



Clinical trial results:

A Phase 3, Randomized, Double-Blind, Multinational, Placebo-Controlled Study to Evaluate Efficacy and Safety of Teplizumab (PRV-031), a Humanized, FcR Non-Binding, anti-CD3 Monoclonal Antibody, in Children and Adolescents with Newly Diagnosed Type 1 Diabetes (T1D)

Summary

EudraCT number	2018-004926-26
Trial protocol	HU CZ PL DE FR FI BE GB
Global end of trial date	01 May 2023

Results information

Result version number	v1 (current)
This version publication date	16 November 2023
First version publication date	16 November 2023

Trial information

Trial identification

Sponsor protocol code	PRV-031-001
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03875729
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Provention Bio, Inc
Sponsor organisation address	55 Broad Street, Second Floor, Red Bank, NJ, United States, 07701
Public contact	Kristin Neff, Provention Bio, Inc., 1 703-345-1819, kristin.neff@sanofi.com
Scientific contact	Linda Arterburn, Provention Bio, Inc., 1 301-648-4284, linda.arterburn@sanofi.com

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	18 October 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 May 2023
Global end of trial reached?	Yes
Global end of trial date	01 May 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine whether two courses of teplizumab slow the loss of β cells and preserve β cell function over 18 months (78 weeks) in children and adolescents 8-17 years old who have been diagnosed with T1D in the previous 6 weeks.

Protection of trial subjects:

An external, independent Data Monitoring Committee (DMC) consisting of individuals with medical, scientific, and biostatistical expertise, provided oversight on safety and efficacy data and the conduct of the study. The DMC was responsible for making recommendations regarding the continuation, termination, or modification of the study.

Before initiating this study, the Investigator was required to have written and dated approval from the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) for the study protocol, informed consent form, Investigator's Brochure (IB), sponsor-approved recruiting materials, and other written information to be provided to participants and their guardians.

The study was conducted in full compliance with the principles of the "Declaration of Helsinki", International Council on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines, and all of the applicable US Code of Federal Regulations (CFR), 21 CFR Parts 50 & 312.

Written informed consent and assent were obtained from each individual and guardian(s). The Investigator was to comply with applicable regulatory requirement(s) and adhere to Good Clinical Practice (GCP) and the ethical principles that have their origin in the Declaration of Helsinki when obtaining and documenting informed consent.

Background therapy:

All enrolled participants, with assistance of their healthcare providers, were to receive intensive diabetes management of their T1D using approved therapies according to the recommendations of American Diabetes Association or local, regional, or national recommendations to achieve target glucose levels. The glycemic goal was to be attempted through proper glycemic monitoring, administration of exogenous insulin, and monitoring of activity level and diet. Exogenous insulin could include rapid, intermediate, and/or long-acting insulins, administered intermittently or via the use of a personal insulin pump.

Evidence for comparator:

A placebo control was used to establish the frequency and magnitude of changes in clinical, safety, metabolic, and exploratory endpoints in the absence of active treatment.

Actual start date of recruitment	27 March 2019
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	42 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 182
Country: Number of subjects enrolled	Canada: 20
Country: Number of subjects enrolled	Poland: 48
Country: Number of subjects enrolled	United Kingdom: 12
Country: Number of subjects enrolled	Belgium: 5
Country: Number of subjects enrolled	Czechia: 27
Country: Number of subjects enrolled	France: 14
Country: Number of subjects enrolled	Germany: 20
Worldwide total number of subjects	328
EEA total number of subjects	114

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)	136
Adolescents (12-17 years)	192
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Participants had to be positive for at least one T1D-associated autoantibody and have a peak stimulated C-peptide of ≥ 0.2 pmol/mL at screening. They also had to meet all of the specific inclusion criteria and none of the exclusion criteria. The screening period could last for up to 6 weeks.

Period 1

Period 1 title	Post-randomization period (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

Blinding implementation details:

Blinding was maintained for all study participants, Investigators, and study coordinators throughout the study. In addition, the study team remained blinded to the treatment assignment through the completion of the study. Teplizumab and placebo were supplied to the sites in vials and kits that appeared identical. Each kit had a unique number printed on all labels, including the outer carton label and the label of each vial inside the kit.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Matching placebo control

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use, Infusion

Dosage and administration details:

Placebo was administered via intravenous infusion in two courses, with the first course starting on Day 1 (Week 1) and the second course approximately 6 months later at Day 182 (Week 26). Participants who were unable to receive the second 12-day course due to COVID-19 pandemic restrictions were given the second course at approximately 12 months (Week 52 visit). Each course of treatment included daily infusions for 12 days.

