjects affected / exposed	0 / 44 (0.00%)	1 / 32 (3.13%)	
occurrences (all)	0	1	
Phlebitis (including superficial thrombosis)			
subjects affected / exposed	0 / 44 (0.00%)	1 / 32 (3.13%)	
occurrences (all)	0	2	
General disorders and administration site conditions			
fatigue			
subjects affected / exposed	1 / 44 (2.27%)	0 / 32 (0.00%)	
occurrences (all)	1	0	
Fever (in the absence of neutropenia, where neutropenia is defined as ANC <1.0 x 10e9/L)			
subjects affected / exposed	2 / 44 (4.55%)	0 / 32 (0.00%)	
occurrences (all)	3	0	
Flu-like syndrome			
subjects affected / exposed	2 / 44 (4.55%)	0 / 32 (0.00%)	
occurrences (all)	7	0	
Pain			
subjects affected / exposed	10 / 44 (22.73%)	4 / 32 (12.50%)	
occurrences (all)	13	6	
Weight gain			
subjects affected / exposed	1 / 44 (2.27%)	0 / 32 (0.00%)	
occurrences (all)	1	0	
Immune system disorders			
Allergic reaction/hypersensitivity (including drug fever)			
subjects affected / exposed	3 / 44 (6.82%)	0 / 32 (0.00%)	
occurrences (all)	4	0	
Allergic rhinitis (including sneezing, nasal stuffiness)			
subjects affected / exposed	2 / 44 (4.55%)	0 / 32 (0.00%)	
occurrences (all)	2	0	
Alpha-Gal Allergy			

subjects affected / exposed	1 / 44 (2.27%)	0 / 32 (0.00%)	
occurrences (all)	1	0	
Cytokine release syndrome/acute infusion reaction			
subjects affected / exposed	1 / 44 (2.27%)	0 / 32 (0.00%)	
occurrences (all)	3	0	
Reproductive system and breast disorders			
Breast function/lactation			
subjects affected / exposed	0 / 44 (0.00%)	1 / 32 (3.13%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Bronchospasm, wheezing			
subjects affected / exposed	4 / 44 (9.09%)	0 / 32 (0.00%)	
occurrences (all)	4	0	
Cough			
subjects affected / exposed	3 / 44 (6.82%)	0 / 32 (0.00%)	
occurrences (all)	5	0	
Dyspnea (shortness of breath)			
subjects affected / exposed	2 / 44 (4.55%)	0 / 32 (0.00%)	
occurrences (all)	2	0	
Hypoxia			
subjects affected / exposed	1 / 44 (2.27%)	0 / 32 (0.00%)	
occurrences (all)	1	0	
Nasal cavity/paranasal sinus reactions			
subjects affected / exposed	2 / 44 (4.55%)	0 / 32 (0.00%)	
occurrences (all)	4	0	
Pneumonitis/pulmonary infiltrates			
subjects affected / exposed	1 / 44 (2.27%)	0 / 32 (0.00%)	
occurrences (all)	1	0	
Pulmonary/Upper Respiratory Infection			
subjects affected / exposed	4 / 44 (9.09%)	1 / 32 (3.13%)	
occurrences (all)	5	2	
Cardiac disorders			
Hypertension			

subjects affected / exposed	2 / 44 (4.55%)	1 / 32 (3.13%)	
occurrences (all)	2	1	
Arrhythmia			
subjects affected / exposed	0 / 44 (0.00%)	1 / 32 (3.13%)	
occurrences (all)	0	1	
Cardiac Arrhythmia			
subjects affected / exposed	0 / 44 (0.00%)	1 / 32 (3.13%)	
occurrences (all)	0	1	
Hypotension			
subjects affected / exposed	0 / 44 (0.00%)	1 / 32 (3.13%)	
occurrences (all)	0	1	
Palpitations			
subjects affected / exposed	0 / 44 (0.00%)	1 / 32 (3.13%)	
occurrences (all)	0	2	
Nervous system disorders			
Mood alteration			
subjects affected / exposed	2 / 44 (4.55%)	2 / 32 (6.25%)	
occurrences (all)	4	6	
Cognitive Disturbance			
subjects affected / exposed	1 / 44 (2.27%)	0 / 32 (0.00%)	
occurrences (all)	1	0	
Neuropathy: motor			
subjects affected / exposed	1 / 44 (2.27%)	1 / 32 (3.13%)	
occurrences (all)	2	2	
Seizure			
subjects affected / exposed	1 / 44 (2.27%)	0 / 32 (0.00%)	
occurrences (all)	1	0	
Neuropathy: sensory			
subjects affected / exposed	0 / 44 (0.00%)	1 / 32 (3.13%)	
occurrences (all)	0	2	
Personality/behavioral			
subjects affected / exposed	0 / 44 (0.00%)	1 / 32 (3.13%)	
occurrences (all)	0	1	
Syncope (fainting)			
subjects affected / exposed	0 / 44 (0.00%)	1 / 32 (3.13%)	
occurrences (all)	0	1	

