



Clinical trial results:

Open-Label Study to Evaluate Long Term Safety and Treatment Effect of DiaPep277® in Subjects who Have Completed Study 1001 (EudraCT No.: 2009-015929-37)

Summary

EudraCT number	2013-002775-17
Trial protocol	IT CZ HU AT LT ES PL
Global end of trial date	02 December 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	1010
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01898286
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., 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., 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	02 December 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 September 2014
Global end of trial reached?	Yes
Global end of trial date	02 December 2014
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

This is an extension study to evaluate the safety and tolerability of long-term treatment with DiaPep277® and to determine the long-term treatment effect of DiaPep277® on parameters of metabolic control and on preservation of beta-cell function in subjects who have long exposure to DiaPep277®.

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 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:

Not applicable (Intervention Model: Single Group Assignment)

Actual start date of recruitment	08 October 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 3
Country: Number of subjects enrolled	Poland: 3
Country: Number of subjects enrolled	Russian Federation: 10
Country: Number of subjects enrolled	United States: 13
Country: Number of subjects enrolled	Czech Republic: 5
Country: Number of subjects enrolled	Germany: 4
Worldwide total number of subjects	38
EEA total number of subjects	15

Notes:

Subjects enrolled per age group

In utero	0
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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)	38
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects diagnosed with Type 1 diabetes mellitus up to six months before randomization to Study 1001 (EudraCT No.: 2009-015929-37), from medical sites in the EU, US, Russia, and Israel.

Pre-assignment

Screening details:

Ninety-nine subjects were screened for the study, 61 subjects failed screening and 38 subjects were enrolled: all 38 enrolled subjects completed the Baseline-Ext Visit (Month 0).

The total duration of this study was planned to be up to 26 months: due to the early termination of the study, no subject reached the 9 month visit.

Period 1

Period 1 title	Treatment period (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

Open-Label

Arms

Arm title	All 1010 Study Subjects treated with DiaPep277®
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Arm description:

All subjects enrolled in the 1010 study, whether previously treated with DiaPep277 or placebo in the 1001 study (EudraCT No.: 2009-015929-37).

Subjects who completed the 1001 study and maintained clinically significant beta-cell function were offered a 2-year continuation of active treatment, since they were likely to benefit from use of the medication.

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

Dosage and administration details:

Administration of DiaPep277® to subjects previously enrolled in the Phase 3 Study 1001 (EudraCT No.: 2009-015929-37): 1 mg of DiaPep277® subcutaneously in the upper arm at 0, 3, 6, 9, 12, 15, 18, and 21 months, for a total of 8 administrations.

Number of subjects in period 1	All 1010 Study Subjects treated with DiaPep277®
Started	38
Completed	0
Not completed	38
Consent withdrawn by subject	1
Premature Termination by the Sponsor	36
Dermal hypersensitivity	1

Baseline characteristics

Reporting groups

Reporting group title	Treatment period
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Reporting group description:

Treatment with DiaPep277® is expected to be long-term; stopping treatment may result in the eventual loss of the preserved beta-cell function. Indeed, extension of phase 2 studies has shown that subjects who were initially treated with DiaPep277® and maintained their initial beta-cell function, required continuation of treatment, losing beta-cell function if switched to Placebo. These extension studies were too small for the outcome to be statistically significant, but they suggested that continuation of treatment is needed for long-term maintenance of efficacy.

Therefore, in this extension study, subjects who completed the 1001 study and maintained clinically significant beta-cell function were offered a 2-year continuation of active treatment, since they were likely to benefit from use of the medication.

Sponsor prematurely ended the study hence this report presents the data of subjects assessed until the study end.

Reporting group values	Treatment period	Total	
Number of subjects	38	38	
Age categorical Units: Subjects			
≤ 27 years	11	11	
> 27 years	27	27	
Age continuous Units: years arithmetic mean standard deviation	33.16 ± 7.343	-	
Gender categorical Units: Subjects			
Female	11	11	
Male	27	27	
Race Units: Subjects			
Caucasian	33	33	
Hispanic	1	1	
Black	3	3	
Asian	1	1	

End points

End points reporting groups

Reporting group title	All 1010 Study Subjects treated with DiaPep277®
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Reporting group description:

All subjects enrolled in the 1010 study, whether previously treated with DiaPep277 or placebo in the 1001 study (EudraCT No.: 2009-015929-37).

Subjects who completed the 1001 study and maintained clinically significant beta-cell function were offered a 2-year continuation of active treatment, since they were likely to benefit from use of the medication.

Subject analysis set title	DiaPep277® - DiaPep277® group
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Subject analysis set type	Sub-group analysis
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Subject analysis set description:

Subjects who received DiaPep277® in both 1001 (EudraCT No.: 2009-015929-37) and the current study.

Subject analysis set title	Placebo - DiaPep277® group
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Subject analysis set type	Sub-group analysis
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Subject analysis set description:

Subjects who received Placebo in 1001 (EudraCT No.: 2009-015929-37) and DiaPep277® in the current study

Primary: Hypoglycemic events

End point title	Hypoglycemic events ^[1]
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End point description:

The number of hypoglycemic events recorded by each subject over the course of the study: due to this study's early termination and the submission of an abbreviated CSR, the number of hypoglycemic events of all 38 study subjects were not reported separately by the two subject analysis sets DiaPep277® - DiaPep277® and Placebo-DiaPep277®.

End point type	Primary
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End point timeframe:

At early termination visit, up to 25 months.

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Due to the early termination of the study, many of the endpoints described in the protocol could not be adequately assessed and a full SAP was not written.

Hypoglycemic events from Continuous Glucose Monitoring System (CGMS) were listed as efficacy parameters: CGMS data were not evaluated

End point values	All 1010 Study Subjects treated with DiaPep277®			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: Hypoglycemic events				
arithmetic mean (standard deviation)	3.3 (± 3.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Glucagon-stimulated C-peptide AUC at Early

Termination Visit - Pancreatic Beta-cell Function

End point title	Change From Baseline in Glucagon-stimulated C-peptide AUC at Early Termination Visit - Pancreatic Beta-cell Function
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End point description:

Beta-cell function, measured as change in stimulated C-peptide secretion measured 0, 2, 6, 10 and 20 minutes post administration [area under the curve (AUC), 0-20 minutes] at Baseline and the early termination visit (up to 25 months), during a glucagon stimulation test (GST). Change was calculated for each subject by subtracting the baseline AUC value (defined as the last non-missing assessment prior to first dose in the 1010 study but after the end of study 1001 - EudraCT No.: 2009-015929-37) from the early termination visit AUC.

End point type	Secondary
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End point timeframe:

Baseline and Early Termination Visit, up to 25 months.

End point values	All 1010 Study Subjects treated with DiaPep277®	DiaPep277® - DiaPep277® group	Placebo - DiaPep277® group	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	9 ^[2]	4 ^[3]	5 ^[4]	
Units: nmol*minute/L				
arithmetic mean (standard deviation)	0.2 (± 2.334)	1.1 (± 2.022)	-0.53 (± 2.518)	

Notes:

[2] - Mean change from Baseline-Ext

[3] - Mean change from Baseline-Ext

[4] - Mean change from Baseline-Ext

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Glycemic Control

End point title	Glycemic Control
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End point description:

Change From Baseline in % HbA1c

Due to this study's early termination and the submission of an abbreviated CSR, the number of hypoglycemic events of all 38 study subjects were not reported separately by the two subject analysis sets DiaPep277® - DiaPep277® and Placebo-DiaPep277®.

End point type	Other pre-specified
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End point timeframe:

Baseline and Early Termination Visit, Up to 25 Months

End point values	All 1010 Study Subjects treated with DiaPep277®			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: percent				
arithmetic mean (standard deviation)	0.46 (± 0.907)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change From Baseline in Daily Insulin Dose, Per kg Body Weight, at Early Termination Visit

End point title	Change From Baseline in Daily Insulin Dose, Per kg Body Weight, at Early Termination Visit
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End point description:

Due to this study's early termination and the submission of an abbreviated CSR, the number of hypoglycemic events of all 38 study subjects were not reported separately by the two subject analysis sets DiaPep277® - DiaPep277® and Placebo-DiaPep277®.

End point type	Other pre-specified
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End point timeframe:

Baseline and Early Termination Visit, up to 25 months.

End point values	All 1010 Study Subjects treated with DiaPep277®			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: IU/Kg				
arithmetic mean (standard deviation)	0.025 (± 0.027)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events (AE) data were collected from the time of subject enrollment through each subject's early termination visit.

Adverse event reporting additional description:

Due to this study's early termination and the submission of an abbreviated CSR, the AE of all 38 study subjects were not reported separately by the two study arms of DiaPep277®-DiaPep277® and Placebo-DiaPep277®.

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	All 1010 Study Subjects treated with DiaPep277®
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Reporting group description:

Treatment with DiaPep277® is expected to be long-term; stopping treatment may result in the eventual loss of the preserved beta-cell function. Indeed, extension of phase 2 studies has shown that subjects who were initially treated with DiaPep277® and maintained their initial beta-cell function, required continuation of treatment, losing beta-cell function if switched to Placebo. These extension studies were too small for the outcome to be statistically significant, but they suggested that continuation of treatment is needed for long-term maintenance of efficacy.

Therefore, in this extension study, subjects who completed the 1001 study and maintained clinically significant beta-cell function were offered a 2-year continuation of active treatment, since they were likely to benefit from use of the medication.

