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Fully Automated glycemic control with ultrarapid insulin in a bihormonal closed loop System in patients with Type 1 diabetes (FAST 1)

Statistical Analysis Plan

Short title	FAST 1
Protocol ID	NL79588.091.22
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Responsible for data management	T.J.P. Jansen
Based on protocol version	1.2 (dd 16-06-2022)

General

1 Content

2 Scope

This statistical analysis plan (SAP) applies to the main study of the FAST 1 trial and is developed for the statistical analysis performed by Inreda Diabetic B.V.

3 Sample size

It is hypothesized that the time above range is reduced in subjects using the artificial pancreas (AP) in combination with Lyumjev compared to Humalog. To detect a 3,125% (45 min per day – 15 min per meal) improvement in time spent in hyperglycemia (>10 mmol/l) with a power of 0.90 and alpha of 0.05, 10 subjects are required. To account for drop out of subjects, the sample size will be increased with 2 patients. The sample size calculation has been performed with the program G*Power 3.1.9.4. The percentage time above target range and corresponding standard deviations (SDs) are based on data from the APPEL 5 study.

The following data were used to calculate sample size:

- T-Test: Difference between two dependent means (matched pairs)
- Alpha = 0.05
- Power = 0.90
- Mean 1 = 12.8
- Mean 2 = 9.675
- SD of mean 1 = 3.3
- SD of mean 2 = 3.3
- Correlation = 0.70

4 Randomization and blinding procedure

Block randomization with an equal allocation ratio is used to randomize patients to determine the order of the insulin types (Lyumjev followed by Humalog), and vice versa).

Block sizes of 2, 4 and 6 are used to prevent potential guessing of allocation. Randomization is performed in the electronic CRF (Case Report Forms) of *MyResearchManager.*

No blinding will be applied.

5 Statistical analysis

5.1 Available sets for analysis

See also the Data Management Plan of the FAST 1 trial.

There are 2 data sources for this trial.

- Electronic data management system:
  - CRF
  - Study visits

- Artificial Pancreas

5.1.1 CRF Dataset

The CRF data will be collected with an eCRF implemented in *MyResearchManager*. The following data will be collected with the CRF:

- In- and exclusion criteria;
- Gold/Clarke questionnaire;
- Date of informed consent;
- Demography;
- Weight, length, HbA1c;
- Medical history;
- Randomization results;
- Visits information (including telephone contact, decided 'actions' and rationale);
- Concomitant medication;
- Adverse events;
- Device deficiencies;
- Adjustment of AP settings;
- End of study.

5.1.2 Artificial Pancreas dataset

The AP sends data to the AP Portal system every 10 minutes. The following data will be collected in the AP Portal system:

- AP, transmitters and mobile access point identification;
- Sensor glucose concentration;
- Sensor glucose slope;
- Sensor state;
- Insulin and glucagon administrations;
- Physical activity parameter measured by accelerometers;
- Control algorithm state;
- Events registered by the AP (e.g., low and high glucose alarm, calibrations, infusion set occlusion and replacements, sensor replacements).

5.2 Statistical analysis program

Python will be used for statistical analysis. Preparation of the dataset before statistical analysis will be done in Python as well. For a list of the used scripts, functions, as well as the version numbers of the used libraries refer to the Data Analysis Plan.

5.3 Standard analysis

The distribution of each parameter (primary, secondary and other study parameters) will be assessed with a histogram and/or q-q plot. For the parameters that are being compared with dependent/paired tests, the distribution of the difference between the groups will be assessed. Based on these assessments, the decision for using data transformations and parametric or nonparametric descriptive analysis and statistical testing will be made for each (group of) parameter(s).

Subsequently, carry-over and period effects will be assessed because of the cross-over design of the study. For each parameter that will be compared between open loop and closed loop, the two randomization groups are first compared using two unpaired t-tests or Mann-Whitney U-tests:

- Sum of open loop and closed loop result (carry-over);
- Difference between the open loop and closed loop result (period).

If a significant difference is found in one of these tests, a carry-over/period effect is present. In that case, the results for that parameter of the second study period cannot be used for the analysis (to estimate the treatment effect) and paired testing will not be possible.

