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CONFIDENTIAL

STATISTICAL ANALYSIS PLAN

A Phase IIb, 2-Arm, Randomized, Double-blind, Placebo-Controlled, Multicentre Study to Optimize Diamyd® Therapy Administered into Lymph Nodes Combined with Oral Vitamin D to Investigate the Impact on the Progression of Type 1 diabetes

Sponsor Study Code: DIAGNODE-2[redacted]

[redacted]

Sponsor	Diamyd Medical AB
Product/Compound/Device	Diamyd® intralymphatic injection
Phase of the study	IIb
EudraCT number	2017-001861-25
Author	[redacted]
Company	[redacted]
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Version	Final 1.0 **Date** 23-JUN-2020

SIGNATURES

Sponsor Study Code: DIAGNODE-2[redacted]

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Sponsor Approval

Name, highest academic level, job title: [redacted]

Company Diamyd Medical AB

Signature: _____ Date: _____

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ABBREVIATIONS

AE	Adverse Event
AUC	Area Under the Curve
CIs	Confidence Intervals
CRF	Case Report Form
ELISPOT	Enzyme Linked Immunosorbent Spot Forming Cell Assay
FAS	Full Analysis Set
FGM	Flash Glucose Monitoring
IDAA1c	Insulin-Dose-Adjusted HbA1c
IFNγ	Interferon tumour
IgE	Immunoglobulin E
IMP	Investigational Medicinal Product
LSM	Least Square Mean
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model Repeated Measures
MMTT	Mixed Meal Tolerance Test
PBMCs	Peripheral Blood Mononuclear Cells
PPS	Per Protocol Set
PT	Preferred Term
QALYs	Quality adjusted life years
QoL	Quality of Life
REML	REstricted Maximum Likelihood
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class
T1D	Type 1 Diabetes
TEAE	Treatment-Emergent Adverse Event
TNFα	Tumour Necrosis Factor
WHO	World Health Organization

1 INTRODUCTION

This Statistical Analysis Plan (SAP) is based on Clinical Study Protocol Version 8 (including Protocol Amendment 7), dated May 15 2020.

2 STUDY OBJECTIVES

The main goal is to find a reasonably safe and tolerable treatment for young and adult patients with Type 1 Diabetes (T1D) which can preserve residual insulin secretion, improve the patients' quality of life (QoL) and reduce the risk of both short- and long-term complications.

2.1 Primary Objective

The primary objective is to evaluate the efficacy of Diamyd, administered into lymph nodes in combination with an oral vitamin D regimen, compared to placebo in terms of preserving endogenous insulin secretion as measured by C-peptide.

2.2 Secondary Objectives

The secondary objectives are to compare Diamyd, administered into lymph nodes in combination with an oral vitamin D regimen and placebo treatment with respect to the effects on the diabetes status, treatment safety, immune system and QoL of the patients.

3 EFFICACY AND SAFETY ENDPOINTS

3.1 Primary Efficacy Endpoint

The primary endpoint in this study is:

- Change in C-peptide (Area Under the Curve [AUC]mean 0-120 min) during a Mixed Meal Tolerance Test (MMTT) between baseline and 15 months.

3.2 Secondary Efficacy Endpoints

The key secondary endpoints in this study are:

1. Change in insulin-dose-adjusted HbA1c (IDAA1c) between baseline and 15 months.
2. Change in HbA1c between baseline and 15 months.
3. Change in daily exogenous insulin consumption between baseline and 15 months.

The primary endpoint and the key secondary endpoints will be tested hierarchically as described in Section 6.4.

The other secondary endpoints to evaluate diabetic status are:

- Change in glycemic variability/fluctuations (evaluated from data from continuous glucose monitoring FreeStyle LibrePro, Flash Glucose Monitoring [FGM]) over 14 day period between Screening and 15 months.
- Proportion of patients with IDAA1c ≤ 9 at 15 months.
- Proportion of patients with a stimulated maximum C-peptide level above 0.2 nmol/L (0.6 ng/ml) at 15 months.

- Proportion of patients with a stimulated 90min C-peptide level above 0.2 nmol/L (0.6 ng/ml) at 15 months.
- Number of self-reported episodes of severe hypoglycemia (Severe hypoglycemia defined as needing help from others and/or seizures and/or unconscious) between baseline and 15 months.
- Change in Rate of hypoglycemic events between baseline and 15 months.
- Number of patients having at least 1 severe hypoglycemic event between baseline and 15 months.
- Change in maximum C-peptide during MMTT between baseline and 15 months.
- Change in Fasting C-peptide between baseline and 15 months.
- C-peptide measured at 30, 60, 90, and 120 minutes during MMTT at 15 months.
- Change in body weight and BMI between baseline and 15 months

The secondary endpoints of QoL are:

- Change in QoL as measured by questionnaire EQ-5D-5L between baseline and Month 15.
- Quality adjusted life years (QALYs) based on the EQ-5D-5L questionnaire.

3.3 Safety Endpoints

The secondary endpoints to evaluate safety are:

- Injection site reactions
- Occurrence of Adverse Events (AE)s
- Laboratory measurements (hematology and clinical chemistry)
- Urine analysis (microalbuminuria, creatinine)
- Physical examinations, including neurological assessments
- GAD65-antibody titer
- Vital signs (blood pressure)

The secondary endpoints to evaluate the influence on the immune system are:

- Concentrations of serum autoantibodies towards GAD65 and IA-2.
- Concentrations of serum autoantibody isotypes towards GAD65.
- Secretion of cytokines interleukin (IL)-1, IL-2, IL-5, IL-13, IL-10, IL-17, interferon (IFN)γ, and tumour necrosis factor (TNF)α by peripheral blood mononuclear cells (PBMCs) upon stimulation with GAD65.
- Serum concentrations of cytokines IL-1, IL-2, IL-5, IL-13, IL-10, IL-17, IFNγ, and TNFα
- Secretion of cytokines IL-1, IL-2, IL-5, IL-13, IL-10, IL-17, IFNγ, and TNFα by PBMCs upon stimulation with anti-CD3 and anti-CD28
- Proliferation of PBMCs upon stimulation with GAD65.
- Further exploratory immunological characterization.

3.4 Exploratory Endpoints

All data collected at the 24-month follow-up visit (Visit 8) will be regarded as exploratory endpoints and will be presented using summary statistics including data from the main study period where only the patients that participated in the Extended Study Period will be included. The following statistical analyses will be repeated for the whole study period:

- The change in log-transformed C-peptide AUCmean 0-120 min during an MMTT from baseline to Month 24
- Change in HbA1c between baseline and 24 months
- Change in daily exogenous insulin consumption between baseline and 24 months
- Change in Fasting C-peptide between baseline and 24 months.
- Change in glycemic variability/fluctuations (evaluated from data from continuous glucose monitoring FreeStyle LibrePro, FGM) over 14 day period between Screening and 24 months.
- Rate of hypoglycemic events using Poisson regression including randomization strata (GAD65A)
- Number of patients having at least 1 severe hypoglycemic event using Cochran/Mantel-Haenszel Test stratified for randomization strata (GAD65A)
- Change in body weight and BMI between baseline and 24 months

4 OVERALL STUDY DESIGN

4.1 Overview of Study Design

The study is a 2-arm, randomized, double-blind, placebo-controlled study in GAD65A positive T1D 12 to <25 years old patients, diagnosed within 6 months prior to screening with fasting C-peptide levels of 0.12 nmol/L (0.36 ng/ml) or higher.

The study aim is to recruit 106 patients which will be followed for 15 months in the Main Study Period. All patients that have not performed Visit 7 (Month 15) when protocol version 7 was approved and implemented will be asked to participate in the Extension Study Period which includes an additional visit at month 24.

At Visit 2, patients eligible for the study will be randomized in a 1:1 ratio stratified by GAD65A level and country to receive either:

- three intralymphatic injections with 4 µg Diamyd and oral vitamin D 2000 IE daily for 4 months
- three intralymphatic injections of Placebo for Diamyd and oral Placebo for vitamin D daily for 4 months

The schedule of study events are given in Table 1.

Table 1 Schedule of Study Events

Event	V1 Screening	V2 Baseline Visit	V3 Month 1	V4 [a] Month 2	V5 [a] Month 3	V6 Month 6	V7 Month 15	V8[n] Month 24
DAY	**-14 to -28**	**1**	**30 (±5)**	**60 (±5)**	**90 (±5)**	**180 (±14)**	**450 (±14)**	**720 (±14)**
Informed Consent	X							
Eligibility check[b]	X	X						
Demographics	X							
Randomization		X						
Diamyd/placebo [a]			X [c]	X [c]	X [c]			
Vitamin D/placebo [d] start /end		X				X (day 120)		
Medical History	X							
Family history of T1D	X							
General Physical Exam [e]	X	X	X	X	X	X	X	X
Neurological Assessment	X	X	X	X	X	X	X	X
Concomitant Medication	X	X	X	X	X	X	X	X
Vital signs (BP)	X	X	X	X	X	X	X	X
Pubertal Stage, if applicable [f]	X					X	X	X
Distribution of patient eDiary		X						
eDiary use compliance			X	X	X	X	X	X
Injection Site Inspection; investigator/study nurse [g]			X	X	X			
Injection Site Inspection; in eDiary [h]			X	X	X			
Insulin Dose Collected [i]		X	X	X	X	X	X	X
FreeStyle LibrePro, FGM [j]	X					X	X	X
AEs		X	X	X	X	X	X	X
Urine Pregnancy Test (menarchal females only)	X	X	X	X	X	X	X	X
Self-reported severe hypoglycemia [k]		X	X	X	X	X	X	X
QoL questionnaire		X				X	X	X
MMTT[l]		X				X	X	X
Blood Sampling for Safety, Genetics, Vitamin D levels and Immunology:								
Hematology	X	X	X	X	X	X	X	X
Clinical Chemistry	X	X	X	X	X	X	X	X
GAD65A titer	X	X	X	X	X	X	X	X
HLA characterization			X					
Vitamin D level	X	X	X	X	X	X	X	X
Covid-19 serological test[m]							X	X
Other immunological parameters as specified in Section ***Error! Reference source not found.***		X	X	X	X	X	X	X
Urine Analysis:								
Microalbuminuria	X	X	X	X	X	X	X	X
Creatinine	X	X	X	X	X	X	X	X
Blood Sampling for Diabetes Status:								
Fasting C-peptide	X	X	X	X	X	X	X	X
MMTT-induced C-peptide [l]		X				X	X	X
HbA1c	X	X	X	X	X	X	X	X

Fasting Glucose	X	X	X	X	X	X	X	X
MMTT-induced Glucose[l]		X				X	X	X

Abbreviations: AEs=Adverse Events; BP= Blood Pressure; eDiary=electronic Diary; GAD65A=Antibodies to glutamic acid decarboxylase with molecular mass 65kDa; HBA1c=Hemoglobin A1c; HLA=Histocompatibility antigen; MMTT=mixed meal tolerance test; FGM=Flash Glucose Monitoring; GAD65=Glutamine acid decarboxylase with a molecular mass of 65kDa; GAD65A= antibodies to GAD65; MMTT=Mixed Meal Tolerance Test; T1D=Type 1 Diabetes; QoL=Quality of Life

a. Study drug administration: For Visit 4 and 5 the visit date must be set in accordance with Visit 3 and 4, respectively, so that the first, second and third doses will be 30 days apart (± 5days).
b. If the fasting c-peptide concentration is not ≥0,12 nmol/L (0.36 ng/ml) at the screening visit this test can be repeated on another day within a period of 2 weeks (maximum 2 tests on different days within a 2-week period).
c. The Diamyd/placebo injection directly into the inguinal lymph node is to be done by an appropriately qualified person at the X-ray department by help of ultrasound technique. For more information regarding the injection please refer to the operations manual for the injection procedure.
d. Treatment with vitamin D/placebo starts at Visit 2 if the Vitamin D serum levels are below 100 nmol/L (40 ng/ml) at screening. If the patient has Vitamin D serum levels above 100 nmol/L (40 ng/ml) at screening, no Vitamin D/placebo treatment will be given for that patient.
e. General Physical Exam also to include height and weight
f. Pubertal Stage should be measured when applicable. Not applicable >1.5 years after the patient have reached final height
g. The investigator/study nurse will inspect the injection site before and after the injection is given and record any injection site reactions in the electronic Case Report Form (eCRF)
h. The patient will record injection site reactions in the eDiary starting the day after injection and for 7 days following the injection. Injection site reactions reported by patients in the electronic diary during day 1-7 following an injection should not be reported as an AE in the eCRF. Any injections site reactions reported after the 1 week recording period will be recorded as AEs in the eCRF.
i. Patients will record insulin dose in the eDiary for 4 days prior each visit starting from Visit 2. Insulin dose collected at Visit 2 (for the 4 days prior to Visit 2) will be done by the Investigator and recorded in the eCRF.
j. FGM during 2 weeks post visit for Visits 1, 6 and 7. Patients will be given instructions on when and where to return the device after the testing period. For instruction on how to return the Freestyle Libre Pro sensor, please refer to the Freestyle Libre Pro Worksheet.
k. The number of self-reported severe hypoglycemia (defined as needing help from others and/or seizures and/or unconsciousness) should be recorded in the eCRF and each event will be recorded separately.
l. See Procedure for MMTT in the Operations Manual
m. Only applicable to patients completing their Visit 7 after 01 January 2020. Applicable to all patients performing Visit 8.
n. Patients that are ongoing, i.e. have not performed Visit 7 (Month 15) when protocol version 7 is approved and implemented, will be asked to consent for the Extension Study Period an additional visit at Month 24.

4.2 Determination of Sample Size

A total sample size of 106 patients is planned for a 1:1 randomization in order to provide 90% power to detect a 50% difference in geometric mean C-peptide ($AUC_{mean\ 0\text{-}120\ min}$) during an MMTT at 15 months between the active arm and placebo arm using a two-sided test at the 0.05 significance level. The sample size has been adjusted to allow for 10% loss to follow-up. This is based upon a t-test employing ln(X+1) normalizing transformation of C-peptide ($AUC_{mean\ 0\text{-}120\ min}$) during an MMTT at 15 months and assumed mean and standard deviation estimates, on the transformed scale, of 0.134 and 0.20, respectively. It is estimated that there will be a screening failure rate of 16%. To ensure that 106 patients are screened and enrolled approximately 127 patients will be screened.

5 DATA SETS TO BE ANALYSED

The following analysis sets will be used for the statistical analysis and presentation of data:

- **The screened set** will consist of all patients that were screened for participation in this study.
- **The randomized set** will consist of all patients that were randomized.
- **The safety set** will consist of all randomized patients who received at least one injection.
- **The full analysis set (FAS)** will consist of all randomized patients who have received at least one dose of study medication and have at least one post-baseline assessment and corresponding baseline measurement of any efficacy variable.
- **The Extension set** will consist of the subset of the FAS that participated in the Extension Study Period.
- **The Completers Set** will consist of all patients in the FAS who have completed the main study period and who have primary efficacy data available at Visit 7.
- **The per protocol set (PPS)** will consist of all patients in the FAS who received all three study drug injections, and do not have any other major protocol violations which will affect the assessment of efficacy. Major protocol violations include:
    - Missed at least one scheduled injection of Investigational Medicinal Product (IMP)
    - C-peptide samples received by lab later than 48 hours after sampling

The final criteria for PPS, regarding which protocol deviations that warrant exclusions, will be determined when all data on protocol violations/deviations are available and before breaking the blind. The final criteria will be documented in the Pre-Analysis Review form issued by the statistician prior to unblinding.

The Screened set will be used for presentation of study disposistion of patients.

The FAS is considered as the primary analysis dataset for or all primary, secondary and exploratory efficacy endpoints. The primary efficacy analyses will be repeated using the PPS and the completers set and these analyses will be regarded as sensitivity analyses. Any discrepancy between the results from the FAS and the PPS or the completers set will be discussed in the Clinical Study Report.

Baseline presentations will be based on the safety set and the FAS.

Safety presentations will be based on the safety set.

FAS will be analysed according to randomised (planned) treatment. Safety and PPS will be analysed on actual treatment received.

6 STATISTICAL AND ANALYTICAL PLANS

An overview of the planned tables, figures and listings are presented in Section 8.

6.1 Changes in the Planned Analyses

No changes were made to the planned analyses.

6.2 Blind Review

Before breaking the blind of this study, a blind Pre-Analysis Review will be performed. The following assessments will be made:

- Determine exclusions from analysis data sets.
- The distribution of the primary endpoint and whether the log transformation is justified.
- The completeness of insulin doses as recorded in diaries.
- Identify ePRO and diaries that were completed outside time windows
- Review of reports of glucose monitoring FreeStyle LibrePro, FGM data for patients whose devices were discarded.

6.3 Hypotheses and Statistical Methods

6.3.1 Definitions

Baseline: Generally, a baseline measurement refers to the last non-missing assessment made before the first administration of IMP (i.e., at Visit 1 or Visit 2).

Relative day: For events occurring or starting on or after the date of first administration of IMP, the relative day is derived as:

(Start date) - (Date of first administration of IMP) + 1

For events occurring or starting before the date of first administration of IMP, the relative day is derived as:

(Start date) - (Date of first administration of IMP)

In this way, there will be no Day 0. Day 1 is the same day as the day of first administration of IMP, and Day -1 is the day before.

6.3.2 Summary Statistics

For all statistical analyses, p-values and 95% Confidence Intervals (CIs) will be given as applicable and follow the decimal rules given below.

Summary statistics will be presented by treatment group and assessment time and/or visit, as applicable.

<u>Continuous variables</u>

Summary statistics will include number of observations, number of missing observations, mean, standard deviation, minimum, median, and maximum. The number of decimals will be based on the mean value and given in accordance with the three significant digit rule, i.e.:

mean ≥100:	no decimals
100 > mean ≥10:	one decimal
10 > mean ≥1:	two decimals
1 > mean ≥0.1:	three decimals
0.1 > mean:	to be determined case by case (possibly consider change in unit)

Categorical variables

Categorical variables will be presented as frequencies and percentages.

The number and percentage of missing data points will be given and percentages will be based on all patients in analysis dataset used. Percentages will given with one decimal with the exception of 100% (no decimal) and the case of no observation for which only a 0 will appear in the table.

Graphical display

Summary statisics (mean ± standard deviation) will be given graphically for certain parameters as indicated in Section 8.

6.3.3 Patient/Subject Data Listings

Data collected in the CRF will generally be listed in Appendix 16.2 (see section 8.1.1). CRF check questions [e.g. Lab samples taken (Yes/No)] and reminders will not be listed.

Listings will be sorted by treatment group, study centre and patient/subject number.

For AEs and medications, the relative day and duration will be included in the listings. Relative days will only be calculated for records with complete dates.

6.3.4 Demographic and Other Baseline Characteristics

Unless stated otherwise, the presentations in this section will be performed on both the Safety set and the FAS.

Subject disposition
Number of screened, randomized and completed study as well as reason for not completing the study (with number of non-completers as denominator) will be presented using summary statistics. This presentation will be based on the screened set.

Subject disposition in analysis data sets:
Number of patients in the Safety set, the FAS, the Completers set and the PPS as well as number of excluded patients for each dataset (with number of exclusions for respective dataset will be used as denominator) will be presented using summary statistics. This presentation will be based on the randomized set.

Study visits
Number of subjects at each study visit will be presented using summary statistics.

Demography
Age, sex, family history of T1D, relation to patient, height, weight, BMI and time since diagnosis will be presented using summary statistics.

Medical history

Medical history will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) system. System Organ Class (SOC) and by Preferred Term (PT) will be presented using summary statistics.

6.3.5 Primary Efficacy analysis

Absolute and change from baseline values of C-peptide AUCmean 0-120 min during an MMTT will be presented using summary statistics. If this endpoint is log-transformed for the purpose of statistical analysis, this presentation will be done for log-transformed values as well and the back-transformed summary statistics will be given in the table.

The primary efficacy variable will be change in log-transformed C-peptide AUCmean 0-120 min during an MMTT from baseline to Month 15. Mean changes from baseline will be analyzed using a Restricted Maximum Likelihood (REML)-based repeated measures approach (Mixed Model Repeated Measures [MMRM]). The model for analysis will include fixed, categorical effects of treatment, randomization strata (GAD65A level), visit and treatment by visit interaction, as well as the continuous, fixed covariate of log-transformed baseline C-peptide AUCmean 0-120 min during an MMTT. An unstructured (co)variance structure will be used to model the within-patient errors. If this analysis fails to converge, compound symmetry and autoregressive (1) will be tested (the (co)variance structure converging to the best fit of the two models, as determined by Akaike's information criterion will be used as the primary analysis). The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. The primary treatment comparison will be the contrast between treatments at Month 15 for active treatments versus placebo. This analysis will be repeated on the PPS and PPS analysis will be regarded as a sensitivity analysis.

Back-transformed Least Square Mean (LSM) estimate and 95% CIs for change from baseline to 15 months in C-peptide $AUC_{mean\ 0\text{-}120\ min}$ during MMTT will be given together with the p-value. The back-transformed estimates of the treatment difference will provide an estimate for the (Diamyd/placebo)-ratio in the relative change from baseline in AUC. Here a ratio of e.g. 0.80 will mean that the change from baseline to month 15 in C-peptide level was 20% smaller for Diamyd than for placebo at Month 15. This presentation will be repeated for the PPS.

An additional sensitivity analysis where the hypotheses will also be assessed using Analysis of Covariance (ANCOVA) adjusted for randomization strata (GAD65A level) and baseline value of C-peptide ($AUC_{mean\ 0\text{-}120\ min}$) using the completers set.

Back-transformed Least Square Mean (LSM) estimate and 95% CIs for change from baseline to 15 months in C-peptide $AUC_{mean\ 0\text{-}120\ min}$ during MMTT will be given together with p-value. The back-transformed estimates of the treatment difference will provide an estimate of the ratio of AUC for Diamyd and AUC for placebo at Month 15.

The primary analysis and the sensitivity analyses, the MMRM will be repeated on the Completers set and the ANCOVA will be repeated using the FAS and the PPS.

The primary endpoint will be further explored using covariate (Section 6.5) and subgroup (Section 6.8) analyses.

6.3.6 Key Secondary Efficacy Analyses

Absolute and change from baseline values of all secondary efficacy endpoints will be presented using summary statistics.

The following key secondary efficacy endpoint variables will be analysed with the same model (MMRM) as the primary efficacy endpoint:

1. Change in IDAA1c between baseline and 15 months.
2. Change in HbA1c between baseline and 15 months.
3. Change in daily exogenous insulin consumption between baseline and 15 months.

The analysis of key secondary endpoints will be subject to the same sensitivity analyses as the primary efficacy analysis. However, exploration of key secondary endpoints by covariate and subgroups analyses will be based on the observed results for respective endpoint.

6.3.7 Secondary Efficacy Analyses

Absolute and change from baseline values of all secondary efficacy endpoints will be presented using summary statistics. These analyses will be based on the FAS.

Summary statistics (including Student's t based 95% CIs and p-value for the difference between Diamyd and Placebo) for change in glycemic variability/fluctuations (evaluated from data from continuous glucose monitoring FreeStyle LibrePro, FGM) over 14-day period between Screening and 15 months:

- Change in time in glycaemic target range 70-180 mg/dL (evaluated from continuous glucose monitoring data over a 14-day period) between baseline and 15 months, as compared to placebo.
- Change in time in hypoglycaemic range 50-70 mg/dL (evaluated from continuous glucose monitoring data over a 14-day period) between baseline and 15 months, as compared to placebo.
- Change in time in severe hypoglycaemic range <50 mg/dL (evaluated from continuous glucose monitoring data over a 14-day period) between baseline and 15 months, as compared to placebo.

At one of the sites the Study Nurse discarded the FreeStyle LibrePro glucose sensors by mistake. However, the data was downloaded as summary reports which will be reviewed during the Pre-Analysis Review to evaluate the possibility of using them to generate estimates.

The FreeStyle LibrePro, FGM data is given in mmol/L this will be converted to mg/dL by multiplication with 18.

The following secondary efficacy endpoint variables will be analyzed with the same model (MMRM) as the primary efficacy endpoint:

- Proportion of patients with by IDAA1c less or equal to 9 at 15 months.
- Change in maximum C-peptide during MMTT between baseline and 15 months.
- Change in Fasting C-peptide between baseline and 15 months.
- Change in C-peptide measured at 30, 60, 90, and 120 minutes during MMTT at 15 months.
- The results from these analyses will be presented in the same way as the results from the primary analysis.

The summary statistics presentations for the following endpoints will include p-values from Cochran/Mantel-Haenszel Test stratified for randomization strata (GAD65A level) and 95% CIs calculated according to the Clopper-Pearson method:

- Proportion of patients with a stimulated maximum C-peptide level above 0.2 nmol/L (0.6 ng/ml) at 15 months.
- Proportion of patients with a stimulated 90min C-peptide level above 0.2 nmol/L (0.6 ng/ml) at 15 months.

- Number of patients having at least 1 severe hypoglycemic event using Cochran/Mantel-Haenszel Test stratified for randomization strata (GAD65A level).
- Change in body weight and BMI between baseline and 15 months

In addition, the number of self-reported episodes of severe Hypoglycaemia (severe Hypoglycaemia defined as needing help from others and/or seizures and/or unconscious) between baseline and 15 months will be assessed using Poisson regression including randomization strata (GAD65A level) where rate ratios with 95% CI and p-value will be given.

6.3.8 Quality of Life

QoL was measured by the EQ-5D™. It consists a Visual Analogue Scale (VAS) and a descriptive system of health-related quality of life states consisting of five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression). The EQ-5D VAS is a standard vertical 20 cm visual analogue scale for recording an individual's rating for their current health-related quality of life state. It ranges from 0 (worst imaginable health state) to 100 (best imaginable health state). In this study the EQ-5D-5L version was used. The EQ-5D-5L each item can take one of five responses (no problems/slight problems/moderate problems/severe problems/ extreme problems). This means that for the EQ-5D-5L there are 3125 ($=5^5$) possible health states or health profiles that can be represented by 5 figures, 11111 representing the best possible health state and 55555 the worst. The Spanish EQ-5D-5L Value Set (Ramos-Goni et al., 2107) will be used to derive the EQ-5D-5L total score.

The EQ-5D-5L total score, the answers to the VAS and the EQ-5D-5L items will be presented using summary statistics (for the total score and the VAS 95% CI will be given) by visit.

6.3.9 Exploratory Efficacy Analyses

All data collected at the 24-month follow-up visit (Visit 8) will be regarded as exploratory endpoints and will be presented using summary statistics including data from the Main Study Period where only the patients that participated in the Extension Study Period will be included. The following endpoints will have the statistical analyses repeated for all data up to and including Visit 8:

The statistical analyses, as specified above, will be repeated for the whole study period for the following endpoints:

- The change in log-transformed C-peptide AUCmean 0-120 min during an MMTT from baseline to Month 24
- Change in HbA1c between baseline and 24 months
- Change in daily exogenous insulin consumption between baseline and 24 months
- Change in Fasting C-peptide between baseline and 24 months
- Change in glycemic variability/fluctuations (evaluated from data from continuous glucose monitoring FreeStyle LibrePro, FGM over 14-day period between Screening and 24 months
- Rate of hypoglycemic events using Poisson regression
- Number of patients having at least 1 severe hypoglycemic event using Cochran/Mantel-Haenszel Test stratified for randomization strata (GAD65A level)
- Change in body weight and BMI between baseline and 24 months

Exploratory efficacy analyses will be performed for the Extension set only.

6.3.10 Exposure to Treatment

In total five Vitamin D bottles were distributed, and the subjects were instructed to use four over 120 days with one extra bottle being a spare. Compliance will be calculated as the number of used bottles divided by four and can therefore take the values 0%, 25%, 50%, 75%, 100% and 125% (in case the fifth bottle was used). In addition, patients that were not given any Vitamin D due to their Vitamin D level at study entry will form a category of their own, 'Vitamin D not needed'. Summary statistics will be given for Vitamin D/Placebo compliance.

Extent of exposure to Diamyd/Placebo will be given as number (percentage) of patients who received all three injections according to protocol as well as reasons for not receiving all three injections according to protocol (where number of patients who did not receive all three injections according to protocol will be the denominator).

These presentations will be based on the safety set.

6.3.11 Concomitant Medications

All concomitant medications/therapies will be classified according to ATC level 3 group text and World Health Organization (WHO) Drug Dictionary preferred name. The medications will be divided into three categories based on start date and end date: Prior Medications, Concomitant Medications and Post-Medications:

- Prior Medications: start date and end date before first day of Investigational Medicinal Product (IMP)
- Concomitant Medications:
    - Start date before first day of IMP and end date after or on same day as first day of IMP or no end date, i.e. ongoing after first day of IMP; or
    - Start date after or on same day as first day of IMP or on same day as last day of IMP, but not after last day of IMP
- Post-Medications: Start date after last day of IMP

The concomitant medications will be presented in a summary table broken down on timing in relation to IMP (i.e., prior, concomitant and post). Each subject will be counted once for each medication and timing category.

This presentation will be based on the safety set.

6.3.12 Adverse Events

AEs will be coded according to the MedDRA system and will be tabulated by SOC and PT. A unique AE is defined as being counted once within each subject at the preferred term level.

A Treatment Emergent AE (TEAE) is an AE that start on the same day as the first injection of IMP or later or an ongoing event that is worsening at the time of first injection of IMP or later.

For AEs, SAEs, related AEs, AEs leading to discontinuation of IMP/withdrawal and AEs leading to death the following will be given:

- total number of events
- number of unique events
- number of subjects with at least one event

TEAEs will also be summarized by SOC and PT;

- total number of AEs (at SOC and PT level)
- number of subjects with at least one AE (at SOC and PT level)

This table will be repeated for SAEs, IMP related AEs, vitamin D related AEs and the severity categories (mild, moderate and severe).

The total number AEs and the number of subjects with at least one AE will be given by SOC, PT, intensity (mild, moderate and severe) and relationship to treatment (related [unlikely related, possibly related or probably related]) and not related) will also be summarized. If a subject has more than one event with the same PT, then the worst intensity and the worst relationship will be used.

Deaths, other SAEs, and other significant AEs will be listed, these include:

- AEs leading to death
- laboratory abnormalities, abnormal vital signs and abnormal physical observations that were considered SAEs
- laboratory abnormalities other than those meeting the definition of serious, i.e., judged as clinically significant by the investigator
- non-SAEs that led to an intervention, including withdrawal of test drug/investigational product treatment, dose reduction, or significant additional concomitant therapy

AE listings will be divided on AEs occurring before first dose of Vitamin D, AEs occurring after first Vitamin D but before first IMP and AEs occurring after first IMP. It will include AE term as reported by the investigator, SOC, PT, start (date and time), start day relative to first dose of Vitamin D, time (if occurring on the same day as IMP) or day relative to first IMP, end (date and time), duration (time if ending on the same day as IMP, otherwise days), intensity, serious, relation to Vitamin D, relation to IMP, action taken and outcome.

TEAEs will also be listed sorted by SOC, PT and time of occurrence. The SAEs listing will include seriousness category.

All AE tables and listings divided by time period as prior to first dose of Vitamin D, the period between first dose of Vitamin D and the first injection of IMP and TEAEs.

All AE presentations will be based on the safety set.

6.3.13 Other Safety Assessments

All other safety assessments will be based on the safety set.

Vital Signs

For all vital sign body measurement parameters (height, weight and BMI) summary statistics will be produced for observed values and change from baseline by sex and visit.

For all other vital sign parameters (systolic and diastolic blood pressure) summary statistics will be produced for observed values and change from baseline by visit. In addition, a shift table will be given (Table 2).

Table 2 Vital signs shift table

			Baseline status							
			Diamyd				Placebo			
			Normal	NCS	CS	Unknown	Normal	NCS	CS	Unknown
Parameter	Month X	Normal	n (xx.x%)	n (xx.x%)	n (xx.x%)	n (xx.x%)	n (xx.x%)	n (xx.x%)	n (xx.x%)	n (xx.x%)
		NCS	n (xx.x%)	n (xx.x%)	n (xx.x%)	n (xx.x%)	n (xx.x%)	n (xx.x%)	n (xx.x%)	n (xx.x%)

		CS	n (xx.x%)	n (xx.x%)	n (xx.x%)	n (xx.x%)	n (xx.x%)	n (xx.x%)	n (xx.x%)	n (xx.x%)
		Unknown	n (xx.x%)	n (xx.x%)	n (xx.x%)	n (xx.x%)	n (xx.x%)	n (xx.x%)	n (xx.x%)	n (xx.x%)
NCS: Not Clinically Significant, CS: Clinically significant.										

Clinical Laboratory Measurements

If laboratory values are below the limit of quantification, the value corresponding to the limit of quantification will be used when summarizing data (e.g. if the result is <x.x then the value x.x will be used).

Abnormal clinically significant laboratory values will be listed separately including site id, patient id, laboratory category, laboratory parameter, visit, data and time for sample, reference range and lab result.

Summary statistics will be given for observed values and change from baseline for hematology (basophils, eosinophils, hemoglobin, leucocytes, lymphocytes, MCH, MCHC, MCV, monocytes, neutrophils and platelets), clinical chemistry (alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, bilirubin indirect (unconjugated), bilirubin total, calcium and creatinine), Vitamin D, GAD65A titer fasting glucose and MMTT-induced glucose. Urine analysis (microalbuminuria, urine creatinine) and HLA characterization data will also be summarized.

Shift tables will be given for hematology, clinical chemistry and urinalysis. These tables will have the same layout as the shift table for vital signs (Table 2).

6.3.14 Immunology

Summary statistics will be given for observed values and change from baseline for other immunological parameters:

- Concentrations of serum autoantibodies towards GAD65 and IA-2
- Concentrations of serum autoantibody isotypes towards GAD65
- Secretion of cytokines IL-1, IL-2, IL-5, IL-13, IL-10, IL-17, IFNγ and TNFα by peripheral blood mononuclear cells (PBMCs) upon stimulation with GAD65
- Secretion of cytokines IL-1, IL-2, IL-5, IL-13, IL-10, IL-17, IFNγ, and TNFα by PBMCs upon stimulation with anti-CD3 and anti-CD28
- Serum concentrations of cytokines IL-1, IL-2, IL-5, IL-13, IL-10, IL-17, IFNγ, and TNFα
- Proliferation of PBMCs upon stimulation with GAD65

In Table 3 details on variables and data presentations are given. Statistical analysis to determine 95% CIs and p-values will be done using student's t-test or other test as deemed necessary, e.g., if testing is deemed to be non-parametrically). All presentations will be given by timepoint and treatment group.

Immunological parameters will also be broken down on the HLA and COVID-19 subgroups (Section 6.5).

Table 3 Details on statistical analysis of other immunological parameters

Category	Raw data results variable	Statistical variables	Analysis
Proliferation	Pr_unst Pr_GAD Pr_aCD3-aCD28	 Pr_SI = Pr_GAD/Pr_unst Pr_aCD3-aCD28_SI = Pr_aCD3-aCD28/Pr_unst	1, 2, 3 3
IA-2	IA-2	IA-2	1, 2, 3
GADA	GADA	GADA	1, 2, 3
GADA subclasses	GADA_IgG1 GADA_IgG2 GADA_IgG3 GADA_IgG4	GADA_IgG1 GADA_IgG2 GADA_IgG3 GADA_IgG4 GADA_quotient = GADA_IgG4/GADA_IgG1	1, 2, 3
GAD Stimulated Cytokine Secretion	IL-1_unst IL-1_GAD IL-2_unst IL-2_GAD IL-5_unst IL-5_GAD IL-13_unst IL-13_GAD IL-10_unst IL-10_GAD IL-17_unst IL-17_GAD INFg_unst INFg_GAD TNF_unst TNF_GAD	IL-1_stim = IL-1_GAD - IL-1_unst IL-2_stim = IL-2_GAD - IL-2_unst IL-5_stim = IL-5_GAD - IL-5_unst IL-13_stim = IL-13_GAD - IL-13_unst IL-10_stim = IL-10_GAD - IL-10_unst IL-17_stim = IL-17_GAD - IL-17_unst IFNg_stim = IFNg_GAD - INFg_unst TNF_stim = TNF_GAD - TNF_unst Stim_cyt_quotient = IL-10_stim/IFNg_stim	1, 2 1, 2 1, 2, 3
Serum cytokines	IL-1_serum IL-2_serum IL-5_serum IL-13_serum IL-10_serum IL-17_serum INFg_serum TNF_serum	IL-1_serum IL-2_serum IL-5_serum IL-13_serum IL-10_serum IL-17_serum INFg_serum TNF_serum	1, 2, 3
Control Stimulated Cytokine Secretion	IL-1_aCD3-aCD28 IL-2_aCD3-aCD28 IL-5_aCD3-aCD28 IL-13_aCD3-aCD28 IL-10_aCD3-aCD28 IL-17_aCD3-aCD28 INFg_aCD3-aCD28 TNF_aCD3-aCD28	IL1_cntrl = IL-1_aCD3-aCD28 - IL-1_unst IL2_cntrl = IL-2_aCD3-aCD28 - IL-2_unst IL-5_cntrl = IL-5_aCD3-aCD28 - IL-5_unst IL-13_cntrl = IL-13_aCD3-aCD28 - IL-13_unst IL-10_cntl = IL-10_aCD3-aCD28 - IL-10_unst IL-17_cntrl = IL-17_aCD3-aCD28 - IL17_unst INFg_cntrl = INFg_aCD3-aCD28 - INFg_unst TNF_cntrl = TNF_aCD3-aCD28 - TNF_unst	3