The placebo solution consisted of the same formulation as the study drug but without teplizumab. Placebo was administered in the same dose volume and by the same treatment schedule as the active drug.

Arm title	Teplizumab
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Arm description:

Study drug

Arm type	Experimental
Investigational medicinal product name	Teplizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Infusion , Intravenous use

Dosage and administration details:

Teplizumab was administered via intravenous infusion in two courses, with the first course starting on Day 1 (Week 1) and the second course approximately 6 months later at Day 182 (Week 26).

Participants who were unable to receive the second 12-day course due to COVID-19 pandemic restrictions were given the second course at approximately 12 months (Week 52 visit). Each course of treatment included daily infusions for 12 days.

Each course included:

- Day 1: 106 µg/m²
- Day 2: 425 µg/m²
- Days 3-12: 850 µg/m²

Total per course: 9.0 mg/m²

The doses of study drug were calculated based on the participant's body surface area (BSA) measured on the first day of each treatment course.

Number of subjects in period 1	Placebo	Teplizumab
Started	111	217
Completed	101	195
Not completed	10	22
Personal reasons	2	-
Consent withdrawn by subject	8	11
Adverse event, non-fatal	-	5
Pregnancy	-	1
Lost to follow-up	-	5

Baseline characteristics

Reporting groups

Reporting group title	Placebo
Reporting group description:	
Matching placebo control	
Reporting group title	Teplizumab
Reporting group description:	
Study drug	

Reporting group values	Placebo	Teplizumab	Total
Number of subjects	111	217	328
Age categorical			
Units: Subjects			
Children (2-11 years)	46	90	136
Adolescents (12-17 years)	65	127	192
Age continuous			
Units: years			
arithmetic mean	12.3	12.0	
standard deviation	± 2.55	± 2.53	-
Gender categorical			
Units: Subjects			
Female	42	98	140
Male	69	119	188
Race			
Units: Subjects			
White	94	189	283
Black or African American	6	5	11
Asian	3	4	7
American Indian or Alaskan Native	0	1	1
Native Hawaiian or Other Pacific Islander	1	0	1
Multiple	0	6	6
Other	1	4	5
Not reported	6	8	14
Ethnicity			
Units: Subjects			
Hispanic or Latino	4	14	18
Not Hispanic or Latino	101	193	294
Not reported	6	10	16
Peak C-peptide			
Stratification Factor 1 - Peak C-peptide at screening			
Units: Subjects			
0.2 - 0.7 pmol/mL	47	91	138
>0.7 pmol/mL	64	126	190
Age group at randomization			
Stratification factor 2			
Units: Subjects			
8-12 years	62	120	182

>12 - 17 years	49	97	146
Number of positive T1D autoantibodies			
Units: Subjects			
None	0	1	1
One	3	10	13
Two	13	38	51
Three	30	47	77
Four	39	66	105
Five	26	55	81
History of DKA			
Units: Subjects			
Yes	4	0	4
No	107	217	324
HLA genotyping - DR3			
Units: Subjects			
Positive	56	96	152
Negative	53	119	172
No data	2	2	4
HLA genotyping - DR4			
Units: Subjects			
Positive	75	137	212
Negative	34	78	112
No data	2	2	4
Anti-GAD65 autoantibody			
Units: Subjects			
Positive	96	183	279
Negative	15	34	49
Anti-IA-2 autoantibody			
Units: Subjects			
Positive	87	165	252
Negative	24	52	76
Anti-ZnT8 autoantibody			
Units: Subjects			
Positive	83	162	245
Negative	28	55	83
Anti-insulin autoantibody			
Units: Subjects			
Positive	85	144	229
Negative	26	73	99
Anti-ICA autoantibody			
Units: Subjects			
Positive	54	112	166
Negative	57	105	162
Height			
Height at baseline			
Units: cm			
arithmetic mean	158.48	155.35	
standard deviation	± 14.977	± 15.358	-
Weight			
Weight at baseline			
Units: kg			

arithmetic mean	49.19	46.68	
standard deviation	± 15.889	± 14.992	-
BMI			
Body Mass Index at baseline			
Units: kg/m2			
arithmetic mean	19.063	18.868	
standard deviation	± 3.6415	± 3.4517	-
BMI z-score			
Body Mass Index z-score at baseline			
Units: none			
arithmetic mean	0.0557	0.0627	
standard deviation	± 1.0957	± 1.0723	-
Time from T1D diagnosis			
Units: weeks			
arithmetic mean	5.20	5.37	
standard deviation	± 0.812	± 0.730	-
C-peptide AUC			
C-peptide AUC at baseline			
Units: pmol/mL			
arithmetic mean	0.7237	0.7445	
standard deviation	± 0.3190	± 0.3653	-
Insulin use			
At baseline			
Units: Unit/kg/day			
arithmetic mean	0.383	0.447	
standard deviation	± 0.2535	± 0.3093	-
HbA1c			
Hemoglobin A1c at baseline			
Units: percent			
arithmetic mean	9.18	8.90	
standard deviation	± 1.918	± 1.729	-

Subject analysis sets

Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All randomized participants.	
Subject analysis set title	PP
Subject analysis set type	Per protocol
Subject analysis set description:	
Per protocol population. The main reason participants were excluded from the PP population was for treatment compliance <80% (15 of 16 excluded participants in the placebo group and 32 of 37 in the teplizumab group). Other reasons included took prohibited medication (1 in placebo group, 3 in teplizumab group), received incorrect treatment (2 in teplizumab group), and pregnancy (1 in teplizumab group).	

Reporting group values	ITT	PP	
Number of subjects	328	275	
Age categorical			
Units: Subjects			
Children (2-11 years)	136		
Adolescents (12-17 years)	192		

Age continuous Units: years arithmetic mean standard deviation	12.1 ± 2.54	±	
Gender categorical Units: Subjects			
Female	140		
Male	188		
Race Units: Subjects			
White	283		
Black or African American	11		
Asian	7		
American Indian or Alaskan Native	1		
Native Hawaiian or Other Pacific Islander	1		
Multiple	6		
Other	5		
Not reported	14		
Ethnicity Units: Subjects			
Hispanic or Latino	18		
Not Hispanic or Latino	294		
Not reported	16		
Peak C-peptide			
Stratification Factor 1 - Peak C-peptide at screening			
Units: Subjects			
0.2 - 0.7 pmol/mL	138		
>0.7 pmol/mL	190		
Age group at randomization			
Stratification factor 2			
Units: Subjects			
8-12 years	182		
>12 - 17 years	146		
Number of positive T1D autoantibodies Units: Subjects			
None	1		
One	13		
Two	51		
Three	77		
Four	105		
Five	81		
History of DKA Units: Subjects			
Yes	4		
No	324		
HLA genotyping - DR3 Units: Subjects			
Positive	152		
Negative	172		
No data	4		

HLA genotyping - DR4			
Units: Subjects			
Positive	212		
Negative	112		
No data	4		
Anti-GAD65 autoantibody			
Units: Subjects			
Positive	279		
Negative	49		
Anti-IA-2 autoantibody			
Units: Subjects			
Positive	252		
Negative	76		
Anti-ZnT8 autoantibody			
Units: Subjects			
Positive	245		
Negative	83		
Anti-insulin autoantibody			
Units: Subjects			
Positive	229		
Negative	99		
Anti-ICA autoantibody			
Units: Subjects			
Positive	166		
Negative	162		
Height			
Height at baseline			
Units: cm			
arithmetic mean	156.41		
standard deviation	± 15.279	±	
Weight			
Weight at baseline			
Units: kg			
arithmetic mean	47.53		
standard deviation	± 15.323	±	
BMI			
Body Mass Index at baseline			
Units: kg/m2			
arithmetic mean	18.934		
standard deviation	± 3.5127	±	
BMI z-score			
Body Mass Index z-score at baseline			
Units: none			
arithmetic mean	0.0603		
standard deviation	± 1.0786	±	
Time from T1D diagnosis			
Units: weeks			
arithmetic mean	5.31		
standard deviation	± 0.762	±	
C-peptide AUC			
C-peptide AUC at baseline			