For all statistical tests described in this chapter, a p-value ≤ 0.05 is defined to indicate statistical significance. Descriptive analyses will be performed on the subjects presented in 5.3.3.

5.3.1 Primary study parameter

The primary objective is to determine the efficacy of Lyumjev in the AP. The main parameter to express efficacy is the time above range (>10 mmol/l). It is hypothesized that the time above range is lower using Lyumjev compared to the standard use of care: Humalog by a margin of 3.125%. The proportion of time spent above the target range will be compared between the two types of insulin using a dependent t-test or Wilcoxon signed rank test for paired measurements.

H_0: ($\mu_{Lyumjev} - \mu_{Humalog}$) ≥ -3.125%

H_1: ($\mu_{Lyumjev} - \mu_{Humalog}$) < -3.125%

5.3.2 Secondary study parameters

The secondary safety and performance parameters will be compared between the two types of insulin using dependent t-tests or Wilcoxon signed rank tests. T-tests or Wilcoxon signed rank tests for:

- Time in hypoglycemia. It is hypothesized that the time below range is not higher for Lyumjev when compared to Humalog. A one tailed test shall be performed with:
  H_0: $\mu_{Lyumjev} \leq \mu_{Humalog}$
  H_1: $\mu_{Lyumjev} > \mu_{Humalog}$
- Time in euglycemia. It is hypothesized that the time in range is not lower for Lyumjev when compared to Humalog. A one tailed test shall be performed with

H_0: $\mu_{Lyumjev} \geq \mu_{Humalog}$,

H_1: $\mu_{Lyumjev} < \mu_{Humalog}$

- Mean or median glucose. It is hypothesized that the mean or median glucose is not higher for Lyumjev when compared to Humalog. A one tailed test shall be performed with:

  H_0: $\mu_{Lyumjev} \leq \mu_{Humalog}$

  H_1: $\mu_{Lyumjev} > \mu_{Humalog}$
- Glycemic variability expressed as coefficient of variation and interquartile range. It is hypothesized that the glycemic variability is not higher for Lyumjev when compared to Humalog. A one tailed test shall be performed with:

  H_0: $\mu_{Lyumjev} \leq \mu_{Humalog}$

  H_1: $\mu_{Lyumjev} > \mu_{Humalog}$

The pharmacodynamic parameters and the main endpoint will be calculated for the whole study period and for daytime (06:00–00:00 h) and nighttime (00:00–06:00h) separately.

Other endpoints are the AP-related parameters:

- Daily administered dosage of glucagon;
- Daily administered dosage of insulin;
- The percentage of time that the closed loop algorithm is active.

No statistical testing will be performed on these parameters.

6 Missing data

Missing sensor glucose readings will be kept empty. In Python, missing samples will be represented as NaN (not a number). For all glucose parameters that are calculated as proportion of time, the NaN samples do not count as time fulfilling the requirement of the parameter or as total time. All percentages of time are calculated as percentage of available measurement samples. The calculations for the other glucose parameters will also not include the NaN values. The number of missing sensor glucose measurement samples will be calculated per patient as proportion of the total time. If this proportion of missing sensor data is > 5 % for a specific patient, a note will be made in the clinical investigation report (CIR). Thus, the percentage of time that the algorithm is active will be calculated as a percentage of the 25-day study period.

Missing data for the parameters that reflect total numbers/event counts cannot be considered in the parameter calculations. The calculation of the parameters that reflect daily averages (insulin use, glucagon use) will be corrected as follows in case of missing data:

- X = number of 24-hour periods without data for the parameter in the specific study period;
- Daily average = sum of the total for the 25-day study period / (30 days – X);

It will be noted in the clinical investigation report for which parameters and in how many instances this correction has been applied. For each baseline parameter, the number of patients included in the

descriptive analysis will be noted if this number is less than the total number of patients included in the standard data analysis.

As all questions on the questionaries shall be set to mandatory, no missing answers are possible. In the case of a completely blank questionnaire, the specific questionnaire cannot be included and a remark shall be made in the CIR about the total number of completions.