1. Diagram over time, per treatment group
2. Difference within treatment group from baseline over time (including 95% CIs and p-values)
3. Difference between Diamyd and Placebo (including 95% CIs and p-values)

Physical and Neurological Examinations
Normal, abnormal not clinically significant and abnormal clinically significant findings from physical (general appearance including skin, throat, mouth, cardiovascular, abdomen, lymphatic glands and neurological/musculoskeletal [including reflexes]) and neurological (extremity reflexes, Romberg [balance and coordination], walk on a line 2 meters [balance and coordination], standing on 1 leg, left and right, 15 seconds per leg [balance and coordination], finger-nose [coordination], mimic [cranial nerves], Babinski reflex [central function] and muscle strength [shake hands], biceps, triceps, distal extensors and flexors) examinations will be given by summary statistics by body system and visit.

Pubertal Stage
Tanner pubertal stage will be given by summary statistics by visit for boys (Tanner genital development, pubertal hair and testicular volume) and girls (Tanner breast and pubertal hair), respectively.

6.4 Level of Significance, Multiple Comparisons and Multiplicity

The primary endpoint and the key secondary endpoints will be tested hierarchically at the 5% significance level. This implies the following testing sequence:

1. Change in C-peptide (Area Under the Curve [AUC]mean 0-120 min) during a Mixed Meal Tolerance Test (MMTT) between baseline and 15 months.
2. Change in insulin-dose-adjusted HbA1c (IDAA1c) between baseline and 15 months.
3. Change in HbA1c between baseline and 15 months.
4. Change in daily exogenous insulin consumption between baseline and 15 months.

As long as the p-value from an analysis is less or equal to 0.0500 formal statistical testing will continue but once the p-value is greater than 0.0500 formal statistical testing will be stopped. The outcome of all analyses with a p-value less or equal to 0.0500 prior to the stop of testing will be regarded as statistically significant result. An overview of the hierarchical testing will be given in a separate table.

Table 4 Overview of Hierarchical Testing Procedure

Endpoint	p-value
Change in C-peptide (Area Under the Curve [AUC]mean 0-120 min) during a Mixed Meal Tolerance Test (MMTT) between baseline and 15 months	[a]
Change in insulin-dose-adjusted HbA1c (IDAA1c) between baseline and 15 months	[a]
Change in HbA1c between baseline and 15 months	[a]
Change in daily exogenous insulin consumption between baseline and 15 months	[a]

[a] All p-values less or equal to 0.0500 until testing is stopped stop will be given. First test with a p-value greater than 0.0500 'Stop' will appear. For all subsequent tests 'Not performed' will appear.

No other adjustment for multiple analyses will be made and p-values from analyses other than the primary analysis (at 15 months) will be regarded as descriptive.

6.5 Adjustment for Covariates

In general, statistical analyses will be adjusted for randomization strata (GAD65A level) and analyses assessing change from baseline to follow-up will be adjusted for the baseline value for the variable being assessed.

The impact on the primary efficacy analysis will be assessed by adding the following covariates to the MMRM model (continuous variables will be modelled as continuous, categories given are for subgroup presentation of the results):

- Sex (Male, Female)
- Age group (12-17 and 18-24 years old)
- Country (Czech Republic, Spain, Sweden and the Netherlands)
- Baseline BMI
- Maximum stimulated C peptide at baseline (TBD)
- Baseline HbA1c
- Number of days since T1D diagnosis
- HLA type as DR3-DQ2 versus not DR3-DQ2
- Pubertal stage (TBD)
- Baseline GADA
- Baseline fasting C-peptide
- Baseline insulin dose
- Timing of IMP injections (based on month of the first injection)
  - Spring: January, February, March and April
  - Summer: May, June, July and August
  - Autumn/Winter: September, October, November and December
- Timing of COVID-19 epidemic (Month 15 data collected prior to 2020-01-01, or after 2020-01-01)

All covariates will be entered one at the time and the univariate effects as well as the impact on the estimated difference between Diamyd and placebo will be given with 95% CIs and p-values in a table. A step-wise selection will also be performed in order to find the subset of covariates in the data set resulting in the best performing model. All effects in the best performing model as well as the impact on the estimated difference between Diamyd and placebo will be given with 95% CIs and p-values in a table.

For the purpose of sub-group presentations, continuous variables will be split into two groups using the empirical medians.

The COVID-19 covariate will only be included in analyses of for the primary and key secondary endpoints.

6.6 Handling of Dropouts and Missing Data

6.6.1 Primary Endpoint

The primary endpoint will be analyzed using MMRM. This analysis does not require imputation of missing data. Instead missing data is modeled based on the patient's available data and on other patients' developments over time.

6.6.2 Partially Missing Dates

If the date for a medication or an AE is completely missing, it will be assumed that the medication/AE started before treatment.

If the year and/or month are available, imputed date variables will be created in order to determine medication/AE start/end in relation to first IMP administration. For start dates first day in month will be imputed when day is missing and January if month is missing. E.g., 2018 will be imputed as 2018-01-01 and 2018-09 will be imputed as 2018-09-01. For end dates last day in month will be imputed when day is missing and December if month is missing. E.g., 2018 will be imputed as 2018-12-31 and 2018-09 will be imputed as 2018-09-30.

6.7 Multicentre Studies

As the number of centers are large in relation to the number of patients to be included, no by-center displays are planned. Country will be assessed as part of the covariate analyses (Section 6.5).

6.8 Examination of Subgroups

Efficacy will be explored within the subgroup of patients with HLA type DR3-DQ2. This will be done by adding a class variable (HLA type as DR3-DQ2 versus not DR3-DQ2) and the interaction term between this variable and the treatment variable (i.e., treatment*Visit*HLA) in the MMRM analysis of the primary endpoint, key secondary endpoints and secondary endpoints.

The results will be presented as outlined in Section 6.3.5 for Diamyd and Placebo (and difference/ratio between Diamyd and Placebo) within the subgroups HLA type as DR3-DQ2 versus not DR3-DQ2. The p-value for the treatment by HLA type interaction will also be reported.

In addition, the estimated treatment effect in each of the two HLA classes will be visualized together with the corresponding 95% confidence interval in forest plots as appropriate, i.e. such that endpoints where the estimated treatment effect are on the same scale are shown in the same forest plot. The endpoints will be sorted as follows in the forest plot: the primary endpoint will appear as the first endpoint (from the top), the key secondary endpoints will appear below the primary endpoint whereas the remaining secondary endpoints will appear under the key secondary endpoints in alphabetically order.

In addition, the primary analysis will be given for subgroups as outlined in the sections on covariates above (both table and graphical display).

6.9 Interim Analysis

No formal interim analysis will be performed.

6.10 Data Monitoring

An independent DSMB will be appointed. The DSMB will review the safety data throughout the study period twice a year. For further details, please see the DSMB charter and the DSMB SAP.

7 REFERENCES

Ramos-Goñi JM, Craig B, Oppe M, Ramallo-Fariña Y, Pinto-Prades JL, Luo N, Rivero-Arias O. Handling data quality issues to estimate the Spanish EQ-5D-5L Value Set using a hybrid interval regression approach. Value in Health 2017. In Press

8 LIST OF OUTPUT

Data from subjects screened but not included in the study will not be presented in any listings or tables.

8.1 Tables to be Produced for the Clinical Study Report (Section 14 according to ICH E3)

14.1 DEMOGRAPHIC DATA

Section 14.1

1. Subject Disposition (Screened set)
2. Subject Disposition in Analysis Sets (Randomized set)
3. Number of Subjects by Visit (Safety set)
4. Number of Subjects by Visit (FAS)
5. Demographics (Safety set)
6. Demographics (FAS)
7. Medical History (Safety set)
8. Medical History (FAS)

14.2 EFFICACY DATA

Section 14.2.1 Primary Endpoint

1. C-peptide $AUC_{mean\ 0\text{-}120\ min}$ during MMTT (FAS) [Summary statistics]
2. C-peptide $AUC_{mean\ 0\text{-}120\ min}$ during MMTT (FAS) [Graphical display]
3. Primary Analysis of Change from Baseline to Month 15 in C-peptide $AUC_{mean\ 0\text{-}120\ min}$ during MMTT (MMRM, FAS)
4. Change from Baseline to Month 15 in C-peptide $AUC_{mean\ 0\text{-}120\ min}$ during MMTT (MMRM, PPS)
5. Change from Baseline to Month 15 in C-peptide $AUC_{mean\ 0\text{-}120\ min}$ during MMTT (ANCOVA, Completers set)
6. Change from Baseline to Month 15 in C-peptide $AUC_{mean\ 0\text{-}120\ min}$ during MMTT (MMRM, Completers set)
7. Change from Baseline to Month 15 in C-peptide $AUC_{mean\ 0\text{-}120\ min}$ during MMTT (ANCOVA, FAS)
8. Change from Baseline to Month 15 in C-peptide $AUC_{mean\ 0\text{-}120\ min}$ during MMTT (ANCOVA, PPS)

Section 14.2.2 Key Secondary Endpoints

1. IDAA1c (FAS) [Summary statistics]
2. IDAA1c (FAS) [Graphical display]
3. Change in IDAA1c Between baseline and Month 15. (MMRM FAS)
4. Change in IDAA1c Between baseline and Month 15. (MMRM PPS)
5. Change in IDAA1c Between baseline and Month 15. (MMRM Completers set)
6. Change in IDAA1c Between baseline and Month 15. (ANCOVA FAS)
7. Change in IDAA1c Between baseline and Month 15. (ANCOVA PPS)
8. Change in IDAA1c Between baseline and Month 15. (ANCOVA Completers set)
9. HbA1c (FAS) [Summary statistics]
10. HbA1c (FAS) [Graphical display]
11. Change in HbA1c between baseline and Month 15. (MMRM FAS)
12. Change in HbA1c between baseline and Month 15. (MMRM PPS)
13. Change in HbA1c between baseline and Month 15. (MMRM Completers set)
14. Change in HbA1c between baseline and Month 15. (ANCOVA FAS)

15. Change in HbA1c between baseline and Month 15. (ANCOVA PPS)
16. Change in HbA1c between baseline and Month 15. (ANCOVA Completers set)
17. Daily Exogenous Insulin Consumption (FAS) [Summary statistics]
18. Daily Exogenous Insulin Consumption (FAS) [Graphical display]
19. Change in Daily Exogenous Insulin Consumption Between Baseline and Month 15 (MMRM FAS)
20. Change in Daily Exogenous Insulin Consumption Between Baseline and Month 15 (MMRM PPS)
21. Change in Daily Exogenous Insulin Consumption Between Baseline and Month 15 (MMRM Completers set)
22. Change in Daily Exogenous Insulin Consumption Between Baseline and Month 15 (ANCOVA FAS)
23. Change in Daily Exogenous Insulin Consumption Between Baseline and Month 15 (ANCOVA PPS)
24. Change in Daily Exogenous Insulin Consumption Between Baseline and Month 15 (ANCOVA Completers set)
25. Hierarchical Testing Procedure Overview (FAS) [Table]
26. Hierarchical Testing Procedure Overview (FAS) [Graphical display]

Section 14.2.3 Secondary Endpoints

1. Change in Time in Glycaemic Target Range 70-180 mg/dL between Baseline and Month 5 months [Summary statistics+95% CI & p-value]
2. Change in Time in Hypoglycaemic Range 50-70 mg/dL between Baseline and Month 15 [Summary statistics+95% CI & p-value]
3. Change in Time in Severe Hypoglycaemic Range <50 mg/dL between Baseline and Month 15 [Summary statistics+95% CI & p-value]
4. IDAA1c Less or Equal to 9 at Month 15 (FAS) [Summary statistics+95% CI & p-value]
5. Stimulated Maximum C-Peptide Level Above 0.2 nmol/L (0.6 ng/ml) at Month 15 (FAS) [Summary statistics+95% CI & p-value]
6. Stimulated 90 Minutes C-Peptide Level Above 0.2 nmol/L (0.6 ng/ml) at Month 15 (FAS) [Summary statistics+95% CI & p-value]
7. Hypoglycemic Events (FAS) [Summary statistics+95% CI & p-value]
8. Hypoglycemic Events (Poisson Regression, FAS)
9. Maximum C-Peptide (FAS) [Summary statistics]
10. Change in Maximum C-Peptide during MMTT between Baseline and Month 15. (MMRM FAS)
11. Fasting C-Peptide (FAS) [Summary statistics]
12. Change in Fasting C-Peptide between baseline and Month 15. (MMRM FAS)
13. C-Peptide Measured at 30, 60, 90, and 120 Minutes (FAS) [Summary statistics]
14. Change in C-Peptide Measured at 30, 60, 90, and 120 Minutes during MMTT at Month 15. (MMRM FAS)

Section 14.2.4 EQ-5D

1. EQ-5D-5L and Visual Analogue Scale (FAS) [Summary statistics+95% CI]

Section 14.2.5 Covariate and subgroup analyses

1. C-peptide AUCmean 0-120 min during MMTT: HLA Adjusted Analysis (MMRM, FAS)
2. C-peptide AUCmean 0-120 min during MMTT: HLA Adjusted Analysis Forest Plot (FAS)
3. C-peptide AUCmean 0-120 min during MMTT: Univariate Covariate Analyses Overview (MMRM, FAS)
4. C-peptide AUCmean 0-120 min during MMTT: Final Multivariable Model (MMRM, FAS)

5. C-peptide AUCmean 0-120 min during MMTT by Subgroups (FAS) [Summary statistics]
6. C-peptide AUCmean 0-120 min during MMTT by Subgroups (FAS) [Graphical display]
7. Change in IDAA1c between baseline and Month 15: HLA Adjusted Analysis (MMRM, FAS)
8. Change in IDAA1c between baseline and Month 15: HLA Adjusted Analysis Forest Plot (FAS)
9. Change in IDAA1c between baseline and Month 15: Univariate Covariate Analyses Overview (MMRM, FAS)
10. Change in IDAA1c between baseline and Month 15: Final Multivariable Model (MMRM, FAS)
11. Change in IDAA1c between baseline and Month 15 by Subgroups (FAS) [Summary statistics]
12. Change in IDAA1c between baseline and Month 15 by Subgroups (FAS) [Graphical display]
13. Change in HbA1c between baseline and Month 15: HLA Adjusted Analysis (MMRM, FAS)
14. Change in HbA1c between baseline and Month 15: HLA Adjusted Analysis Forest Plot (FAS)
15. Change in HbA1c between baseline and Month 15: Univariate Covariate Analyses Overview (MMRM, FAS)
16. Change in HbA1c between baseline and Month 15: Final Multivariable Model (MMRM, FAS)
17. Change in HbA1c between baseline and Month 15 by Subgroups (FAS) [Summary statistics]
18. Change in HbA1c between baseline and Month 15 by Subgroups (FAS) [Graphical display]
19. Change in Daily Exogenous Insulin Consumption Between Baseline and Month 15: HLA Adjusted Analysis (MMRM, FAS)
20. Change in Daily Exogenous Insulin Consumption Between Baseline and Month 15: HLA Adjusted Analysis Forest Plot (FAS)
21. Change in Daily Exogenous Insulin Consumption Between Baseline and Month 15: Univariate Covariate Analyses Overview (MMRM, FAS)
22. Change in Daily Exogenous Insulin Consumption Between Baseline and Month 15: Final Multivariable Model (MMRM, FAS)
23. Change in Daily Exogenous Insulin Consumption Between Baseline and Month 15 by Subgroups (FAS) [Summary statistics]
24. Change in Daily Exogenous Insulin Consumption Between Baseline and Month 15 by Subgroups (FAS) [Graphical display]