Serious adverse events	All 1010 Study Subjects treated with DiaPep277®		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 38 (2.63%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Immune system disorders			
Anaphylactic shock			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	All 1010 Study Subjects treated with DiaPep277®		
Total subjects affected by non-serious adverse events subjects affected / exposed	9 / 38 (23.68%)		
Investigations			
Electrocardiogram QT prolonged subjects affected / exposed occurrences (all)	2 / 38 (5.26%) 2		
Blood cholesterol increased subjects affected / exposed occurrences (all)	1 / 38 (2.63%) 1		
Low density lipoprotein increased subjects affected / exposed occurrences (all)	1 / 38 (2.63%) 1		
Urine albumin/creatinine ratio increased subjects affected / exposed occurrences (all)	1 / 38 (2.63%) 1		
Injury, poisoning and procedural complications			
Contusion subjects affected / exposed occurrences (all)	1 / 38 (2.63%) 1		
Vascular disorders			
Hypertension subjects affected / exposed occurrences (all)	1 / 38 (2.63%) 1		
Nervous system disorders			
Syncope subjects affected / exposed occurrences (all)	1 / 38 (2.63%) 1		
Headache subjects affected / exposed occurrences (all)	1 / 38 (2.63%) 1		
General disorders and administration site conditions			
Injection site erythema subjects affected / exposed occurrences (all)	1 / 38 (2.63%) 1		
Non-cardiac chest pain			

subjects affected / exposed occurrences (all)	1 / 38 (2.63%) 1		
Blood and lymphatic system disorders Pancytopenia subjects affected / exposed occurrences (all)	1 / 38 (2.63%) 1		
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all) Social phobia subjects affected / exposed occurrences (all)	1 / 38 (2.63%) 1 1 / 38 (2.63%) 1		
Renal and urinary disorders Dysuria subjects affected / exposed occurrences (all)	1 / 38 (2.63%) 1		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) Influenza subjects affected / exposed occurrences (all) Urinary tract infection subjects affected / exposed occurrences (all)	2 / 38 (5.26%) 2 1 / 38 (2.63%) 1 1 / 38 (2.63%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 January 2014	The original protocol dated 18 June 2013, Version 1.0, was amended once during the study with the protocol version 2.0 (dated 20 January 2014). The major changes made in Protocol Version 2.0 are given below: - Modified the study title and study timelines. - Revised text on efficacy parameters and added a new efficacy parameter of CGMS in a subset of subjects. - Clarified text on solvent emulsion that would be supplied. - Added text for abnormal LFTs. - Added text in the study assessment schedule regarding Baseline-Ext visit and CGMS. - Added text on additional laboratory tests on serum antibodies. - Revised text in statistical methods. - Added text regarding informed consent process for optional CGMS.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
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08 September 2014	The study was terminated by Hyperion Therapeutics Inc. on 08 September 2014: - All subject enrollment was stopped and no further sites were initiated. - The active sites with active subjects were instructed to follow the procedures for "Data Collection and Follow-up for Early Withdrawn Subjects" as outlined in the protocol. - The Investigators were instructed to bring all active subjects in for an Early Termination visit (Visit 21A) and complete all assessments for this visit according to the study schedule. However, many subjects refused to complete all of the assessments that were outlined for Visit 21A, and hence minimal data was collected at this Early Termination visit. - Due to the early termination of the study, many of the endpoints described in the protocol could not be adequately assessed and a full SAP was not written. The key changes between the planned analyses described in Protocol Version 2.0 and the Final SAP (Version 1.0. dated 23 December 2014) are as follows: 1. Efficacy parameters not evaluated: a. Percent of subjects who achieve $HbA1c \leq 7\%$. However, as per the Final SAP, only the change from baseline in HbA1c by visit was evaluated. b. "Percent of subjects whose daily dose of insulin is ≤ 0.5 IU/kg at endpoint weighted total insulin dose (units per kg body weight per day) average value". However, as per the Final SAP, only the change from baseline in daily insulin dose per body weight by visit was evaluated. c. "Mean amplitude of glucose excursions by 4-point glucose profile, average value and change from baseline" d. AUC C-peptide level obtained by the MMTT e. Peak Cmax as an efficacy parameter f. Proportion of subjects in partial remission g. Hypoglycemic and hyperglycemic events (from CGMS) and post-prandial glucose excursions (from CGMS); CGMS data were not evaluated. 2. Safety parameters not evaluated: a. Incidence of treatment-emergent ECG findings b. DiaPep277® specific antibodies	-
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Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The study was prematurely terminated by Sponsor on 08Sep2014 and many of the endpoints described in the protocol could not be adequately assessed and a full SAP was not written (please refer to the above global Interruptions section).

Notes: