1 TITLE PAGE

Andromeda Biotech Ltd., a wholly owned subsidiary of Horizon Pharma, Inc.

A Phase III, Multinational, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Investigate the Clinical Efficacy and Safety of DiaPep277® in Newly Diagnosed Type 1 Diabetes Patients (901)

ADDENDUM TO CLINICAL STUDY REPORT

EUDRACT Number:	2005-002590-73
Name of Product:	DiaPep277®
Phase of Development:	III
Date of First Observation:	29 September 2005
Date of Last Observation:	31 August 2011
Indication Studied:	Type 1 Diabetes
Study Design:	Multinational, randomized, double-blind, placebo-controlled, parallel group
Sponsor's Contact:	Horizon Pharma
Date of Original Report:	05 September 2012
Date of Addendum to the Report:	17 September 2015

This study was performed in accordance with Good Clinical Practice, including the archiving of essential documents.

2 SYNOPSIS

NAME OF COMPANY: Andromeda Biotech Ltd., wholly owned subsidiary of Horizon Pharma, Inc. **NAME OF FINISHED PRODUCT:** DiaPep277® **NAME OF ACTIVE INGREDIENT:** Po-102	**INDIVIDUAL STUDY SYNOPSIS – ADDENDUM** **INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	(FOR NATIONAL AUTHORITY USE ONLY)

Title of Study: A Phase III, Multinational, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Investigate the Clinical Efficacy and Safety of DiaPep277® in Newly Diagnosed Type 1 Diabetes Patients. (ADDENDUM)

Investigators: A list of Investigators is included in Appendix 16.1.4 of the original clinical study report.

Study Sites: There were 46 sites across Austria, the Czech Republic, Finland, France, Germany, Greece, Israel, Italy, Republic of South Africa, Spain, and the United Kingdom.

Publication (Reference): None.

Studied Period: 29 September 2005 to 31 August 2011	Phase of Development: III

Study Primary Objective:

- To demonstrate the efficacy of add-on therapy with DiaPep277 in preserving pancreatic beta-cell function in patients with newly diagnosed Type 1 diabetes mellitus (T1D) on intensive insulin therapy. The hypothesis was that pancreatic beta-cell function with DiaPep277 treatment is superior to placebo after 24 months (9 administrations, 21 months treatment, and 3 months follow-up).

Addendum to the Study Report:

- Outlines the additional analyses of the 901 data set intended to provide regulatory authorities with an accurate summary of the DIA-AID 1 study findings.

Methodology: This was a Phase III, multinational, randomized, double-blind, parallel-group study designed to evaluate the efficacy and safety of DiaPep277 versus placebo.

Patients were randomized and stratified according to the following criteria:

- HbA1c value (HbA1c < 7.0% and HbA1c ≥ 7.0%)
- Basal fasting C-peptide concentration (C-peptide < 0.40 nmol/L and C-peptide ≥ 0.40 nmol/L)

Number of Patients: It was planned to randomize at least 400 patients, 200 per treatment group. A total of 679 patients were screened, 457 were randomized (225 to DiaPep277 and 232 to placebo), and 355 patients completed the study (175 in DiaPep277 group and 180 in the Placebo group).

Addendum Analyses:

Analysis Populations

ITT - Safety Evaluation Population: The intent-to-treat (ITT) population included all randomized patients who received at least one dose of study medication. The ITT population was used for all the safety evaluations. The ITT population included all available data but there was no imputation of missing visit data.

MITT Population: The modified intent-to-treat (MITT) population consisted of all randomized patients who received at least one dose of study medication and who entered the study according to the definition of the target population, as defined by the inclusion and exclusion criteria in the study protocol. Patients who were not newly diagnosed with T1D or who were in major violation of the protocol inclusion and exclusion criteria were not to be included in the MITT evaluation of efficacy. The list of patients to be excluded from the MITT population was to have been determined by a blinded clinical review prior to database lock.

Results:

There was no benefit demonstrated with DiaPep277 compared to placebo.

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Conclusion: The study was not successful on the primary endpoint (area under the concentration-time curve-glucagon-stimulated C-peptide or AUC-GST) or on the related secondary endpoint (area under the concentration-time curve-mixed meal tolerance test or AUC-MMTT)		

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3 LIST OF ABBREVIATIONS

AUC-GST	area under the concentration-time curve-glucagon-stimulated C-peptide
AUC-MMTT	area under the concentration-time curve-mixed meal tolerance test
CI	confidence interval
CRO	Contract Research Organization
CSR	clinical study report
DiaPep	DiaPep277
EC	Ethics Committee
GCP	Good Clinical Practices
GST	glucagon-stimulated C-peptide
IND	Investigational New Drug
IRB	Institutional Review Board
ITT	intent to treat
LS	least squares
MHRA	Medicines and Healthcare Products Regulatory Agency
MITT	modified intent to treat
MMTT	mixed meal tolerance test
SAP	Statistical Analysis Plan
SE	standard error
T1D	type one diabetes mellitus
UN	unstructured
VC	variance covariance

4 BACKGROUND

In June, 2014, Hyperion Therapeutics, Inc. ("Hyperion", subsequently acquired by Horizon Pharma in May, 2015) completed the acquisition of Andromeda Biotech Ltd ("Andromeda"). Andromeda is the sponsor for IND 063380, DiaPep277 (DiaPep), protocol 901 (DIA-AID 1), and protocol 1001 (DIA-AID 2). Shortly after the acquisition, Hyperion received the final complete 901 dataset. In the course of analyzing the 901 dataset for the purpose of finalizing the statistical analysis plan (SAP) for the still ongoing 1001 study, Hyperion performed a number of post-hoc analyses summarized below which raised questions regarding the conduct of the study. Hyperion's investigation, which included review of Andromeda emails and employee interviews revealed the following:

- Certain employees of the sponsor, Andromeda, received unblinded data, including glucagon-stimulated C-peptide (GST) data corresponding to the primary efficacy measure, while 901 was ongoing and ostensibly still blinded.
- Patients were excluded from the modified intent-to-treat (MITT) population, which was the population for the primary efficacy analyses, with knowledge of improperly unblinded data so as to obtain a more favorable result.
- The primary endpoint of DIA-AID 1 was changed from C-peptide response to a mixed meal (mixed meal tolerance test or MMTT) to GST with knowledge of improperly unblinded data.
- The SAP was finalized with knowledge of improperly unblinded data.

The same Andromeda employees involved in the improper unblinding concealed these Good Clinical Practices (GCP) violations from Hyperion, regulatory health authorities, Institutional Review Boards (IRB) and Independent Ethics Committees (EC), investigators, advisors and vendors. A notification of a major GCP breach was submitted to Medicines and Healthcare Products Regulatory Agency (MHRA) on February 7, 2012, with a follow-up report on March 1, 2012 by the Contract Research Organization (CRO), I3 (subsequently acquired by InVentiv Health) which disclosed that the same biostatistician who had been unblinded during the 2008 interim analysis was responsible for preparation of the 901 SAP. However, the improper unblinding of 901 study data as outlined above was not recognized or disclosed.

This addendum to the original clinical study report (CSR) outlines the additional analyses of the 901 data set intended to provide regulatory authorities with an accurate summary of the DIA-AID 1 study findings.

5 SUMMARY OF ANALYSES

The analyses were re-done for area under the concentration-time curve-glucagon-stimulated C-peptide (AUC-GST) (area under the curve for glucagon-stimulated C-peptide) (primary endpoint) and area under the concentration-time curve-mixed meal tolerance test (area under the

curve for mixed meal tolerance test) (AUC-MMTT) (a secondary endpoint) on the MITT and intent-to–treat (ITT) populations. The MITT population was the same as in the original CSR. The ITT population included all available data but there was no imputation of missing visit data. The term ITT was used as a flag in the database to identify the patient population with available data, and this report continues to use that term. The definitions for these populations are:

> **ITT - Safety Evaluation Population**: The ITT population included all randomized patients who received at least one dose of study medication. The ITT population was used for all the safety evaluations.
>
> **MITT Population**: The MITT population consisted of all randomized patients who received at least one dose of study medication and who entered the study according to the definition of the target population, as defined by the inclusion and exclusion criteria in the study protocol. Patients who were not newly diagnosed with type one diabetes mellitus (T1D) or who were in major violation of the protocol inclusion and exclusion criteria were not to be included in the MITT evaluation of efficacy. The list of patients to be excluded from the MITT population was to have been determined by a blinded clinical review prior to database lock. However, as summarized above, data for some subjects were removed from the MITT population in light of improperly unblinded data.

For analysis of AUC-GST and AUC-MMTT, the original CSR used a mixed model with terms for treatment, time, treatment by time interaction, baseline C-peptide, and country. The variance covariance (VC) option in SAS / PROC MIXED was used to model the variance covariance structure. For the analyses in this addendum, the model was updated in the following 2 ways: (a) for baseline C-peptide, the model in the original CSR used the on-treatment values; this was replaced with the C-peptide values prior to start of randomized treatment and (b) the VC option for modeling the variance covariance structure assumes independence of repeated measures. This was replaced with the UN (for unstructured) option.

6 RESULTS

In the 4 tables below, the treatment effect is shown for DiaPep – Placebo at the Month 12 and Month 24 visits. An assessment of the results is provided for the final Month 24 visit. Positive values for the treatment difference favor DiaPep and negative values favor placebo. (Note the in-text tables are equivalent to the statistical output tables, therefore no Section 14 tables are included.)

6.1 Primary Endpoint: AUC-GST

Tables 1 and 2 show the result for the primary endpoint for the MITT and ITT populations.

Table 1: DiaPep Addendum: AUC Change of C-Peptide of GST from Baseline MITT Population

Variable	DiaPep	Placebo	LS Mean Diff - LS Mean (SE)	LS Mean Diff - 95% CI	P-value
Month 24	-3.848 (0.4666)	-4.348 (0.4584)	0.5003 (0.4673)	(-0.4191, 1.4197)	0.2851
Month 12	-2.016 (0.4397)	-2.745 (0.435)	0.7289 (0.4171)	(-0.0915, 1.5494)	0.0815
Treatment					0.1180
Visit					<.0001
Treatment*Visit					0.5791
Baseline Fasting C-peptide					<.0001
Country					0.0312

Note: Results from a PROC MIXED repeated measurement model with terms for treatment, visit, treatment by visit interaction, baseline C-peptide, and country with the UN (= unstructured) option for the variance-covariance matrix.

Note: P-values were obtained for treatment differences of least squares means at each visit and for each fixed effect, respectively.

Source: csr_addendum_analyses.sas * rrowell

Output: W:\DiaPep_Indication\901\prod\programs\adhoc\csr_addendum_GST_MITT.rtf * 17SEP15 05:56

Table 2: DiaPep Addendum: AUC Change of C-Peptide of GST from Baseline ITT Population

Variable	DiaPep	Placebo	LS Mean Diff - LS Mean (SE)	LS Mean Diff - 95% CI	P-value
Month 24	-4.291 (0.5489)	-3.822 (0.5352)	-0.469 (0.529)	(-1.5097, 0.5712)	0.3757
Month 12	-2.273 (0.5231)	-2.172 (0.5143)	-0.102 (0.4809)	(-1.0474, 0.8443)	0.8330
Treatment					0.5236
Visit					<.0001
Treatment*Visit					0.4368
Baseline Fasting C-peptide					0.0005
Country					0.1998

Note: Results from a PROC MIXED repeated measurement model with terms for treatment, visit, treatment by visit interaction, baseline C-peptide, and country with the UN (= unstructured) option for the variance-covariance matrix.

Note: P-values were obtained for treatment differences of least squares means at each visit and for each fixed effect, respectively.

Source: csr_addendum_analyses.sas * rrowell

Output: W:\DiaPep_Indication\901\prod\programs\adhoc\csr_addendum_GST_ITT.rtf * 17SEP15 05:56

Tables 1 and 2 show that there is no benefit in AUC-GST with DiaPep compared to placebo at Month 24 (0.2851 and 0.3757, respectively). In fact, Table 2 shows that the result is in favor of placebo (ITT population). Month 12 shows a similar pattern as Month 24. The individual effects of Visit and baseline fasting C-peptide were also highly statistically significant (p <

0.0001 for both tables). Country was also highly significant in Table 1. However, no adjustments have been made for multiplicity and unadjusted p-values should be interpreted with caution.

6.2 Related Secondary Endpoint: AUC-MMTT

Tables 3 and 4 show the result for the MITT and ITT populations.

Table 3: DiaPep Addendum: AUC Change of C-Peptide of MMTT from Baseline MITT Population

Variable	DiaPep	Placebo	LS Mean Diff - LS Mean (SE)	LS Mean Diff - 95% CI	P-value
Month 24	-44.33 (3.6884)	-43.24 (3.5898)	-1.093 (3.7164)	(-8.4018, 6.2167)	0.7690
Month12	-29.59 (3.4876)	-27.29 (3.3846)	-2.301 (3.3294)	(-8.8487, 4.2465)	0.4899
Treatment					0.5994
Visit					<.0001
Treatment*Visit					0.6717
Baseline Fasting C-peptide					<.0001
Country					0.0321

Note: Results from a PROC MIXED repeated measurement model with terms for treatment, visit, treatment by visit interaction, baseline C-peptide, and country with the UN (= unstructured) option for the variance-covariance matrix.
Note: P-values were obtained for treatment differences of least squares means at each visit and for each fixed effect, respectively.
Source: csr_addendum_analyses.sas * rrowell
Output: W:\DiaPep_Indication\901\prod\programs\adhoc\csr_addendum_MMTT_MITT.rtf * 17SEP15 05:56

Table 4: DiaPep Addendum: AUC Change of C-Peptide of MMTT from Baseline ITT Population

Variable	DiaPep	Placebo	LS Mean Diff - LS Mean (SE)	LS Mean Diff - 95% CI	P-value
Month 24	-48.82 (4.0736)	-39.39 (3.9461)	-9.43 (4.0728)	(-17.438, -1.422)	0.0211
Month12	-31.69 (3.7667)	-25.23 (3.6355)	-6.461 (3.4583)	(-13.26, 0.3377)	0.0625
Treatment					0.0218
Visit					<.0001
Treatment*Visit					0.3363
Baseline Fasting C-peptide					<.0001
Country					0.0329

Note: Results from a PROC MIXED repeated measurement model with terms for treatment, visit, treatment by visit interaction, baseline C-peptide, and country with the UN (= unstructured) option for the variance-covariance matrix.
Note: P-values were obtained for treatment differences of least squares means at each visit and for each fixed effect, respectively.
Source: csr_addendum_analyses.sas * rrowell
Output: W:\DiaPep_Indication\901\prod\programs\adhoc\csr_addendum_MMTT_ITT.rtf * 17SEP15 05:56

Tables 3 and 4 show that there is no benefit in AUC-GST with DiaPep compared to placebo at Month 24 (0.7690 and 0.0211, respectively). In fact, both tables at Month 24 show that the result is in favor of placebo (ITT population). Month 12 shows a similar pattern as Month 24. The individual effects of Visit, Country, and baseline fasting C-peptide were also statistically

significant in both tables. Treatment was also significant (in favor of placebo, 0.0218) in Table 4. However, no adjustments have been made for multiplicity and unadjusted p-values should be interpreted with caution.

7 CONCLUSION

The updated results described in this addendum indicate that the study was not successful on the primary endpoint (AUC-GST) or on the related secondary endpoint (AUC-MMTT).