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

RESEARCH PROTOCOL

(Version 1.2, 16-06-2022)

Revision history

Version	Date	Change description
1.0	23-02-2022	First version
1.1	13-04-2022	Study has been classified as clinical trial with medicinal product. Study file is supplemented with required documentation.
1.2	16-06-2022	Adjustments following the comments of MREC

PROTOCOL TITLE: Fully Automated glycemic control with ultra rapid insulin in a bihormonal closed loop System in patients with Type 1 diabetes

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

AE	**Adverse Event**
AP	**Artificial Pancreas**
AR	**Adverse Reaction**
CA	**Competent Authority**
CCMO	**Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek**
CRC	**Clinical research center**
DSMB	**Data Safety Monitoring Board**
GCP	**Good Clinical Practice**
GDPR	**General Data Protection Regulation; in Dutch: Algemene Verordening Gegevensbescherming (AVG)**
IB	**Investigator's Brochure**
IC	**Informed Consent**
IMP	**Investigational Medicinal Product**
IMPD	**Investigational Medicinal Product Dossier**
IQR	**Interquartile range**
METC	**Medical research ethics committee (MREC); in Dutch: medisch-ethische toetsingscommissie (METC)**
RA	**Rapid acting**
(S)AE	**(Serious) Adverse Event**
SAP	**Sensor Augmented Pump**
SPC	**Summary of Product Characteristics; in Dutch: officiële productinformatie**
Sponsor	**The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.**
SUSAR	**Suspected Unexpected Serious Adverse Reaction**
UAVG	**Dutch Act on Implementation of the General Data Protection Regulation; in Dutch: Uitvoeringswet AVG**
URA	**Ultrarapid acting**
WMO	**Medical Research Involving Human Subjects Act; in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen**

SUMMARY

Rationale: Inreda Diabetic B.V. (Goor, The Netherlands) developed a bihormonal reactive closed loop system to automate glucose regulation (artificial pancreas; AP) in patients with diabetes mellitus. In the current CE-marked AP, Humalog (Eli Lilly) is used as insulin which is a rapid acting insulin lispro. Lyumjev (Eli Lilly) also consists of insulin lispro but is ultra-rapid acting due to the addition of 2 excipients. Using Lyumjev instead of Humalog insulin could therefore result in better glycemic control.

Objective: The main objective is to determine the efficacy of Lyumjev in the Inreda AP system. Secondary objectives are: to assess safety, differences in pharmacodynamics and differences in AP-related outcome measures.

Study design: This study is a multicenter, open-labeled, randomized, cross-over trail.

Study population: The study population will be 12 patients with type 1 diabetes. The patients will be recruited from the following outpatients clinics: Rijnstate Hospital, Hospital Gelderse Vallei or Slingeland Hospital. The patients are already using the Inreda AP system.

Intervention: The intervention entails use of Lyumjev administered by the Inreda AP system. The subjects will be randomized to receive either Lyumjev or Humalog during the first study period of thirty days. After a wash-out period of eight days, the subject will be switched to the alternate treatment according to randomization.

Main study parameters/endpoints: Main parameter to express efficacy is the time above range (>10 mmol/l), which will be compared between Lyumjev and Humalog.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: There are no major risks associated with this study, since the subjects will use their usual kind of diabetes therapy, in which only the type of insulin is adjusted for thirty days. The most prominent risk is potential altered effectiveness of Lyumjev compared to the currently used insulin, which could lead to hypo- and hyperglycemia, but high and low glucose values will be indicated by alarms given by the Inreda AP system. The burden of the study is relatively low. The participants have to visit the CRC at most 2 times and the only additional burden for participants is to keep a Wi-Fi access point with them during both study periods.

1. INTRODUCTION AND RATIONALE

Over the last decade insulin delivery and blood glucose monitoring have evolved, facilitating better glucose control for patients with type 1 diabetes mellitus. Continuous subcutaneous insulin infusion and glucose sensors combined with an insulin delivery algorithm constitute a closed loop system or artificial pancreas. A closed-loop system can be categorized as mono-hormonal (subcutaneous insulin administration) or bi-hormonal (subcutaneous insulin and glucagon administration).

Inreda Diabetic B.V. (Goor, the Netherlands) developed a bi-hormonal artificial pancreas (AP) to provide automated glycemic control for insulin treated adult patients. The AP consists of two subcutaneous glucose sensors to continuously measure glucose values and an algorithm to determine the amount of insulin (Humalog, Eli Lilly) or glucagon (GlucaGen®, Novo Nordisk) to be administered.

The AP is CE-certified in February 2020. Different clinical studies (called APPEL 1 to 5: 'Algorithm to control Postprandial, Post exercise and night glucose Excursions in a portable closed Loop format') were performed to test feasibility, safety and performance. These studies facilitated market approval. The APPEL 4 study showed comparable median glucose levels for closed loop and open loop (standard insulin pump) therapy, while the time in range (3.9–10 mmol/l) was higher for closed loop [1]. Improvements were made to the prototype to allow patients to operate the system independently. Hereafter, the device was tested for two weeks in order to include multiple replacements of disposables (glucose sensors, infusion sets, and insulin- and glucagon cartridges) and observe the self-learning glucose control algorithm adapting to the individual patient (APPEL 5 study) [2]. This study demonstrated that the bi-hormonal closed-loop system provides better glycemic control than standard open loop therapy. The median time in range was higher during closed-loop (86.6% [IQR 84.9-88.3]) compared to patients' usual diabetes care (53.9% [49.7-67.2], p<.001) Time below range (<3.9 mmol/l) also significantly improved during closed-loop compared to usual diabetes care (0.4% [IQR 0.1-0.8] vs 2.0% [IQR 0.7-3.6]).

The insulin used in the current CE marked AP is Humalog (Eli Lilly). Humalog is administered when glucose levels are high or increasing rapidly and reduces the occurrence of hyperglycemic events. Therefore, the performance of the AP system depends partly on the efficacy of insulin.

Humalog is classified as a rapid acting (RA) insulin. In clinical practice, type 1 diabetes mellitus patients need to administer this insulin approximately 20 minutes before meal intake to reduce postprandial hyperglycemia. The Inreda AP is a reactive system, and thus the insulin will not be administered before the meal, but will be administered when glucose levels rise rapidly. The AP results in strongly improved glycemic control compared to standard diabetes therapy, although postprandial glucose peaks are still present after the meal.

Lyumjev (Eli Lilly) is classified a ultra-rapid acting (URA) insulin. In clinical practice patients are required to administer this insulin approximately 1 minute before meal intake to reduce postprandial hyperglycemia.

Although Lyumjev insulin looks promising for the AP, Lyumjev has not yet been tested in a reactive closed-loop system. Therefore, the aim of this study is to determine the efficacy of Lyumjev in the AP.

2. OBJECTIVES

Primary Objective:

The primary objective is to determine the efficacy of Lyumjev in the AP. 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.

Secondary Objectives:

Secondary objectives are:

- to assess safety parameters;
- to assess differences in pharmacodynamics between Lyumjev and Humalog;
- to assess differences in AP-related outcomes between Lyumjev and Humalog.

3. STUDY DESIGN

Design:

This study is a multicenter, open-label, randomized, cross-over trial which will be performed in a free-living environment.

Duration:

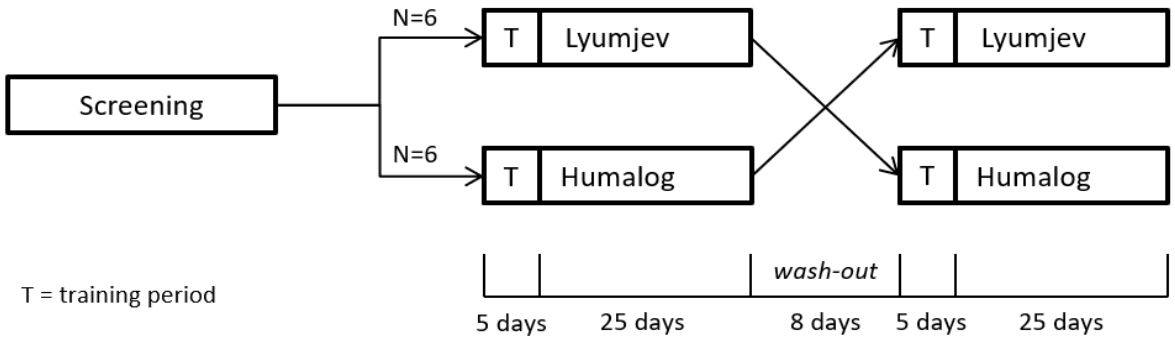
The duration of the study per subject is 68 days. During the first thirty days the subject will be randomized to receive the first kind of insulin. After a wash-out period of eight days, the subject will receive the second kind of insulin for another thirty days according to the randomization. The following insulin formulations will be used: Lyumjev 100 units/ml in a 3 ml cartridge and Humalog 100 units/ml in a 3 ml cartridge as standard use of care.

Setting:

This study will be performed at home and patients can live according to their own daily routine. There are two study periods. Each study period lasts thirty days. The first five days of both study periods consist of a training period, which enables the investigator to optimize the settings of the Inreda AP system.

At the beginning of a study period the patient will receive the insulin cartridges according to the randomization. A wash-out period of eight days is included between the two study periods. Subjects will use Humalog during this period, as this in the standard care with the AP. Figure 3.1 shows the flow chart of the study design. During the study conduct there will be four study visits by the investigator: at the beginning and end of the intervention and control period. The training period is included to optimize the settings of the AP if necessary. This data will not be included in the analysis.

Figure 3.1 Flow chart of the study design



4. STUDY POPULATION

4.1 Population (base)

The study population will be 12 patients with type 1 diabetes. The subjects will be recruited from the following clinics: Rijnstate Hospital, Hospital Gelderse Vallei or Slingeland Hospital.

4.2 Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

- Diagnosed with type 1 diabetes mellitus;
- Treated with the Inreda AP system for a minimum of 1 month;
- Age between 18 and 75 years;
- Willing and able to sign informed consent.

Since patients are treated with the Inreda AP, the following inclusion criteria will be met:

- Treated with sensor augmented pump (SAP) therapy or CSII for a minimum of 6 months;
- HbA1c <97 mmol/mol;
- BMI <35 kg/m^2;
- No use of acetaminophen, as this may influence glucose sensor measurements.

4.3 Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

- Impaired awareness of hypoglycemia (score ≥4) according to the Gold and/or Clarke questionnaire [3], [4];
- Pregnancy and/or breastfeeding;
- Use of oral antidiabetic agents;
- Insulinoma;
- Hypersensitivity reactions to Lyumjev insulin or any of the excipients;

4.4 Sample size calculation

It is hypothesized that the time above range is reduced in subjects using 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 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

5. TREATMENT OF SUBJECTS

5.1 Investigational product/treatment

The investigational product is Lyumjev in combination with the AP. Subjects will use their usual diabetes therapy (the AP), but the currently used insulin will be replaced by the investigational product (Lyumjev) for thirty days. The other thirty days of the study will be the control period, where Humalog will be used.

5.2 Use of co-intervention

Patients are not allowed to use acetaminophen, undergo treatment with Magnetic Resonance Imaging, Computed Tomography scan, X-ray or high frequency electrical heat (diathermy), or receive dialysis during the study period. However, these criteria also apply during use of the AP outside of this study.

5.3 Escape medication

Not applicable, as the escape medication does not change from normal AP use.

6. INVESTIGATIONAL PRODUCT

6.1 Name and description of investigational product

The investigational product is Lyumjev (Eli Lilly) administered by the Inreda AP system. The AP is CE marked and Lyumjev is a registered medicinal product.

Lyumjev (Eli Lilly) is classified as an ultra-rapid acting (URA) insulin. Lyumjev has an identical indication compared to Humalog (rapid acting (RA)) and is referred to as insulin lispro-aabc. Although Lyumjev's active substance is identical to Humalog, two additional substances are added which transforms it from rapid acting into ultra-rapid acting insulin. These substances are: treprostinil and citrate, these excipients induce local vasodilation and increase vascular permeability, respectively. This facilitates faster insulin absorption.

6.2 Summary of findings from non-clinical studies

Not applicable.

