



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 |
|-----------------------|------|

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 |
|----------|---|

| | |
|---|----|
| 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® |
|------------------|---|

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 |
|-----------------------|------------------|
|-----------------------|------------------|

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 | 33.16 | - | |
| standard deviation | ± 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® |
|-----------------------|---|

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 |
|----------------------------|-------------------------------|

| | |
|---------------------------|--------------------|
| Subject analysis set type | Sub-group analysis |
|---------------------------|--------------------|

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 |
|----------------------------|----------------------------|

| | |
|---------------------------|--------------------|
| Subject analysis set type | Sub-group analysis |
|---------------------------|--------------------|

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] |
|-----------------|------------------------------------|

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 |
|----------------|---------|

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 |
|-----------------|--|

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 |
|----------------|-----------|

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 |
|-----------------|------------------|

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 |
|----------------|---------------------|

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 |
|-----------------|--|

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 |
|----------------|---------------------|

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 |
|-----------------|----------------|

Dictionary used

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|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 17.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---|
| Reporting group title | All 1010 Study Subjects treated with DiaPep277® |
|-----------------------|---|

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: <ul style="list-style-type: none">- 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 |
|------|--------------|--------------|
|------|--------------|--------------|

| | | |
|-------------------|--|---|
| 08 September 2014 | <p>The study was terminated by Hyperion Therapeutics Inc. on 08 September 2014:</p> <ul style="list-style-type: none"> - 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: <ul style="list-style-type: none"> 1. Efficacy parameters not evaluated: <ul style="list-style-type: none"> 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: <ul style="list-style-type: none"> a. Incidence of treatment-emergent ECG findings b. DiaPep277® specific antibodies | - |
|-------------------|--|---|

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: