



Clinical trial results:

A Phase 3, Multinational, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Investigate the Clinical Efficacy and Safety of DiaPep277® in Newly Diagnosed Type 1 Diabetes Subjects Summary

EudraCT number	2009-015929-37
Trial protocol	HU ES DE IT AT CZ LT FI
Global end of trial date	28 October 2014

Results information

Result version number	v1 (current)
This version publication date	16 July 2016
First version publication date	16 July 2016

Trial information

Trial identification

Sponsor protocol code	1001
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01103284
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Andromeda Biotech Ltd.
Sponsor organisation address	42 Hayarkon St., Yavne, Israel, 81227
Public contact	42 Hayarkon St. Industrial Area, Yavne 81227, Israel, Andromeda Biotech Ltd., +972 8 9387777,
Scientific contact	42 Hayarkon St. Industrial Area, Yavne 81227, Israel, Andromeda Biotech Ltd., +972 8 9387777,

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	28 October 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 October 2014
Global end of trial reached?	Yes
Global end of trial date	28 October 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary efficacy objective was to compare in subjects with Type 1 diabetes (T1D) the effect of DiaPep277® to Placebo on endogenous insulin secretion or pancreatic beta-cell function as measured by area under curve from 0 to 20 minutes (AUC 0-20min) of C-peptide concentration versus time from a glucagon stimulation test (GST).

Protection of trial subjects:

The Guidelines of the World Medical Association Declaration of Helsinki in its revised edition (64th World Medical Association General Assembly, Fortaleza, Brazil, October 2013), the Guidelines of International Conference of Harmonization (ICH) Good Clinical Practice (GCP) (CPMP/ICH/135/95), and the demands of national drug and data protection laws and other applicable regulatory requirements were strictly followed during this study.

This study also conformed to the laws and regulations of the countries in which it was conducted, as well as any applicable guidelines. All personnel involved in the study worked within the confines of the European Data Protection Directive as interpreted by each country's laws.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	25 May 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	Czech Republic: 18
Country: Number of subjects enrolled	Austria: 6
Country: Number of subjects enrolled	Germany: 34
Country: Number of subjects enrolled	Israel: 61
Country: Number of subjects enrolled	Italy: 39
Country: Number of subjects enrolled	Belarus: 24
Country: Number of subjects enrolled	Spain: 12
Country: Number of subjects enrolled	Hungary: 16
Country: Number of subjects enrolled	Lithuania: 19
Country: Number of subjects enrolled	Poland: 30
Country: Number of subjects enrolled	Romania: 12
Country: Number of subjects enrolled	Russian Federation: 78
Country: Number of subjects enrolled	Serbia: 16
Country: Number of subjects enrolled	Canada: 2
Country: Number of subjects enrolled	United States: 96

Country: Number of subjects enrolled	Argentina: 11
Worldwide total number of subjects	474
EEA total number of subjects	186

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)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	474
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Newly diagnosed adult Type 1 Diabetes (T1D) subjects with residual beta-cell function were the target population for treatment with DiaPep277®, as it has the potential to prevent or delay further loss of beta-cell function.

Pre-assignment

Screening details:

897 subjects entered the study: 422 subjects failed screening; 475 subjects were randomized:

- a. 236 subjects randomized to DiaPep277® group: 194 completed study
- b. 239 subjects randomized to Placebo group but 1 subject was not treated with study drug: a total of 238 subjects in this group were included in Safety Population. 195 completed study

Period 1

Period 1 title	Treatment (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

Arms

Are arms mutually exclusive?	Yes
Arm title	DiaPep277®

Arm description:

Administration of 1 mg DiaPep277®, subcutaneously (s.c.) in the upper arm at 0, 1, 3, 6, 9, 12, 15, 18, 21, and 24 months, for a total of 10 administrations.

DiaPep277: 1.0 mg dose in 0.5 mL of solution

Arm type	Experimental
Investigational medicinal product name	DiaPep277®
Investigational medicinal product code	DiaPep277®
Other name	
Pharmaceutical forms	Powder and solvent for emulsion for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

The fixed dose of DiaPep277® 1.0 mg was administered subcutaneously (s.c.) as a sterile 0.5 mL solution.

Arm title	Placebo
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Arm description:

Administration of placebo, subcutaneously (s.c.) in the upper arm at 0, 1, 3, 6, 9, 12, 15, 18, 21, and 24 months, for a total of 10 administrations.

Placebo: 40 mg mannitol in 0.5 mL of solution.

Dosing: 0, 1, 3, 6, 9, 12, 15, 18, 21, 24 months

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

The fixed dose of 1.0 mg placebo was administered subcutaneously (s.c.) as a sterile 0.5 mL solution.

Number of subjects in period 1	DiaPep277®	Placebo
Started	236	238
At Least One Post-baseline Visit (FAS)	233	235
Completed	194	195
Not completed	42	43
Use of unacceptable medication	2	-
Termination by the Sponsor	-	1
Consent withdrawn by subject	14	18
Failed to meet entry criteria	1	-
Adverse event, non-fatal	-	5
Missing CRF entries	1	1
Death	2	-
Other	2	1
Pregnancy	3	1
Non-compliance	6	3
Lost to follow-up	9	10
Protocol deviation	2	2
Dermal hypersensitivity	-	1

Baseline characteristics

Reporting groups

Reporting group title	DiaPep277®
Reporting group description:	
Administration of 1 mg DiaPep277®, subcutaneously (s.c.) in the upper arm at 0, 1, 3, 6, 9, 12, 15, 18, 21, and 24 months, for a total of 10 administrations.	
DiaPep277: 1.0 mg dose in 0.5 mL of solution	
Reporting group title	Placebo
Reporting group description:	
Administration of placebo, subcutaneously (s.c.) in the upper arm at 0, 1, 3, 6, 9, 12, 15, 18, 21, and 24 months, for a total of 10 administrations.	
Placebo: 40 mg mannitol in 0.5 mL of solution.	
Dosing: 0, 1, 3, 6, 9, 12, 15, 18, 21, 24 months	

Reporting group values	DiaPep277®	Placebo	Total
Number of subjects	236	238	474
Age categorical			
Overall, the mean age was 28.6 years (range: 20 to 45 years), with just over half of the subjects (51.7%) being 27 years of age or younger.			
Units: Subjects			
≤ 27 years	120	125	245
> 27 years	116	113	229
Age continuous			
Units: years			
arithmetic mean	28.87	28.5	-
standard deviation	± 6.75	± 6.56	-
Gender categorical			
Units: Subjects			
Male	157	165	322
Female	79	73	152
Race			
Race			
Units: Subjects			
Caucasian	224	225	449
Hispanic	6	6	12
Black	3	4	7
Oriental	1	1	2
Asian	1	0	1
Other	0	2	2
Unknown	1	0	1
Daily Insulin Dose			
Units: IU/kg/day			
arithmetic mean	0.305	0.317	-
standard deviation	± 0.1587	± 0.1649	-
Fasting C-Peptide			
Units: nmol(s)/L			
arithmetic mean	0.388	0.407	-
standard deviation	± 0.1473	± 0.1731	-

Subject analysis sets

Subject analysis set title	Safety population
Subject analysis set type	Safety analysis
Subject analysis set description: The Safety population, defined as all subjects who received at least one dose of study medication, consisted of 236 subjects in the DiaPep277® group and 238 subjects in the Placebo group.	
Subject analysis set title	FAS population
Subject analysis set type	Full analysis
Subject analysis set description: The FAS population, defined as all randomized subjects who had a Baseline Visit and at least one scheduled post-Baseline Visit, consisted of 233 subjects in the DiaPep277® group and 234 subjects in the Placebo group. Note: Number of subjects in the Placebo group for the FAS is different in the analysis population table (234) versus the efficacy tables (235). This discrepancy is due to one subject who had a scheduled post-baseline visit, but did not have a post-baseline medication administration date. This subject was excluded from the Placebo group of the FAS in the analysis population table. However, this was not the intent of the Final SAP, and hence this subject was included in the Placebo group of the FAS in the efficacy tables (total: 468 patients).	
Subject analysis set title	DiaPep277® (FAS)
Subject analysis set type	Full analysis
Subject analysis set description: The DiaPep277® FAS population, defined as all randomized subjects who had a Baseline Visit and at least one scheduled post-Baseline Visit, consisted of 233 subjects (98.7%) in the DiaPep277® group.	
Subject analysis set title	Placebo (FAS)
Subject analysis set type	Full analysis
Subject analysis set description: The Placebo FAS population, defined as all randomized subjects who had a Baseline Visit and at least one scheduled post-Baseline Visit, consisted of 234 subjects (97.9%) in the Placebo group.	
Subject analysis set title	DiaPep277® (Safety population)
Subject analysis set type	Safety analysis
Subject analysis set description: The DiaPep277® Safety population, defined as all subjects who received at least one dose of study medication, consisted of 236 subjects (100.0%) in the DiaPep277® group.	
Subject analysis set title	Placebo (Safety population)
Subject analysis set type	Safety analysis
Subject analysis set description: The Placebo Safety population, defined as all subjects who received at least one dose of study medication, consisted of 238 subjects (99.6%) in the Placebo group.	

Reporting group values	Safety population	FAS population	DiaPep277® (FAS)
Number of subjects	474	468	233
Age categorical			
Overall, the mean age was 28.6 years (range: 20 to 45 years), with just over half of the subjects (51.7%) being 27 years of age or younger.			
Units: Subjects			
≤ 27 years	245		
> 27 years	229		
Age continuous			
Units: years			
arithmetic mean	28.6		
standard deviation	± 6.65	±	±
Gender categorical			
Units: Subjects			
Male	322		
Female	152		

Race			
Race			
Units: Subjects			
Caucasian	449		
Hispanic	12		
Black	7		
Oriental	2		
Asian	1		
Other	2		
Unknown	1		
Daily Insulin Dose			
Units: IU/kg/day			
arithmetic mean	0.311		
standard deviation	± 0.1618	±	±
Fasting C-Peptide			
Units: nmol(s)/L			
arithmetic mean	0.398		
standard deviation	± 0.1609	±	±

Reporting group values	Placebo (FAS)	DiaPep277® (Safety population)	Placebo (Safety population)
Number of subjects	235	236	238
Age categorical			
Overall, the mean age was 28.6 years (range: 20 to 45 years), with just over half of the subjects (51.7%) being 27 years of age or younger.			
Units: Subjects			
≤ 27 years		120	125
> 27 years		116	113
Age continuous			
Units: years			
arithmetic mean		28.87	28.5
standard deviation	±	± 6.75	± 6.56
Gender categorical			
Units: Subjects			
Male		157	165
Female		79	73
Race			
Race			
Units: Subjects			
Caucasian		224	225
Hispanic		6	6
Black		3	4
Oriental		1	1
Asian		1	0
Other		0	2
Unknown		1	0
Daily Insulin Dose			
Units: IU/kg/day			
arithmetic mean		0.305	0.317
standard deviation	±	± 0.1587	± 0.1649
Fasting C-Peptide			
Units: nmol(s)/L			

arithmetic mean		0.388	0.407
standard deviation	±	± 0.1473	± 0.1731

End points

End points reporting groups

Reporting group title	DiaPep277®
Reporting group description: Administration of 1 mg DiaPep277®, subcutaneously (s.c.) in the upper arm at 0, 1, 3, 6, 9, 12, 15, 18, 21, and 24 months, for a total of 10 administrations. DiaPep277: 1.0 mg dose in 0.5 mL of solution	
Reporting group title	Placebo
Reporting group description: Administration of placebo, subcutaneously (s.c.) in the upper arm at 0, 1, 3, 6, 9, 12, 15, 18, 21, and 24 months, for a total of 10 administrations. Placebo: 40 mg mannitol in 0.5 mL of solution. Dosing: 0, 1, 3, 6, 9, 12, 15, 18, 21, 24 months	
Subject analysis set title	Safety population
Subject analysis set type	Safety analysis
Subject analysis set description: The Safety population, defined as all subjects who received at least one dose of study medication, consisted of 236 subjects in the DiaPep277® group and 238 subjects in the Placebo group.	
Subject analysis set title	FAS population
Subject analysis set type	Full analysis
Subject analysis set description: The FAS population, defined as all randomized subjects who had a Baseline Visit and at least one scheduled post-Baseline Visit, consisted of 233 subjects in the DiaPep277® group and 234 subjects in the Placebo group. Note: Number of subjects in the Placebo group for the FAS is different in the analysis population table (234) versus the efficacy tables (235). This discrepancy is due to one subject who had a scheduled post-baseline visit, but did not have a post-baseline medication administration date. This subject was excluded from the Placebo group of the FAS in the analysis population table. However, this was not the intent of the Final SAP, and hence this subject was included in the Placebo group of the FAS in the efficacy tables (total: 468 patients).	
Subject analysis set title	DiaPep277® (FAS)
Subject analysis set type	Full analysis
Subject analysis set description: The DiaPep277® FAS population, defined as all randomized subjects who had a Baseline Visit and at least one scheduled post-Baseline Visit, consisted of 233 subjects (98.7%) in the DiaPep277® group.	
Subject analysis set title	Placebo (FAS)
Subject analysis set type	Full analysis
Subject analysis set description: The Placebo FAS population, defined as all randomized subjects who had a Baseline Visit and at least one scheduled post-Baseline Visit, consisted of 234 subjects (97.9%) in the Placebo group.	
Subject analysis set title	DiaPep277® (Safety population)
Subject analysis set type	Safety analysis
Subject analysis set description: The DiaPep277® Safety population, defined as all subjects who received at least one dose of study medication, consisted of 236 subjects (100.0%) in the DiaPep277® group.	
Subject analysis set title	Placebo (Safety population)
Subject analysis set type	Safety analysis
Subject analysis set description: The Placebo Safety population, defined as all subjects who received at least one dose of study medication, consisted of 238 subjects (99.6%) in the Placebo group.	

Primary: Change From Baseline in Glucagon-Stimulated C-Peptide AUC at 24 Months

End point title	Change From Baseline in Glucagon-Stimulated C-Peptide AUC at 24 Months
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End point description:

Change in Beta-cell function, measured as stimulated C-peptide secretion 0, 2, 6, 10 and 20 minutes post administration [area under the curve (AUC), 0-20 minutes] at baseline and 24 months, during a glucagon stimulation test (GST). The change in AUC was calculated per patient by subtracting the baseline AUC from the 24 month AUC.

End point type	Primary
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End point timeframe:

Baseline and 24 months.

End point values	DiaPep277® (FAS)	Placebo (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	233 ^[1]	235 ^[2]		
Units: nmol × minute/L				
arithmetic mean (standard error)	-5.2 (± 0.27)	-4.83 (± 0.3)		

Notes:

[1] - DiaPep277: 1.0 mg dose in 0.5 mL of solution

Dosing: 0, 1, 3, 6, 9, 12, 15, 18, 21, 24 months

[2] - Placebo: 40 mg mannitol in 0.5 mL of solution.

Dosing: 0, 1, 3, 6, 9, 12, 15, 18, 21, 24 months

Statistical analyses

Statistical analysis title	The change from Baseline in AUC0-20min
Comparison groups	DiaPep277® (FAS) v Placebo (FAS)
Number of subjects included in analysis	468
Analysis specification	Pre-specified
Analysis type	other ^[3]
P-value	= 0.33 ^[4]
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.14
upper limit	0.39
Variability estimate	Standard error of the mean
Dispersion value	0.39

Notes:

[3] - The Mixed-Effect Model Repeated Measure (MMRM) was adjusted for the following baseline covariates: age, C-peptide, insulin dose by body weight and AUC

[4] - The a priori threshold for statistical significance was 0.05

Secondary: Percentage of Subjects That Achieve Good Glycemic Control: HbA1c<7%

End point title	Percentage of Subjects That Achieve Good Glycemic Control: HbA1c<7%
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End point description:

The percentage of subjects achieving good glycemic control, i.e. an HbA1c <7% at study end (Month

25). If HbA1c was missing at Month 25, but the Month 24 value was available, then the Month 24 value was used to calculate the percentage of subjects with an HbA1c \leq 7% at study end.

End point type	Secondary
End point timeframe:	
24 and 25 months	

End point values	DiaPep277® (FAS)	Placebo (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	233 ^[5]	235 ^[6]		
Units: Percentage of subjects				
number (confidence interval 95%)	47 (40 to 54)	47 (40 to 55)		

Notes:

[5] - DiaPep277: 1.0 mg dose in 0.5 mL of solution

Dosing: 0, 1, 3, 6, 9, 12, 15, 18, 21, 24 months

[6] - Placebo: 40 mg mannitol in 0.5 mL of solution.

Dosing: 0, 1, 3, 6, 9, 12, 15, 18, 21, 24 months

Statistical analyses

Statistical analysis title	Percentage of Subjects Achieving HbA1c \leq 7%
Comparison groups	DiaPep277® (FAS) v Placebo (FAS)
Number of subjects included in analysis	468
Analysis specification	Pre-specified
Analysis type	other ^[7]
P-value	= 0.68 ^[8]
Method	Mixed models analysis
Parameter estimate	Odds ratio (OR)
Point estimate	0.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.66
upper limit	1.52

Notes:

[7] - The MMRM model was adjusted for the following covariates: age, Baseline C-peptide, Baseline insulin dose adjusted for body weight, and Baseline AUC.