6.3 Summary of findings from clinical studies

There were four studies conducted to compare the pharmacodynamics of Lyumjev with Humalog [5]–[8]. The results of these studies demonstrate that Lyumjev insulin is non-inferior to Humalog in terms of effectiveness and may improve postprandial glucose control. Interestingly, improved postprandial control is seen only after breakfast, but not after lunch or dinner. Nonetheless, this is promising for AP therapy. Moreover, large studies do not give rise to alarm with regard to side-effects, as similar rates of adverse events are observed in most studies. However, an increase in infusion site reactions was observed and requires attention. So far, large outpatient studies did not include patients on pump therapy. To date, the reported studies have not tested Lyumjev insulin in closed-loop systems. Closed-loop systems are generally able to maintain glycemic control, but postprandial peaks are the final hurdle to achieve normoglycemia in patients using these devices. Using Lyumjev in the AP would potentially further improve glycemic control.

No clinical studies were performed with Lyumjev in combination with the AP system.

6.4 Summary of known and potential risks and benefits

See chapter 13 for the complete text.

There are no major risks associated with this study. The subjects will use their usual kind of diabetes therapy, in which only the type of insulin is adjusted for thirty days. The most prominent risk is potential altered effectiveness of Lyumjev compared to the currently used insulin, which could lead to hypo- and hyperglycemia, but high and low glucose values will be indicated by alarms given by the AP system.

The individual benefit for the participating patients could be an improved glycemic control during the study.

The burden of the study is relatively low. The participants have to visit the CRC at most 2 times. Besides, the only additional burden for participants is to keep a Wi-Fi access point with them during both study periods.

6.5 Description and justification of route of administration and dosage

Lyumjev will be administered by the AP system in the same way Humalog (the reference insulin) is administered. This administration is performed by a pump which can administer doses in the order of 0.25 units. One unit corresponds to 0.01 ml which equals 0.01 mg of insulin using a concentration of 1.0 mg/ml (as used during this study). One dose administration is 0.25 units, corresponding to 0.0025 mg insulin. No maximum total dose per day is defined.

6.6 Dosages, dosage modifications and method of administration

The dosage of Lyumjev that will be administered by the Inreda AP system is determined by the control algorithm and depends on the patient's current sensor glucose and the rate of change of the glucose level.

Moreover, maintenance doses are administered by the Inreda AP system to prevent infusion set occlusion. This maintenance dose equals 0.25 units per hour, in case no insulin determined by the control algorithm is administered for 1 hour.

Lyumjev should be stored in the refrigerator (2-8 °C) before use. To protect the insulin from light, it should be stored in the original package. After first use, it should not be stored above 30 °C.

6.7 Preparation and labelling of Investigational Medicinal Product

Both the investigational Lyumjev insulin and the control Humalog insulin will be delivered by the pharmacy in cartridges of 3 ml, applicable for the Inreda AP system.

6.8 Drug accountability

The investigator will maintain adequate records showing dispensing, return, or other disposition of the Lyumjev insulin including the date, quantity, batch or code number, and identification of participants who received Lyumjev insulin. The investigator will not supply the drug to any person except sub-investigators, designated trial personnel, and participants in this trial.

All used and unused Lyumjev insulin will be stored until study closure and final reconciliation have been performed to ensure compliance.

7. NON-INVESTIGATIONAL PRODUCT

Not applicable.

7.1 Name and description of non-investigational product(s)

Not applicable.

7.2 Summary of findings from non-clinical studies

Not applicable.

7.3 Summary of findings from clinical studies

Not applicable.

7.4 Summary of known and potential risks and benefits

Not applicable.

7.5 Description and justification of route of administration and dosage

Not applicable.

7.6 Dosages, dosage modifications and method of administration

Not applicable.

7.7 Preparation and labelling of Non Investigational Medicinal Product

Not applicable.

7.8 Drug accountability

Not applicable.

8. METHODS

8.1 Study parameters/endpoints

8.1.1 Main study parameter/endpoint

The main study parameter is the proportion of time spent above range (>10 mmol/l).