Blood and lymphatic system disorders Lymphopenia subjects affected / exposed occurrences (all)  hemoglobin subjects affected / exposed occurrences (all)  leukocytes (Total WBC) subjects affected / exposed occurrences (all)  Leukocytes subjects affected / exposed occurrences (all)  Neutrophils/granulocytes (ANC/AGC) subjects affected / exposed occurrences (all)	31 / 44 (70.45%)	2 / 32 (6.25%)	
	74	5	
	2 / 44 (4.55%)	0 / 32 (0.00%)	
	6	0	
	8 / 44 (18.18%)	0 / 32 (0.00%)	
	13	0	
Ear and labyrinth disorders Otitis, middle ear (non-infectious) subjects affected / exposed occurrences (all)	2 / 44 (4.55%)	0 / 32 (0.00%)	
	2	0	
	4 / 44 (9.09%)	1 / 32 (3.13%)	
	5	6	
	0 / 44 (0.00%)	1 / 32 (3.13%)	
	0	2	
Eye disorders Vitreous hemorrhage subjects affected / exposed occurrences (all)  Ocular surface disease subjects affected / exposed occurrences (all)  Conjunctivitis subjects affected / exposed occurrences (all)  eyelid disfunction subjects affected / exposed occurrences (all)	1 / 44 (2.27%)	0 / 32 (0.00%)	
	1	0	
	2 / 44 (4.55%)	1 / 32 (3.13%)	
	4	2	
	0 / 44 (0.00%)	1 / 32 (3.13%)	
	0	1	
Gastrointestinal disorders dental periodontal disease subjects affected / exposed occurrences (all)	0 / 44 (0.00%)	1 / 32 (3.13%)	
	0	2	
	1 / 44 (2.27%)	0 / 32 (0.00%)	
	1	0	

Diarrhoea			
subjects affected / exposed	2 / 44 (4.55%)	0 / 32 (0.00%)	
occurrences (all)	2	0	
stomach pain			
subjects affected / exposed	1 / 44 (2.27%)	0 / 32 (0.00%)	
occurrences (all)	2	0	
heartburn/dyspepsia			
subjects affected / exposed	1 / 44 (2.27%)	0 / 32 (0.00%)	
occurrences (all)	2	0	
Nausea			
subjects affected / exposed	2 / 44 (4.55%)	1 / 32 (3.13%)	
occurrences (all)	3	2	
Obstruction, GI			
subjects affected / exposed	1 / 44 (2.27%)	0 / 32 (0.00%)	
occurrences (all)	3	0	
Vomiting			
subjects affected / exposed	2 / 44 (4.55%)	2 / 32 (6.25%)	
occurrences (all)	3	3	
Dental: teeth			
subjects affected / exposed	0 / 44 (0.00%)	2 / 32 (6.25%)	
occurrences (all)	0	4	
Dental: teeth development			
subjects affected / exposed	0 / 44 (0.00%)	1 / 32 (3.13%)	
occurrences (all)	0	1	
Hepatobiliary disorders			
Elevated Bilirubin			
subjects affected / exposed	0 / 44 (0.00%)	1 / 32 (3.13%)	
occurrences (all)	0	2	
Skin and subcutaneous tissue disorders			
Folliculitis			
subjects affected / exposed	1 / 44 (2.27%)	0 / 32 (0.00%)	
occurrences (all)	1	0	
Injection site reaction/extravasation changes			
subjects affected / exposed	1 / 44 (2.27%)	0 / 32 (0.00%)	
occurrences (all)	1	0	
Pruritus/itching			

subjects affected / exposed	4 / 44 (9.09%)	1 / 32 (3.13%)	
occurrences (all)	5	2	
Rash/desquamation			
subjects affected / exposed	13 / 44 (29.55%)	0 / 32 (0.00%)	
occurrences (all)	41	0	
Rash: erythema multiforme (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis)			
subjects affected / exposed	2 / 44 (4.55%)	0 / 32 (0.00%)	
occurrences (all)	2	0	
Rash: hand-foot skin reaction			
subjects affected / exposed	1 / 44 (2.27%)	0 / 32 (0.00%)	
occurrences (all)	2	0	
Urticaria (hives, welts, wheals)			
subjects affected / exposed	1 / 44 (2.27%)	0 / 32 (0.00%)	
occurrences (all)	2	0	
Bruising (in absence of Grade 3 or 4 thrombocytopenia)			
subjects affected / exposed	0 / 44 (0.00%)	2 / 32 (6.25%)	
occurrences (all)	0	4	
Nail changes			
subjects affected / exposed	0 / 44 (0.00%)	1 / 32 (3.13%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Kidney Stones			
subjects affected / exposed	1 / 44 (2.27%)	0 / 32 (0.00%)	
occurrences (all)	1	0	
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	1 / 44 (2.27%)	0 / 32 (0.00%)	
occurrences (all)	1	0	
Hypoglycaemia			
subjects affected / exposed	0 / 44 (0.00%)	2 / 32 (6.25%)	
occurrences (all)	0	3	
Musculoskeletal and connective tissue disorders			
Fracture			

subjects affected / exposed occurrences (all)	3 / 44 (6.82%) 6	1 / 32 (3.13%) 1	
Joint Pain subjects affected / exposed occurrences (all)	1 / 44 (2.27%) 1	3 / 32 (9.38%) 5	
Myositis (inflammation/damage of muscle) subjects affected / exposed occurrences (all)	1 / 44 (2.27%) 4	0 / 32 (0.00%) 0	
Infections and infestations Infection with Normal ANC subjects affected / exposed occurrences (all)	12 / 44 (27.27%) 34	4 / 32 (12.50%) 13	
Infection with unknown ANC subjects affected / exposed occurrences (all)	5 / 44 (11.36%) 9	1 / 32 (3.13%) 3	
Metabolism and nutrition disorders ALT, SGPT (serum glutamic pyruvic transaminase) subjects affected / exposed occurrences (all)	2 / 44 (4.55%) 2	1 / 32 (3.13%) 1	
AST, SGOT (serum glutamic oxaloacetic transaminase) subjects affected / exposed occurrences (all)	1 / 44 (2.27%) 1	1 / 32 (3.13%) 1	
Bilirubin (hyperbilirubinemia) subjects affected / exposed occurrences (all)	0 / 44 (0.00%) 0	2 / 32 (6.25%) 3	
Cholesterol, serum-high (hypercholesteremia) subjects affected / exposed occurrences (all)	0 / 44 (0.00%) 0	1 / 32 (3.13%) 1	



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 June 2010	Addition of language to include Research Ethics Board (REB) responsibilities, pursuant to international sites.
25 June 2012	Removal of Section 3.9.1 Staggered Enrollment.
17 September 2012	a. Addition of updated information from results of related trials. b. Clarification of enrollment criteria related to age. c. Addition of ZnT8 autoantibodies for use toward eligibility. d. Added IgM and EBNA to reflect current monitoring procedures for infections. e. Added eosinophilia and language regarding herpes virus infection related to revised IB (dated 12/22/2011).
25 June 2014	a. Modification to eligibility criteria i. Individuals < 18 years of age may have single abnormal OGTT. ii. Individuals 18 years or older must have two consecutive abnormal OGTTs. iii. Addition of AST or ALT > 1.5 ULN as exclusionary. iv. Addition of language to allow enrollment of those with Gilbert's syndrome. b. Modifications to sample size, accrual period, study power, and study duration. c. Clarifications to drug administration and dosage calculations. d. Clarifications for drug withholding criteria in subjects with Gilbert's Syndrome. e. Clarifications related to primary and secondary analyses.

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported

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### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/31180194>