[8] - A priori threshold for statistical significance was 0.05

Secondary: Frequency of Hypoglycemic Events

End point title	Frequency of Hypoglycemic Events
End point description:	
Total number of days with at least one hypoglycemic event recorded	
End point type	Secondary
End point timeframe:	
Baseline to 25 Months	

End point values	DiaPep277® (FAS)	Placebo (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	233 ^[9]	235 ^[10]		
Units: days	1955	3264		

Notes:

[9] - DiaPep277: 1.0 mg dose in 0.5 mL of solution

Dosing: 0, 1, 3, 6, 9, 12, 15, 18, 21, 24 months

[10] - Placebo: 40 mg mannitol in 0.5 mL of solution

Dosing: 0, 1, 3, 6, 9, 12, 15, 18, 21, 24 months

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Number of Days With at Least One Hypoglycemic Event

End point title	Mean Number of Days With at Least One Hypoglycemic Event
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End point description:

End point type	Secondary
End point timeframe:	
Baseline to 25 Months.	

End point values	DiaPep277® (FAS)	Placebo (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	233 ^[11]	235 ^[12]		
Units: days				
arithmetic mean (standard error)	13 (± 2.3)	35.4 (± 7.6)		

Notes:

[11] - DiaPep277: 1.0 mg dose in 0.5 mL of solution

Dosing: 0, 1, 3, 6, 9, 12, 15, 18, 21, 24 months

[12] - Placebo: 40 mg mannitol in 0.5 mL of solution

Dosing: 0, 1, 3, 6, 9, 12, 15, 18, 21, 24 months

Statistical analyses

Statistical analysis title	Mean Number of Days With at Least One Hypoglycemic
Comparison groups	DiaPep277® (FAS) v Placebo (FAS)
Number of subjects included in analysis	468
Analysis specification	Pre-specified
Analysis type	other ^[13]
P-value	= 0.07 ^[14]
Method	Negative binomial regression
Parameter estimate	Hazard ratio (HR)
Point estimate	0.38
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.02
upper limit	0.79

Notes:

[13] - The number of hypoglycemia events during the study was analyzed using a negative binomial regression model, with number of events as the dependent variable, and treatment, age, baseline daily insulin dose, and baseline C-peptide as covariates. The log of duration in the study for each patient was used as an offset variable in the model.

[14] - Standard multiple imputation was used to predict the number and timing of hypoglycemic events after discontinuing the study for subjects who did not remain in the study until Month 25.

Other pre-specified: Percentage of Subjects Requiring a Daily Insulin Dose ≤ 0.5 IU/kg at End of Study

End point title	Percentage of Subjects Requiring a Daily Insulin Dose ≤ 0.5 IU/kg at End of Study
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End point description:

Percentage of subjects requiring a daily insulin dose ≤ 0.5 IU/kg at end of study (25 Months). If insulin dose was missing at Month 25, but the Month 24 value was available, then the Month 24 value was used to calculate the percentage of subjects with a daily insulin dose ≤ 0.5 IU/kg at study end.

End point type	Other pre-specified
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End point timeframe:

24 and 25 months

End point values	DiaPep277® (FAS)	Placebo (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	233 ^[15]	235 ^[16]		
Units: Percentage of Subjects	63	57		

Notes:

[15] - DiaPep277: 1.0 mg dose in 0.5 mL of solution

Dosing: 0, 1, 3, 6, 9, 12, 15, 18, 21, 24 months

[16] - Placebo: 40 mg mannitol in 0.5 mL of solution

Dosing: 0, 1, 3, 6, 9, 12, 15, 18, 21, 24 months

Statistical analyses

Statistical analysis title	Percentage subjects requiring daily insulin dose
Comparison groups	Placebo (FAS) v DiaPep277® (FAS)
Number of subjects included in analysis	468
Analysis specification	Pre-specified
Analysis type	other ^[17]
P-value	= 0.44 ^[18]
Method	Mixed models analysis
Parameter estimate	Odds ratio (OR)
Point estimate	1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.66
upper limit	1.52

Notes:

[17] - The MMRM model was adjusted for the following covariates: age, Baseline C-peptide, Baseline insulin dose adjusted for body weight, and Baseline AUC

[18] - The a priori threshold for statistical significance was 0.05

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events (AE) data were collected from the time of subject enrollment through one month after the final product administrations (Total of 25 months after first study product administration)

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	17.0
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Reporting groups

Reporting group title	Placebo
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Reporting group description:

Administration of placebo, subcutaneously (s.c.) in the upper arm at 0, 1, 3, 6, 9, 12, 15, 18, 21, and 24 months, for a total of 10 administrations.

Placebo: 40 mg mannitol in 0.5 mL of solution.

Dosing: 0, 1, 3, 6, 9, 12, 15, 18, 21, 24 months

Reporting group title	DiaPep277®
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Reporting group description:

Administration of 1 mg DiaPep277®, subcutaneously (s.c.) in the upper arm at 0, 1, 3, 6, 9, 12, 15, 18, 21, and 24 months, for a total of 10 administrations.