8.1.2 Secondary study parameters/endpoints (if applicable)

The safety parameters are:

- Side effects of Lyumjev

The pharmacodynamic parameters are:

- Proportion of time spent in euglycemia (3.9-10.0 mmol/l);
- Proportion of time spent in hypoglycemia (<3.9 mmol/l);
- Proportion of time spent in level 2 hypoglycemia (<3.0 mmol/l);
- Proportion of time spent in level 2 hyperglycemia (>13.9 mmol/l);
- Mean/median glucose value;
- Glycemic variability expressed as coefficient of variation and interquartile range (IQR).

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 (00:00–06:00 h) separately.

AP-related parameters are:

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

8.1.3 Other study parameters (if applicable)

Other study parameters include: demographic characteristics, weight, length, HbA1c, relevant medical history and current medication use. Furthermore, occurrence of technical issues with the Inreda AP system will be recorded.

8.2 Randomisation, blinding and treatment allocation

The allocation sequence for the intervention and control arms will be generated by block randomization with an equal allocation ratio.

8.3 Study procedures

The study starts with informing the patients about the study. If patients want to participate the informed consent form will be signed first and thereafter the patients will be screened, which can be performed online or in the CRC. The study will be performed at home and subjects can live according to their own daily routine.

At the start of the first study period the subject will receive the insulin cartridges for the first study period. After the first 30 days, there will be a washout period of 8 days where subjects will use Humalog. After the wash-out period the subjects will receive the second insulin formulation according to randomization. The same procedure as written above will be repeated. During the study conduct there will be four additional visits by the investigator: at the start and end of both the intervention and control period.

If adverse events occur during the study, the subject has to contact the investigator. If desired, an unscheduled visit could take place. If a device deficiency occurs during the study, the subject has to contact the investigator only if this is insulin-related. If there are other technical problems, the patient should follow the regular treatment protocol and contact the customer service of Inreda Diabetic B.V.

During both study periods subjects are asked to keep a Wi-Fi access point with them so researchers can assess the data if necessary. No active real-time monitoring will be performed during the study, the standard monitoring protocol will be complied. This includes monthly portal assessments and assessments at the request of the customer service.

At the start of the study the self-learning algorithm status (on or off) will not be changed. This means that the self-learning algorithm is turned on or off depending on the setting prior to the study.

8.4 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

8.4.1 Specific criteria for withdrawal

Subjects may be removed from the study if any of the following events occur:

- Significant protocol violation or non-compliance;
- Refusal of the subject to continue treatment and/or observations;
- Decision by the investigator that termination is in the subject's best medical interest;
- Subject changes medication that may interfere with the evaluation of the results;
- Illness during the study period;
- Glucose sensor problems.

8.5 Replacement of individual subjects after withdrawal

A maximum of 2 subjects will be replaced after withdrawal from the study during the training period or before and between the first and second study period. Subjects will not be replaced after withdrawal from the study during one of the study periods.

8.6 Follow-up of subjects withdrawn from treatment

There will no follow-up of withdrawn subjects.

8.7 Premature termination of the study

The study will be put on hold in case of severe hypo-/hyperglycemia during the intervention period until the cause of the severe hypo-/hyperglycemia is determined. Hypo-/hyperglycemia is severe in case it leads to requiring intervention by a third party. The METC will be notified of such event.

9. SAFETY REPORTING

9.1 Temporary halt for reasons of subject safety

In accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The sponsor will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

9.2 AEs, SAEs and SUSARs

9.2.1 Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the investigational product. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

If adverse events occur during the study, the subject has to contact the investigator. If desired, an unscheduled visit could take place. If device deficiencies occur during the study, the subject has to contact the investigator only if it is insulin-related. If there are other technical problems, the patient should follow the regular treatment protocol and contact the customer service of Inreda Diabetic.

9.2.2 Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that

- results in death;
- is life threatening (at the time of the event);
- requires hospitalisation or prolongation of existing inpatients' hospitalisation;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect; or
- any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgement by the investigator.

An elective hospital admission will not be considered as a serious adverse event.

The investigator will report all SAEs to the sponsor without undue delay after obtaining knowledge of the events.

The sponsor will report the SAEs through the web portal *ToetsingOnline* to the accredited METC that approved the protocol, within 7 days of first knowledge for SAEs that result in death or are life threatening followed by a period of maximum of 8 days to complete the initial preliminary report. All other SAEs will be reported within a period of maximum 15 days after the sponsor has first knowledge of the serious adverse events.

9.2.3 Suspected unexpected serious adverse reactions (SUSARs)

Adverse reactions are all untoward and unintended responses to an investigational product related to any dose administered.

Unexpected adverse reactions are SUSARs if the following three conditions are met:

1. the event must be serious (see chapter 9.2.2);
2. there must be a certain degree of probability that the event is a harmful and an undesirable reaction to the medicinal product under investigation, regardless of the administered dose;
3. the adverse reaction must be unexpected, that is to say, the nature and severity of the adverse reaction are not in agreement with the product information as recorded in:
   - Summary of Product Characteristics (SPC) for an authorised medicinal product;
   - Investigator's Brochure for an unauthorised medicinal product.

The sponsor will report expedited the following SUSARs to the METC:

- SUSARs that have arisen in the clinical trial that was assessed by the METC;
- SUSARs that have arisen in other clinical trials of the same sponsor and with the same medicinal product, and that could have consequences for the safety of the subjects involved in the clinical trial that was assessed by the METC.

The remaining SUSARs are recorded in an overview list (line-listing) that will be submitted once every half year to the METC. This line-listing provides an overview of all SUSARs from the study medicine, accompanied by a brief report highlighting the main points of concern.

The expedited reporting of SUSARs through the web portal Eudravigilance or ToetsingOnline is sufficient as notification to the competent authority.

The sponsor will report expedited all SUSARs to the competent authorities in other Member States, according to the requirements of the Member States.

The expedited reporting will occur not later than 15 days after the sponsor has first knowledge of the adverse reactions. For fatal or life threatening cases the term will be maximal 7 days for a preliminary report with another 8 days for completion of the report.

This is a multicentre study and if a SUSAR occurs in Rijnstate Hospital the coordinating investigator is responsible for the process, and if a SUSAR occurs in Slingeland Hospital or Hospital Gelderse Vallei the principal investigator of that specific centre is responsible for the process.

A description of the method for breaking the code for SUSAR reporting is not applicable because this is not a blinded study.

9.3 Incidents (MDR vigilance definitions)

9.3.1 Incident

Any malfunction or deterioration in the characteristics or performance of the AP system, including use-error due to ergonomic features, as well as any inadequacy in the information supplied by the manufacturer and any undesirable side-effect.

9.3.2 Serious incident

Means any incident that directly or indirectly led, might have led or might lead to any of the following:

- the death of a patient, user or other person;
- the temporary or permanent serious deterioration of a patient's, user's or other person's state of health;
- a serious public health threat.

9.3.3 Non-serious incident

An incident that is not a serious incident.

9.3.4 Recording of incidents

Patients will be referred to the Customer Service of Inreda Diabetic in case of device issues. Device issues of all participants will be recorded. Subsequently, the PMS system and vigilance procedures at Inreda Diabetic will adequately address or resolve and record incidents according to the MDR requirements.

9.4 Annual safety report

In addition to the expedited reporting of SUSARs, the sponsor will submit, once a year throughout the clinical trial, a safety report to the accredited METC, competent authority, and competent authorities of the concerned Member States.
This safety report consists of:

- a list of all suspected (unexpected or expected) serious adverse reactions, along with an aggregated summary table of all reported serious adverse reactions, ordered by organ system, per study;
- a report concerning the safety of the subjects, consisting of a complete safety analysis and an evaluation of the balance between the efficacy and the harmfulness of the medicine under investigation.

9.5 Follow-up of adverse events

All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist. SAEs need to be reported till end of study within the Netherlands, as defined in the protocol

9.6 Data Safety Monitoring Board (DSMB)

Not applicable.

10. STATISTICAL ANALYSIS

A general description of the statistical methods to be used is given in this chapter, specific details will be provided in the Statistical Analysis Plan. The Statistical Analysis Plan will be prepared before inclusion of the first patient. Deviations from this plan should be reported in the clinical investigation report with a clear statement that this decision was made after preliminary data evaluation and thus post-hoc.

All subjects that completed both study periods will be included in the analysis. Withdrawals will be included in the analysis for adverse events and device deficiencies in order to have an adequate amount of data for analysis. Furthermore, the data collected until their withdrawal will be included in the analysis as well. Carry-over and period effects will be assessed for all parameters.

10.1 Primary study parameter

The proportion of time above range (>10.0 mmol/l) will be compared between Lyumjev insulin and Humalog insulin using a dependent t-test or Wilcoxon signed rank test for paired measurements (significance level of 0.05).

10.2 Secondary study parameters

The pharmacodynamic parameters will be compared between Lyumjev insulin and Humalog insulin using a dependent t-test or Wilcoxon signed rank test for paired measurements (significance level of 0.05).

Pharmacodynamic parameters will be tested for the whole day, daytime and nighttime.

The AP-related parameters will be compared between Lyumjev insulin and Humalog insulin using a dependent t-test or Wilcoxon signed rank test for paired measurements (significance level of 0.05).

10.3 Other study parameters

Demographic characteristics, weight, length and HbA1c will be given as median with IQR.

10.4 Interim analysis

Not applicable.

11. ETHICAL CONSIDERATIONS

11.1 Regulation statement

This study is conducted in full accordance with the principles of the “Declaration of Helsinki” (as amended in Tokyo, Venice, Hong Kong, Somerset West, Edinburgh, Washington, Seoul and Fortaleza) [9], International Standard 14155:2020, this research protocol, the applicable SOPs and the laws and regulations of the Netherlands. The complete text of the “Declaration of Helsinki” is supplied to the investigators upon request. The study shall not begin until the required approval from the Medical Ethical Committee and approval from the CCMO following a marginal review.

11.2 Recruitment and consent

Possible subjects will be approached by his/her treating physician (which may also be the principal investigator). If the subjects indicates to be interested in the study, the treating physician will inform the researcher. The subjects will then be informed by the researcher about the study and will be given enough time to consider participation in the study before signing the informed consent form.
It is the responsibility of the researcher to obtain oral and written informed consent. In obtaining and documenting informed consent, the investigator must comply with applicable regulatory documents and adhere to the ICH GCP guideline [10] and to the requirements in the Declaration of Helsinki (above).

11.3 Objection by minors or incapacitated subjects

Not applicable.

11.4 Benefits and risks assessment, group relatedness

There are no major risks associated with this study since the patients will continue their usual diabetes therapy, in which only the type of insulin is adjusted for 30 days. The most prominent risk is potential altered effectiveness of Lyumjev compared to the currently used insulin, which could lead to hypo- and hyperglycemia, but high and low glucose values will be indicated by alarms given by the AP.

See Chapter 13 for the risk assessment and control measures.

The individual benefit for the participating patients could be improved glycemic control during the study.

11.5 Compensation for injury

The sponsor/investigator has a liability insurance which is in accordance with article 7 of the WMO.

The sponsor (also) has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO). This insurance provides cover for damage to research subjects through injury or death caused by the study.
The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

11.6 Incentives

Participants who will participate in the study will be thanked with a gift card of €50,-.

12. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

12.1 Handling and storage of data and documents

The following data can be recorded directly in to the Case Report Forms (CRFs) using Research Manager and will be collected by Rijnstate Hospital, Hospital Gelderse Vallei and Slingeland Hospital:

- Medical information;
- Demographic characteristics;
- Concomitant medication;
- Adverse events;
- Device deficiencies.

The complete data management process will be described in detail in the Data Management Plan, which will be prepared before inclusion of the first patient.

At the end of the study Inreda Diabetic B.V. collects data from the Inreda AP system of all study participants. This data consists of:

- Glucose measurements;
- Data about insulin and glucagon doses;
- Activity measurements;
- Technical data.

The data from the AP will be exported to a secured computer server, located at Inreda Diabetic B.V. The data is only linked to a study participant number. The database server is secured by authorized access and is password protected. The data at this server can be evaluated for the internal purposes of advancing or improving the device or services for the benefit of future patients, which subjects also sign informed consent for.

Personal data of subjects is available for the researchers to ensure safety. If necessary, monitors or authorities will have access to personal data. Subjects are informed and sign informed consent regarding these procedures.

If the data analysis is performed by Inreda Diabetic B.V., results will be shared with Rijnstate Hospital, Hospital Gelderse Vallei, and Slingeland Hospital.

All of the aspects mentioned above will also be included in the Clinical Trial Agreement (CTA) between Rijnstate Hospital, Hospital Gelderse Vallei, and Slingeland Hospital. The CTA will be agreed upon before the conduct of the study.

12.2 Monitoring and Quality Assurance

An external monitor will be appointed for monitoring. Our first option is the monitor of the APPEL 5 and SMART 1 study: Rachel Derksen (Derksen CSM).

The monitor needs to perform an initiation visit, monitoring visit during the conduct of the study and close-out visit. The monitoring visit during the conduct of the study will be performed when around 4 patients have completed the study.

As a minimum the following requirements apply, verification of:

- 100% of the informed consent forms;
- 100% of the trial subjects (in- and exclusion criteria);
- 10% of the source data;
- Identification and provision of investigational product;
- Use of the correct version of the protocol and procedures.

The monitor needs to set up a monitor plan before the conduct of the study.

In accordance with applicable regulations Inreda Diabetic B.V. may conduct quality assurance audits to ensure processes as defined in the procedures are being carried out as intended.

12.3 Amendments

A ‘substantial amendment’ is defined as an amendment to the terms of the METC application, or to the protocol or any other supporting documentation, that is likely to affect to a significant degree:

- the safety or physical or mental integrity of the subjects of the trial;
- the scientific value of the trial;
- the conduct or management of the trial; or
- the quality or safety of any intervention used in the trial.

All substantial amendments will be notified to the METC and to the competent authority.

Non-substantial amendments will not be notified to the accredited METC and the competent authority, but will be recorded and filed by the sponsor.

12.4 Annual progress report

The sponsor/investigator will submit a summary of the progress of the study to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the study, serious adverse events/serious adverse reactions, other problems and amendments.

12.5 Temporary halt and (prematurely) end of study report

The sponsor will notify the accredited METC and the competent authority of the end of the study within a period of 90 days. The end of the study is defined as the last patient's last visit.

The sponsor will notify the METC immediately of a temporary halt of the study, including the reason of such an action.

In case the study is ended prematurely, the sponsor will notify the accredited METC and the competent authority within 15 days, including the reasons for the premature termination.

Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC and the competent authority.

12.6 Public disclosure and publication policy

Publication of the results of this study will be written by the representatives of Rijnstate Hospital, Slingeland Hospital, Hospital Gelderse Vallei, and Inreda Diabetic. The coordinating investigator of Rijnstate Hospital is responsible for the publication and will determine the order of authors.

13. STRUCTURED RISK ANALYSIS

13.1 Synthesis

Both the Inreda AP and Lyumjev insulin are registered and certified products. In this study both products will be used for the intended patient population and within the indication of use. Therefore, section '13.1: potential issues of concern' was omitted.

Lyumjev is not used in combination with the AP. However, Lyumjev is quite similar to Humalog and thus the Inreda AP system seems to be suitable to interact with Lyumjev insulin. Therefore, risks are minimal.

The following safety issues have to be considered.

1. It is unknown if the effectiveness of Lyumjev is completely comparable to the currently used Humalog. This could lead to hypo- and hyperglycemia, but the algorithm of the system will automatically adjust the doses, if applicable. Moreover, high and low glucose values will be indicated by alarms given by the Inreda AP system;
2. Discomfort caused by the new type of insulin. Since Lyumjev induces local vasodilation this could be more painful for the patient compared to injection with Humalog. However, diabetes patients are already familiar with the discomfort of insulin injection. These patients are therefore expected to be able to assess discomfort in advance.

In conclusion, the risks are low and most of the subjects will be already familiar with the mentioned safety issues during the management of their diabetes. The study is therefore classified as low risk. We believe that the investigational product could be an effective successor for the currently used insulin. Besides, in our opinion, the burden for the participants is acceptable.

14. REFERENCES

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