<u>Section 14.2.6 Exploratory Analyses (Extension Period)</u>

1. C-peptide $AUC_{mean\ 0\text{-}120\ min}$ during MMTT (Extension set) [Summary statistics]
2. Analysis of Change from Baseline to Month 24 in C-peptide $AUC_{mean\ 0\text{-}120\ min}$ during MMTT (MMRM, Extension set)
3. HbA1c (Extension set) [Summary statistics]
4. Change in HbA1c between baseline and Month 24. (MMRM Extension set)
5. Daily Exogenous Insulin Consumption (Extension set) [Summary statistics]
6. Change in Daily Exogenous Insulin Consumption Between Baseline and Month 24. (MMRM Extension set)
7. IDAA1c [Summary statistics]
8. Change in IDAA1c Between baseline and Month 24. (MMRM Extension set)
9. Fasting C-Peptide [Summary statistics+95% CI & p-value]

10. Change in Fasting C-Peptide between baseline and Month 24. (MMRM Extension set)
11. C-Peptide Measured at 30, 60, 90, and 120 Minutes (Extension set)
12. Maximum C-Peptide (Extension set) [Summary statistics+95% CI & p-value]
13. Glycemic Variability/Fluctuations (Extension set)
14. Stimulated Maximum C-Peptide Level Above 0.2 nmol/L (0.6 ng/ml) at Month 24 (Extension set) [Summary statistics+95% CI & p-value]
15. Stimulated 90 Minutes C-Peptide Level Above 0.2 nmol/L (0.6 ng/ml) at Month 24 (Extension set) [Summary statistics+95% CI & p-value]
16. IDAA1c Less or Equal to 9 at Month 24 (Extension set) [Summary statistics+95% CI & p-value]
17. Hypoglycemic Events (Extension set) [Summary statistics+95% CI & p-value]
18. Hypoglycemic Events (Poisson Regression, Extension set)

14.3 SAFETY DATA

Section 14.3.1 Adverse Events

1. Summary of Adverse Events (Safety Set)
2. Treatment Emergent Adverse Events by System Organ Class and Preferred Term (Safety Set)
3. Treatment Emergent Serious Adverse Events by System Organ Class and Preferred Term (Safety Set)
4. Treatment Emergent IMP Related Adverse Events by System Organ Class and Preferred Term (Safety Set)
5. Treatment Emergent Vitamin D Related Adverse Events by System Organ Class and Preferred Term (Safety Set)
6. Treatment Emergent Adverse Events Number of Subjects by System Organ Class, Preferred Term, Intensity and Relationship by Treatment (Safety Set)

Section 14.3.2 Deaths, other SAEs, and other significant AEs

1. Listings of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events (Safety Set)

14.3.3 Reserved for narratives

Section 14.3.4.1 Laboratory Assessments

1. Abnormal Clinically Significant Laboratory Value Listing (Safety set)
2. Hematology and Clinical Chemistry (Safety set)
3. Urinalysis (Safety set)
4. GAD65A titer (Safety set)
5. HLA characterization (Safety set)
6. Vitamin D (Safety set)
7. Fasting Glucose and MMTT-induced Glucose (Safety set)
8. Shift Table Hematology (Safety set)
9. Shift Table Clinical Chemistry (Safety set)
10. Shift Table Urinalysis (Safety set)

Section 14.3.4.2 Immunology

1. Proliferation (FAS)
2. IA-2 (FAS)
3. GADA (Safety Set)
4. GADA (FAS)
5. GADA subclasses (FAS)
6. GAD Stimulated (FAS)

7. Cytokine Secretion (FAS)
8. Serum cytokines (FAS)
9. Control Stimulated (FAS)
10. Cytokine Secretion (FAS)

Section 14.3.5 Exposure

1. Extent of Exposure to Diamyd/Placebo (Safety set)
2. Extent of exposure to Vitamin D/Placebo (Safety set)

Section 14.3.6 Vital Signs

1. Body Measurement Vital Signs (Safety set)
2. Vital Signs (Safety set)
3. Vital Signs Shift Table (Safety set)

Section 14.3.7 Examinations

1. Physical Examination (Safety set)
2. Neurological Examination (Safety set)
3. Tanner Pubertal Stage Boys (Safety set)
4. Tanner Pubertal Stage Girls (Safety set)

Section 14.3.8 Concomitant Medication

1. Concomitant Medication and Therapy (Safety set)

8.1.1 Top Line Results

- Tables 14.1.1-6
- Section 14.2.1 all tables
- Section 14.2.2 all tables
- Table 14.3.1.1
- Tables 14.2.5.1., 14.2.5.2, 14.2.5.7, 14.2.5.8, 14.2.5.13, 14.2.5.14, 14.2.5.19, 14.2.5.20

8.2 Listings of Individual Subject Data and Other Information to be Produced for the Clinical Study Report (Sections 16.1 and 16.2 in ICH E3)

Appendix 16.1.7
1. Randomization Scheme

Appendix 16.2.1
1. Screening Failures, Discontinued Subjects, Reason for Discontinuation
2. Treatment Allocation and Evaluability for All Subjects
3. Visit Dates
4. Study Termination

Appendix 16.2.2
1. Protocol Deviations

Appendix 16.2.3
1. Subjects Excluded from the Efficacy Analysis (Evaluability, Reason for Evaluability Classification)

Appendix 16.2.4
1. Demographics and Other Background Characteristics
2. Medical History
3. Inclusion Criteria Not Met and Exclusion Criteria Met

Appendix 16.2.5
1. Compliance with IMP Injections
2. Compliance with Vitamin D
3. Individual Vitamin D Levels

Appendix 16.2.6
1. Individual Efficacy Response Data

Appendix 16.2.7
1. Adverse Events by Subject and Time of Occurrence (Safety Set)
2. Treatment Emergent Adverse Events by System Organ Class, Preferred Term, Treatment and Subject
3. Serious Adverse Events by Subject and Time of Occurrence (Safety Set)

Appendix 16.2.8
1. Laboratory Reference Ranges
2. Individual Laboratory Measurements by Subject
3. Abnormal Laboratory Values
4. GAD65A titer

5. Individual Mixed Meal Tolerance Test
6. Individual Diabetic Status Parameters
7. Relevant Comments Regarding Laboratory Values
8. Other Immunological Parameters

Appendix 16.2.9
1. Vital Signs
2. Abnormal Vital Signs

Appendix 16.2.10
1. Physical Examination
2. Neurological Examination
3. Pubertal Stage

Appendix 16.2.11
1. Concomitant Medication and Therapy

Appendix 16.2.12
1. Self-Reported Episodes of Severe Hypoglycemia

8.3 US Archival Listings (Appendix 16.4 in ICH E3)

Not applicable.