Units: pmol/mL			
arithmetic mean	0.7375		
standard deviation	± 0.3499	±	
Insulin use			
At baseline			
Units: Unit/kg/day			
arithmetic mean	0.426		
standard deviation	± 0.2928	±	
HbA1c			
Hemoglobin A1c at baseline			
Units: percent			
arithmetic mean	9.00		
standard deviation	± 1.797	±	

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Matching placebo control	
Reporting group title	Teplizumab
Reporting group description:	
Study drug	
Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All randomized participants.	
Subject analysis set title	PP
Subject analysis set type	Per protocol
Subject analysis set description:	
Per protocol population. The main reason participants were excluded from the PP population was for treatment compliance <80% (15 of 16 excluded participants in the placebo group and 32 of 37 in the teplizumab group). Other reasons included took prohibited medication (1 in placebo group, 3 in teplizumab group), received incorrect treatment (2 in teplizumab group), and pregnancy (1 in teplizumab group).	

Primary: Change in C-peptide ln(AUC+1) - ITT Population

End point title	Change in C-peptide ln(AUC+1) - ITT Population
End point description:	
The area under the concentration-time curve (AUC) of C-peptide was measured after a 4-hour mixed meal tolerance test (MMTT), a measure of endogenous insulin production and β cell function. Intent-to-treat population	
End point type	Primary
End point timeframe:	
Baseline to Week 78	

End point values	Placebo	Teplizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	111	217		
Units: pmol/mL				
least squares mean (confidence interval 95%)	-0.2112 (-0.2437 to -0.1786)	-0.0859 (-0.1090 to -0.0628)		

Statistical analyses

Statistical analysis title	LSmean difference change C-peptide ln(AUC+1) - ITT
Statistical analysis description:	
LSmean difference = Teplizumab – Placebo. Estimates and the p-value were obtained from an ANCOVA model that includes treatment, age group at randomization, and baseline C-peptide ln(AUC+1) as independent variables.	

Missing data at Week 78 were multiply imputed using a pattern-mixture model under the missing not at random assumption.

Comparison groups	Placebo v Teplizumab
Number of subjects included in analysis	328
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.1253
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.0852
upper limit	0.1653

Primary: Change in C-peptide ln(AUC+1) - PP Population

End point title	Change in C-peptide ln(AUC+1) - PP Population
End point description:	
The area under the concentration-time curve (AUC) of C-peptide was measured after a 4-hour mixed meal tolerance test (MMTT), a measure of endogenous insulin production and β cell function.	
Per protocol population	
End point type	Primary
End point timeframe:	
Baseline to Week 78	

End point values	Placebo	Teplizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	95	180		
Units: pmol/mL				
least squares mean (confidence interval 95%)	-0.2185 (-0.2501 to -0.1869)	-0.0800 (-0.1030 to -0.0570)		

Statistical analyses

Statistical analysis title	LSmean difference change C-peptide ln(AUC+1) - PP
Statistical analysis description:	
LSmean difference = teplizumab - placebo	
Estimates and the p-value were obtained from an ANCOVA model that includes treatment, age group at randomization, and baseline C-peptide ln(AUC+1) as independent variables.	
Missing data at Week 78 were multiply imputed using a pattern-mixture model under the missing not at random assumption.	
Comparison groups	Placebo v Teplizumab

Number of subjects included in analysis	275
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.1385
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.0994
upper limit	0.1776

Secondary: Average daily exogenous insulin use - ITT population

End point title	Average daily exogenous insulin use - ITT population
End point description:	
Insulin use is reported in Units/kg/day Average daily insulin use was calculated based on participants who have at least 3 days of insulin use recorded in the diary for the Week 78 visit. Intent-to-treat population	
End point type	Secondary
End point timeframe:	
Week 78	

End point values	Placebo	Teplizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	111	217		
Units: units/kg/day				
least squares mean (confidence interval 95%)	0.593 (0.470 to 0.716)	0.463 (0.363 to 0.562)		

Statistical analyses

Statistical analysis title	LSmean difference in daily exogenous insulin - ITT
Statistical analysis description:	
LSmean difference = teplizumab - placebo. Estimates and the p-value were obtained from an ANOVA model that included treatment, age group at randomization, and screening peak c-peptide category as independent variables. Missing data at Week 78 were multiply imputed using a pattern-mixture model under the missing not at random assumption.	
Comparison groups	Placebo v Teplizumab

Number of subjects included in analysis	328
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.085
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.131
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.28
upper limit	0.018

Secondary: Average daily exogenous insulin use - PP population

End point title	Average daily exogenous insulin use - PP population
End point description:	
Insulin use is reported in Units/kg/day Average daily insulin use was calculated based on participants who have at least 3 days of insulin use recorded in the diary for each visit. Per protocol population	
End point type	Secondary
End point timeframe:	
Week 78	

End point values	Placebo	Teplizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	95	180		
Units: units/kg/day				
least squares mean (confidence interval 95%)	0.613 (0.538 to 0.687)	0.446 (0.390 to 0.502)		

Statistical analyses

Statistical analysis title	LSmean difference in daily exogenous insulin - PP
Statistical analysis description:	
LSmean difference = teplizumab - placebo. Estimates and p-values were obtained from an ANCOVA model that included treatment, age group at randomization, and screening peak c-peptide category as independent variables. Missing data at Week 78 were multiply imputed using a pattern-mixture model under the missing not at random assumption.	
Comparison groups	Placebo v Teplizumab

Number of subjects included in analysis	275
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.167
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.256
upper limit	-0.078

Secondary: Change in HbA1c Levels (%) - ITT population

End point title	Change in HbA1c Levels (%) - ITT population
End point description:	
Hemoglobin A1c (%)	
Intent-to-treat population	
End point type	Secondary
End point timeframe:	
Baseline to Week 78	

End point values	Placebo	Teplizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	111	217		
Units: percent				
least squares mean (confidence interval 95%)	-1.89 (-2.16 to -1.62)	-1.98 (-2.17 to -1.78)		

Statistical analyses

Statistical analysis title	LSmean difference in change in HbA1c - ITT
Statistical analysis description:	
LSmean difference = teplizumab - placebo	
Estimates and the p-value were obtained from an ANCOVA model that included treatment, age group at randomization, screening peak C-peptide category, and baseline HbA1c (%) as independent variables.	
Missing data at Week 78 were multiply imputed using a pattern-mixture model under the missing not at random assumption.	
Comparison groups	Placebo v Teplizumab

Number of subjects included in analysis	328
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.606
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.42
upper limit	0.24

Secondary: Time in range for glycemia control - ITT population

End point title	Time in range for glycemia control - ITT population
End point description:	
Time in range (%) for glycemia control was assessed using Continuous Glucose Monitoring (CGM). Time in range was defined as daily average percentage of time a participant's glucose is ≥ 70 mg/dL and ≤ 180 mg/dL. Time in range was calculated based on participants who had at least 3 days of CGM data recorded for Week 78 visit with a range of at least 8 hours on a given day.	
Intent-to-treat population	
End point type	Secondary
End point timeframe:	
Week 78	

End point values	Placebo	Teplizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	111	217		
Units: percent				
least squares mean (confidence interval 95%)	62.65 (57.38 to 67.92)	67.36 (63.70 to 71.03)		

Statistical analyses

Statistical analysis title	LSmean difference in time in range - ITT
Statistical analysis description:	
LSmean difference = teplizumab - placebo.	
Estimates and p-value were obtained from an ANCOVA model that included treatment, age group at randomization, and screening peak C-peptide category as independent variables.	
Missing data were multiply imputed using a pattern-mixture model under the missing not at random assumption.	
Comparison groups	Placebo v Teplizumab

Number of subjects included in analysis	328
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.151
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	4.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.72
upper limit	11.15

Secondary: Time in range for glycemia control - PP population

End point title	Time in range for glycemia control - PP population
End point description:	
Time in range (%) for glycemia control was assessed using Continuous Glucose Monitoring (CGM). Time in range was defined as daily average percentage of time a participant's glucose is ≥ 70 mg/dL and ≤ 180 mg/dL. Time in range was calculated based on participants who had at least 3 days of CGM data recorded for Week 78 visit with a range of at least 8 hours on a given day.	
Per protocol population	
End point type	Secondary
End point timeframe:	
Week 78	