DiaPep277: 1.0 mg dose in 0.5 mL of solution

Serious adverse events	Placebo	DiaPep277®	
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 238 (4.20%)	15 / 236 (6.36%)	
number of deaths (all causes)	0	2	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Benign muscle neoplasm			
subjects affected / exposed	1 / 238 (0.42%)	0 / 236 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Meniscus injury			
subjects affected / exposed	0 / 238 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple injuries			

subjects affected / exposed	1 / 238 (0.42%)	0 / 236 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Hypoglycemic seizure			
subjects affected / exposed	0 / 238 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss of Consciousness			
subjects affected / exposed	1 / 238 (0.42%)	0 / 236 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	0 / 238 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Lymphadenitis			
subjects affected / exposed	1 / 238 (0.42%)	0 / 236 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 238 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer haemorrhage			
subjects affected / exposed	0 / 238 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Incarcerated inguinal hernia			

subjects affected / exposed	0 / 238 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Anal fistula			
subjects affected / exposed	1 / 238 (0.42%)	0 / 236 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Nasal septum deviation			
subjects affected / exposed	0 / 238 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 238 (0.42%)	0 / 236 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Sympathetic posterior cervical syndrome			
subjects affected / exposed	1 / 238 (0.42%)	0 / 236 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle disorder			
subjects affected / exposed	1 / 238 (0.42%)	0 / 236 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Meningitis viral			
subjects affected / exposed	0 / 238 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			

subjects affected / exposed	0 / 238 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tick-borne viral encephalitis			
subjects affected / exposed	0 / 238 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sialoadenitis			
subjects affected / exposed	1 / 238 (0.42%)	0 / 236 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillitis streptococcal			
subjects affected / exposed	0 / 238 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Diabetic ketoacidosis			
subjects affected / exposed	0 / 238 (0.00%)	2 / 236 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hypoglycaemia			
subjects affected / exposed	3 / 238 (1.26%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus inadequate control			
subjects affected / exposed	0 / 238 (0.00%)	1 / 236 (0.42%)	
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: 2 %

Non-serious adverse events	Placebo	DiaPep277®	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	172 / 238 (72.27%)	171 / 236 (72.46%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	5 / 238 (2.10%)	2 / 236 (0.85%)	
occurrences (all)	5	2	
General disorders and administration site conditions			
Injection site pain			
subjects affected / exposed	18 / 238 (7.56%)	20 / 236 (8.47%)	
occurrences (all)	18	20	
Asthenia			
subjects affected / exposed	6 / 238 (2.52%)	3 / 236 (1.27%)	
occurrences (all)	6	3	
Fatigue			
subjects affected / exposed	5 / 238 (2.10%)	3 / 236 (1.27%)	
occurrences (all)	5	3	
Immune system disorders			
Immune system disorder			
subjects affected / exposed	6 / 238 (2.52%)	6 / 236 (2.54%)	
occurrences (all)	6	6	
Reproductive system and breast disorders			
Reproductive system and breast disorder			
subjects affected / exposed	4 / 238 (1.68%)	6 / 236 (2.54%)	
occurrences (all)	4	6	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	8 / 238 (3.36%)	5 / 236 (2.12%)	
occurrences (all)	8	5	
Oropharyngeal pain			
subjects affected / exposed	7 / 238 (2.94%)	4 / 236 (1.69%)	
occurrences (all)	7	4	
Respiratory disorder			
subjects affected / exposed	6 / 238 (2.52%)	4 / 236 (1.69%)	
occurrences (all)	6	4	
Psychiatric disorders			

Psychiatric disorders subjects affected / exposed occurrences (all)	9 / 238 (3.78%) 9	10 / 236 (4.24%) 10	
Investigations Blood creatine phosphokinase increased subjects affected / exposed occurrences (all) Blood thyroid stimulating hormone increased subjects affected / exposed occurrences (all)	 3 / 238 (1.26%) 3 5 / 238 (2.10%) 5	 6 / 236 (2.54%) 6 1 / 236 (0.42%) 1	
Injury, poisoning and procedural complications Laceration subjects affected / exposed occurrences (all) Joint injury subjects affected / exposed occurrences (all)	 5 / 238 (2.10%) 5 5 / 238 (2.10%) 5	 2 / 236 (0.85%) 2 0 / 236 (0.00%) 0	
Cardiac disorders Cardiac disorders subjects affected / exposed occurrences (all)	 6 / 238 (2.52%) 6	 8 / 236 (3.39%) 8	
Nervous system disorders Headache subjects affected / exposed occurrences (all) Migraine subjects affected / exposed occurrences (all)	 25 / 238 (10.50%) 25 5 / 238 (2.10%) 5	 17 / 236 (7.20%) 17 1 / 236 (0.42%) 1	
Blood and lymphatic system disorders Blood and lymphatic system disorders subjects affected / exposed occurrences (all)	 10 / 238 (4.20%) 10	 8 / 236 (3.39%) 8	
Eye disorders Eye disorders subjects affected / exposed occurrences (all)	 6 / 238 (2.52%) 6	 4 / 236 (1.69%) 4	

Gastrointestinal disorders			
Nausea			
subjects affected / exposed	13 / 238 (5.46%)	9 / 236 (3.81%)	
occurrences (all)	13	9	
Diarrhoea			
subjects affected / exposed	7 / 238 (2.94%)	9 / 236 (3.81%)	
occurrences (all)	7	9	
Abdominal pain			
subjects affected / exposed	6 / 238 (2.52%)	5 / 236 (2.12%)	
occurrences (all)	6	5	
Toothache			
subjects affected / exposed	6 / 238 (2.52%)	5 / 236 (2.12%)	
occurrences (all)	6	5	
Abdominal pain upper			
subjects affected / exposed	4 / 238 (1.68%)	5 / 236 (2.12%)	
occurrences (all)	4	5	
Vomiting			
subjects affected / exposed	7 / 238 (2.94%)	4 / 236 (1.69%)	
occurrences (all)	7	4	
Hepatobiliary disorders			
Hepatobiliary disorder			
subjects affected / exposed	5 / 238 (2.10%)	1 / 236 (0.42%)	
occurrences (all)	5	1	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	3 / 238 (1.26%)	7 / 236 (2.97%)	
occurrences (all)	3	7	
Renal and urinary disorders			
Renal and urinary disorders			
subjects affected / exposed	7 / 238 (2.94%)	4 / 236 (1.69%)	
occurrences (all)	7	4	
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	5 / 238 (2.10%)	2 / 236 (0.85%)	
occurrences (all)	5	2	
Musculoskeletal and connective tissue disorders			

Back pain			
subjects affected / exposed	6 / 238 (2.52%)	11 / 236 (4.66%)	
occurrences (all)	6	11	
Arthralgia			
subjects affected / exposed	4 / 238 (1.68%)	5 / 236 (2.12%)	
occurrences (all)	4	5	
Pain in extremity			
subjects affected / exposed	8 / 238 (3.36%)	3 / 236 (1.27%)	
occurrences (all)	8	3	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	60 / 238 (25.21%)	52 / 236 (22.03%)	
occurrences (all)	60	52	
Upper respiratory tract infection			
subjects affected / exposed	13 / 238 (5.46%)	18 / 236 (7.63%)	
occurrences (all)	13	18	
Influenza			
subjects affected / exposed	17 / 238 (7.14%)	15 / 236 (6.36%)	
occurrences (all)	17	15	
Sinusitis			
subjects affected / exposed	4 / 238 (1.68%)	10 / 236 (4.24%)	
occurrences (all)	4	10	
Gastroenteritis			
subjects affected / exposed	9 / 238 (3.78%)	7 / 236 (2.97%)	
occurrences (all)	9	7	
Urinary tract infection			
subjects affected / exposed	8 / 238 (3.36%)	7 / 236 (2.97%)	
occurrences (all)	8	7	
Bronchitis			
subjects affected / exposed	5 / 238 (2.10%)	7 / 236 (2.97%)	
occurrences (all)	5	7	
Pharyngitis			
subjects affected / exposed	9 / 238 (3.78%)	5 / 236 (2.12%)	
occurrences (all)	9	5	
Tonsillitis			