7 Interim analysis types

No interim analysis shall be performed. Statistical analysis shall only be performed after the last study visit of the last patient.

8 SAP deviations

If applicable, when the statistical analysis was not performed according to this SAP, deviations from this plan have to be included in this section. The following points have to be included:

- Rationale of the deviation;
- Detailed description of the deviation (including which data is affected by the deviation);
- Date of decision;
- People involved in the decision, with signature.

8.1 Description of the deviations from the SAP

1. Standard deviation (SD) of the glucose value
    a. Rationale: SD of the glucose value was included as variable because of its added value to indicate glycemic variability.
    b. Detailed description: the SD of the glucose value was added as parameter considering it is a commonly used parameter besides the coefficient of variation and interquartile range of the glucose value to indicate glycemic variability. The SD was calculated for day time, night time and the combination. No data were affected by the addition of this parameter.
    c. Date of decision: May 1, 2023.
    d. People involved in the decision (with signature): M. Klaassen, J. de Haan and T. Jansen.

2. Time below range (TBR) and time above range (TAR)
    a. Rationale: level 1 and level 2 for the TBR and TAR were included in order to report all the important glycemic metrics, following the International Consensus guidelines.
    b. Detailed description: according to the SAP, only the TBR and TAR in total should be calculated (not as separate levels). In addition to the total TBR and TAR, also level 1 and 2 of the TBR and TAR were calculated. These are essential parameters to indicate glycemic control, following the International guidelines on how to report glycemic metrics (Battelino *et al*, Lancet Diabetes Endocrinol (2023)). These metrics were calculated for day time, night time and the combination. These additional parameters had no effect on the data.

c. Date of decision: May 1, 2023.
d. People involved in decision (with signature): M. Klaassen, J. de Haan and T. Jansen.

3. Exclusion of AP data acquired for five participants
   a. Rationale:
      A critical procedural error was discovered in the process of data analysis, which led to invalidity of a part of the FCL data. FCL data from the Lyumjev-Humalog sequence (n=5) had to be excluded. Other data from this sequence could still be included (e.g., adverse events). To mention that all FCL data from the Humalog-Lyumjev sequence (n=7) were included.
   b. Details on deviation:
      Humalog is used as default insulin in the Inreda AP, and study participants who were randomized to the Humalog-Lyumjev sequence already had their settings optimized for Humalog by the diabetes care team over a long period, considering AP treatment was their regular care at the time. However, in case study participants were randomized to the Lyumjev-Humalog sequence, their settings needed optimization to match with the characteristics of the ultra-rapid insulin Lyumjev. For these participants, the settings of their insulin curve and preinjection were adjusted to take the faster and shorter insulin action into account. These substantial adjustments of the insulin settings during Lyumjev use were not changed back to the Humalog settings that equaled the settings before the start of the study. The Lyumjev-specific Inreda AP settings that were still used after switching back to Humalog affected the glucose regulation of these participants. Therefore, the true impact on glycemic control comparing the insulins within that sequence could not be studied correctly and would have led to invalid outcomes derived from the FCL data. The FCL data obtained in the Lyumjev-Humalog sequence could therefore not be used as valid study data. Only FCL data from the Humalog-Lyumjev sequence were included to determine the outcome parameters (7 of the 12 participants), whereas FCL data from the Lyumjev-Humalog sequence were excluded from further data analysis (5 of 12 participants).
   c. Date of decision:
      May 4, 2023.
   d. People involved in decision (with signature): M. Klaassen, J. de Haan and T. Jansen.

8.2 Signatures of the people involved in the decisions:

Name (function): M. Klaassen (Data specialist) Signature: .....

Name (function): J. de Haan (Lead Clinical Operations) Signature: .....

Name (function): T. Jansen (Clinical project manager) Signature: .....

9 Revision History

Rev	Author	Change description	Reviewed by	Approved by	Date
D01	M. Klaassen	New document	T. Jansen	J. de Haan	29-08-2022
D02	T. Jansen	Addition of SAP deviations and signatures of people involved	M. Klaassen	J. de Haan	01-07-2025