End point values	Placebo	Teplizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	95	180		
Units: percent				
least squares mean (confidence interval 95%)	61.44 (56.50 to 66.38)	67.61 (64.09 to 71.14)		

Statistical analyses

Statistical analysis title	LSmean difference in time in range - PP
Statistical analysis description:	
LSmean difference = teplizumab - placebo.	
Estimates and p-value were obtained from an ANCOVA model that included treatment, age group at randomization, and screening peak C-peptide category as independent variables.	
Missing data were multiply imputed using a pattern-mixture model under the missing not at random assumption.	
Comparison groups	Placebo v Teplizumab

Number of subjects included in analysis	275
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.045
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	6.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.13
upper limit	12.22

Secondary: Rate of clinically important hypoglycemic events - ITT population

End point title	Rate of clinically important hypoglycemic events - ITT population
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End point description:

Rate = clinically important hypoglycemic events/patient-year

A clinically important episode was defined as a blood glucose value of <54 mg/dL (3.0 mmol/L) (i.e., Level 2 Hypoglycemia, International Hypoglycemia Study Group, 2017) or a hypoglycemia event of severe cognitive impairment requiring external assistance (such as seizure, syncope, severe confusion with or without a confirmatory low blood glucose reading) (i.e., Level 3 Hypoglycemia, International Hypoglycemia Study Group 2017).

Event rate was calculated for each participant as number of events / total study follow-up time. Total study follow-up time was calculated as (the date of last study contact – the first dose date + 1)/365.25. Intent-to-treat population

End point type	Secondary
End point timeframe:	
Across the entire study	

End point values	Placebo	Teplizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	111	217		
Units: events / patient year				
arithmetic mean (confidence interval 95%)	4.24 (3.06 to 5.89)	4.68 (3.70 to 5.91)		

Statistical analyses

Statistical analysis title	Estimated rate ratio - ITT
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Statistical analysis description:

Rate ratio = teplizumab / placebo.

Estimates and p-values were obtained from a negative binomial regression model using rate of hypoglycemic episodes as dependent variable and treatment, age group at randomization, and screening peak C-peptide category as independent variables.

Comparison groups	Placebo v Teplizumab
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Number of subjects included in analysis	328
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.634
Method	Negative binomial regression model
Parameter estimate	rate ratio
Point estimate	1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.74
upper limit	1.64

Secondary: Change in HbA1c Levels (%) - PP population

End point title	Change in HbA1c Levels (%) - PP population
End point description:	
Hemoglobin A1c (%)	
Per protocol population	
End point type	Secondary
End point timeframe:	
Baseline to Week 78	

End point values	Placebo	Teplizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	95	180		
Units: percent				
least squares mean (confidence interval 95%)	-1.94 (-2.21 to -1.67)	-2.07 (-2.27 to -1.87)		

Statistical analyses

Statistical analysis title	LSmean difference in change in HbA1c - PP
Statistical analysis description:	
LSmean difference = teplizumab - placebo.	
Estimates and the p-value were obtained from an ANOVA model that included treatment, age group at randomization, screening peak C-peptide category, and baseline HbA1c (%) as independent variables.	
Missing data at Week 78 were multiply imputed using a pattern-mixture model under the missing not at random assumption.	
Comparison groups	Placebo v Teplizumab

Number of subjects included in analysis	275
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.454
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.46
upper limit	0.2

Secondary: Rate of clinically important hypoglycemic events - PP population

End point title	Rate of clinically important hypoglycemic events - PP population
End point description:	
<p>Rate = clinically important hypoglycemic events/patient-year</p> <p>A clinically important episode was defined as a blood glucose value of <54 mg/dL (3.0 mmol/L) (i.e., Level 2 Hypoglycemia, International Hypoglycemia Study Group, 2017) or a hypoglycemia event of severe cognitive impairment requiring external assistance (such as seizure, syncope, severe confusion with or without a confirmatory low blood glucose reading) (i.e., Level 3 Hypoglycemia, International Hypoglycemia Study Group 2017).</p> <p>Event rate was calculated for each participant as number of events / total study follow-up time. Total study follow-up time was calculated as (the date of last study contact – the first dose date + 1)/365.25.</p> <p>Per protocol population</p>	
End point type	Secondary
End point timeframe:	
Across the entire study	

End point values	Placebo	Teplizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	95	180		
Units: events / patient-year				
arithmetic mean (confidence interval 95%)	4.63 (3.31 to 6.49)	5.04 (3.94 to 6.44)		

Statistical analyses

Statistical analysis title	Estimated rate ratio - PP
Statistical analysis description:	
<p>Rate ratio = teplizumab / placebo.</p> <p>Estimates and p-values were obtained from a negative binomial regression model using rate of hypoglycemic episodes as dependent variable and treatment age group at randomization, and screening peak C-peptide category as independent variables.</p>	
Comparison groups	Placebo v Teplizumab

Number of subjects included in analysis	275
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.69
Method	Rate ratio
Parameter estimate	Mean difference (final values)
Point estimate	1.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.72
upper limit	1.65

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment-emergent adverse events = from the first dose of study drug administration through the end of the study

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	26.0

Reporting groups

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

Serious adverse events	Placebo	Teplizumab	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 111 (5.41%)	12 / 217 (5.53%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Concussion			
subjects affected / exposed	0 / 111 (0.00%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 111 (0.00%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Syncope			
subjects affected / exposed	1 / 111 (0.90%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			

Cytokine release syndrome subjects affected / exposed	0 / 111 (0.00%)	3 / 217 (1.38%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	0 / 111 (0.00%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 111 (0.90%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Dermatitis atopic			
subjects affected / exposed	0 / 111 (0.00%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Suicidal ideation			
subjects affected / exposed	0 / 111 (0.00%)	2 / 217 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide attempt			
subjects affected / exposed	0 / 111 (0.00%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anxiety			
subjects affected / exposed	1 / 111 (0.90%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Nephrolithiasis			

subjects affected / exposed	0 / 111 (0.00%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Device related bacteraemia			
subjects affected / exposed	1 / 111 (0.90%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	2 / 111 (1.80%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	1 / 111 (0.90%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	0 / 111 (0.00%)	1 / 217 (0.46%)	
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: 5 %

Non-serious adverse events	Placebo	Teplizumab	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	88 / 111 (79.28%)	212 / 217 (97.70%)	
Vascular disorders			
Hypotension			
subjects affected / exposed	10 / 111 (9.01%)	18 / 217 (8.29%)	
occurrences (all)	25	72	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	11 / 111 (9.91%)	53 / 217 (24.42%)	
occurrences (all)	12	80	

Fatigue subjects affected / exposed occurrences (all)	15 / 111 (13.51%) 33	22 / 217 (10.14%) 37	
Chills subjects affected / exposed occurrences (all)	0 / 111 (0.00%) 0	19 / 217 (8.76%) 26	
Immune system disorders Cytokine release syndrome subjects affected / exposed occurrences (all)	1 / 111 (0.90%) 1	16 / 217 (7.37%) 24	
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	12 / 111 (10.81%) 15	20 / 217 (9.22%) 26	
Nasal congestion subjects affected / exposed occurrences (all)	6 / 111 (5.41%) 8	19 / 217 (8.76%) 22	
Oropharyngeal pain subjects affected / exposed occurrences (all)	16 / 111 (14.41%) 21	19 / 217 (8.76%) 21	
Rhinorrhoea subjects affected / exposed occurrences (all)	4 / 111 (3.60%) 4	11 / 217 (5.07%) 13	
Investigations Lymphocyte count decreased subjects affected / exposed occurrences (all)	5 / 111 (4.50%) 6	73 / 217 (33.64%) 203	
White blood cell count decreased subjects affected / exposed occurrences (all)	6 / 111 (5.41%) 11	53 / 217 (24.42%) 134	
Neutrophil count decreased subjects affected / exposed occurrences (all)	11 / 111 (9.91%) 17	33 / 217 (15.21%) 70	
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	0 / 111 (0.00%) 0	28 / 217 (12.90%) 37	

Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	1 / 111 (0.90%) 1	20 / 217 (9.22%) 28	
Cardiac disorders Tachycardia subjects affected / exposed occurrences (all)	1 / 111 (0.90%) 2	12 / 217 (5.53%) 27	
Nervous system disorders Headache subjects affected / exposed occurrences (all) Dizziness subjects affected / exposed occurrences (all)	21 / 111 (18.92%) 37 5 / 111 (4.50%) 8	94 / 217 (43.32%) 184 11 / 217 (5.07%) 19	
Blood and lymphatic system disorders Lymphopenia subjects affected / exposed occurrences (all) Neutropenia subjects affected / exposed occurrences (all) Leukopenia subjects affected / exposed occurrences (all) Anaemia subjects affected / exposed occurrences (all)	0 / 111 (0.00%) 0 1 / 111 (0.90%) 2 1 / 111 (0.90%) 1 5 / 111 (4.50%) 11	50 / 217 (23.04%) 106 28 / 217 (12.90%) 65 26 / 217 (11.98%) 57 13 / 217 (5.99%) 17	
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all) Abdominal pain	21 / 111 (18.92%) 36 15 / 111 (13.51%) 17	92 / 217 (42.40%) 158 68 / 217 (31.34%) 100	

subjects affected / exposed	9 / 111 (8.11%)	37 / 217 (17.05%)	
occurrences (all)	11	50	
Abdominal pain upper			
subjects affected / exposed	12 / 111 (10.81%)	31 / 217 (14.29%)	
occurrences (all)	20	44	
Diarrhoea			
subjects affected / exposed	12 / 111 (10.81%)	31 / 217 (14.29%)	
occurrences (all)	15	34	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	5 / 111 (4.50%)	86 / 217 (39.63%)	
occurrences (all)	9	160	
Rash maculo-papular			
subjects affected / exposed	4 / 111 (3.60%)	29 / 217 (13.36%)	
occurrences (all)	7	35	
Pruritus			
subjects affected / exposed	9 / 111 (8.11%)	17 / 217 (7.83%)	
occurrences (all)	9	25	
Rash macular			
subjects affected / exposed	0 / 111 (0.00%)	11 / 217 (5.07%)	
occurrences (all)	0	17	
Dermatitis contact			
subjects affected / exposed	6 / 111 (5.41%)	9 / 217 (4.15%)	
occurrences (all)	7	10	
Erythema			
subjects affected / exposed	6 / 111 (5.41%)	7 / 217 (3.23%)	
occurrences (all)	6	8	
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	3 / 111 (2.70%)	14 / 217 (6.45%)	
occurrences (all)	3	20	
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	6 / 111 (5.41%)	15 / 217 (6.91%)	
occurrences (all)	6	19	
Arthralgia			

subjects affected / exposed occurrences (all)	5 / 111 (4.50%) 6	14 / 217 (6.45%) 15	
Infections and infestations			
COVID-19			
subjects affected / exposed	26 / 111 (23.42%)	49 / 217 (22.58%)	
occurrences (all)	26	53	
Upper respiratory tract infection			
subjects affected / exposed	23 / 111 (20.72%)	44 / 217 (20.28%)	
occurrences (all)	33	65	
Nasopharyngitis			
subjects affected / exposed	14 / 111 (12.61%)	19 / 217 (8.76%)	
occurrences (all)	17	22	
Gastroenteritis			
subjects affected / exposed	10 / 111 (9.01%)	9 / 217 (4.15%)	
occurrences (all)	10	10	
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	81 / 111 (72.97%)	151 / 217 (69.59%)	
occurrences (all)	1791	2176	
Decreased appetite			
subjects affected / exposed	3 / 111 (2.70%)	11 / 217 (5.07%)	
occurrences (all)	4	11	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 May 2020	Protocol amendment 3: Added modified dosing regimen for participants affected by COVID-19 pandemic restrictions. SARS-CoV-2 PCR testing added to screening visit and before each treatment course to ensure participants were not infected at dosing.
10 December 2020	Treatment withholding criterion based on bilirubin levels was revised. Treatment discontinuation criteria due to certain laboratory abnormalities was revised. Additional blood sample collection was added.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
16 March 2020	Enrollment into the study was temporarily suspended due to COVID-19 pandemic restrictions.	09 June 2020

Notes:

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/37861217>