subjects affected / exposed occurrences (all)	6 / 238 (2.52%) 6	4 / 236 (1.69%) 4	
Rhinitis subjects affected / exposed occurrences (all)	9 / 238 (3.78%) 9	3 / 236 (1.27%) 3	
Metabolism and nutrition disorders Hypercholesterolemia subjects affected / exposed occurrences (all)	5 / 238 (2.10%) 5	0 / 236 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 April 2010	<p>Protocol Version 1.1: version submitted in the initial applications to European regulatory authorities for approval.</p> <p>Summary of changes from original protocol (v.1.0, 08 February 2010)</p> <ol style="list-style-type: none">1. Change of "patient" into "subject" throughout the protocol2. Clarify storage conditions and temperature monitoring3. Add a 10th administration of study medication at Visit 104. Add Visit 11 as the final follow-up/termination visit, at Month 255. Table 2: Add Regular Chemistry tests at all visits where other laboratory tests are run (Visits 1, 2, 4, 6, 8 and 11)6. Added text on the purpose of the CGMS use in the study and how the participating sites will be selected7. Clarify that regardless of CGMS measurements, regular self-measurements of blood glucose should be continued8. Added text on the purpose of performing the HLA typing as an exploratory study and the intended analysis of outcome data9. Correct typo in name of enzyme: aspartate aminotransferase (AST) instead of alanine aminotransferase10. Due to extension of the overall follow-up of period per subject from 24 to 25 months and the addition of an 11th visit (see changes #2 & #3, above), the final follow-up period was shortened from 3 months to 1 month. Accordingly, the follow-up of AE after last administration of study medication11. Contact details for i3 Drug Safety Team in North America was added12. Clarification of the correct form for reporting pregnancy during the study13. Clarification that the Baseline for the MMTT will be either the Qualification Visit or Pre-Visit 1, if Qualification Visit is unnecessary14. Correct typo, Qualification Visit occurs 1-3 weeks before Visit 1, not 2-4 weeks15. Clarification regarding Informed Consent Process:<ol style="list-style-type: none">a. "A person designated by the Investigator" was added as someone who can give the explanations about the studyb. Participation in both HLA typing and CGMS sub-studies is voluntary, and subjects will sign separate ICFs if they wish to participate
14 November 2010	<p>Protocol Version 2.1</p> <p>Rationale for amendment: most of the changes introduced into the protocol were extended explanations and clarifications regarding target population, time lines and procedures; Repeated queries from the sites indicated that some sections were not clear enough and might have resulted in different interpretation by different investigators.</p> <p>Significant issues that had to be clarified included:</p> <ul style="list-style-type: none">- Target population: the eligibility of subjects who were first diagnosed for months or years as T2D or LADA was questioned. This was clearly addressed in this protocol amendment.- Exclusion due to other diseases: subject with resolved basal cell or cervix carcinoma were allowed, as well as subjects that require systemic inhalers to treat/prevent asthma attacks.- Screening-Qualification Period-Randomization: timelines between the visits at the start of the study, how to handle subjects who require more time to reach optimal glycemic control, or who have to be re-screened. Clear time windows were provided for each visit up to randomization/Visit 1- The original protocol required total fasting and no insulin medication on the morning of performing a beta-cell function test: it was recognized that this could often result in blood glucose level higher than the recommended range by the time the test is administered. Detailed recommendations were provided to the investigators in the Study Reference Manual so they could instruct their patients to take some insulin in the morning, according to actual blood glucose.- At the request of the German Federal Agency (BfArM), extra focus was placed on identifying and following-up incipient autoimmune diseases and immune effects.

03 September 2012	<p>Protocol Version 3.0</p> <p>The reason for amending the protocol was mainly to better define the secondary endpoints, the statistical analysis and the handling of missing data. These changes were due to better understanding of the clinical outcome based on the availability of the final results from the first phase 3 study, protocol 901.</p>
17 December 2013	<p>Protocol Version 4.0</p> <p>List of Changes:</p> <ol style="list-style-type: none"> 1. Primary efficacy endpoint defined as the change from Baseline to End of Study of glucagon-stimulated C-peptide secretion, measured as area under the curve (AUC). This is a change from change in mixed-meal induced C-peptide secretion. 2. Major clinical benefit parameters were defined, as suggested by FDA communication and clinical advisory board (CAB). These included glycemic control, insulin dose and hypoglycemic events. These parameters were already defined a secondary endpoints, but then they were highlighted as the main clinical endpoints. 3. Updates were introduced to the statistical section, following recommendations received from the FDA and input from CAB. These include: <ol style="list-style-type: none"> a. Re-definition of Primary, Major Clinical (secondary) efficacy endpoints, as described above. b. Definition of primary population for evaluation of efficacy as ITT subjects who had at least the Baseline and one post-baseline efficacy data (FDA recommendation). c. Definition of Completers Population analysis as main sensitivity analysis for primary efficacy (FDA recommendation). d. Use of mixed-model repeated measurements (MMRM) analysis, with pre-defined co-variants, for analysis of primary and secondary beta-cell function parameters (FDA recommendation). 4. Addition of liver enzyme testing at the visits of 9, 15, 21 & 25 months, according to DSMB recommendations. 5. Definition of how to proceed with safety assessment and IMP administration in cases of elevated liver enzymes, according to DSMB recommendation.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported